PRODUCT MONOGRAPH

Pr ATGAM®

(lymphocyte immune globulin, anti-thymocyte globulin [equine])

Concentrate for solution for infusion / sterile solution - 50 mg/mL

(For Intravenous Use Only)

IMMUNOSUPPRESSANT

Pfizer Canada Inc.
17,300 Trans-Canada Highway
Kirkland, Quebec

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[Pr]ATGAM STERILE SOLUTION®
(lymphocyte immune globulin, anti-thymocyte globulin [equine])

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	50 mg/mL	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) is indicated for any patient in whom reduction of peripheral T-lymphocyte function as measured by rosette-forming cell assay could be desirable.

A. During controlled clinical trials, this immunosuppression has been demonstrated in renal allograft recipients treated with ATGAM. When administered with conventional therapy at the time of rejection, it increases the frequency of resolution of the acute rejection episode. The drug has also been administered as an adjunct to other immunosuppressive therapy to delay the onset of the first rejection episode.

B. In non-controlled clinical studies, ATGAM has been administered to other patients in whom reduction of T-cell function could be desirable. They had aplastic anemia, T-cell malignancies, or graft-versus-host disease, or had received skin, cardiac, liver, or bone-marrow transplants. Anecdotal reports of benefit have been published, but to date controlled studies to establish safety and efficacy in circumstances other than renal transplantation have not been completed.

CONTRAINDICATIONS

Do not administer ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) to a patient who has had a severe systemic reaction during prior administration of ATGAM or any other equine gamma globulin preparation.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]).

- Treatment with ATGAM should be discontinued if any of the following occurs:
  1. Anaphylaxis (see **ADVERSE REACTIONS**)
  2. Severe and unremitting thrombocytopenia
  3. Severe and unremitting leukopenia

- This product is manufactured using components of human blood which may contain the causative agent of hepatitis and other viral diseases. Prescribed manufacturing procedures utilized in blood collection centres and the plasma testing laboratories are designed to reduce the risk of transmitting viral infection. However, the risk of viral infectivity from this product cannot be totally excluded.

- Patients receiving ATGAM should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources.

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

Immune
Because ATGAM is an immunosuppressive agent ordinarily given with corticosteroids and antimetabolites, patients should be monitored carefully for signs of leukopenia, thrombocytopenia or concurrent infection. 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.

Live-virus vaccines may not replicate successfully and antibody response could be reduced when the vaccine is administered after immune globulin infusion. Live-virus vaccines should ideally be administered 6 months after intravenous therapy with ATGAM.

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. Based on the mechanism of action of ATGAM, there is a

potential risk of cytokine release syndrome.

Infection

Some studies have suggested an increase in the incidence of cytomegalovirus infection in patients receiving ATGAM. Some physicians have found that it may be possible to reduce this by decreasing the dosage of other immunosuppressive agents which might be administered concurrently with ATGAM.

Special Populations

Pregnant Women:
There are no adequate and well-controlled studies in pregnant women. ATGAM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women:
It is not known if ATGAM is excreted in human milk. Therefore, because of the potential for serious adverse reactions in nursing neonates and infants, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics:
Experience with children has been limited. ATGAM has been administered safely to a small number of pediatric renal, liver and bone marrow allograft recipients and aplastic anemia patients at dosage levels comparable to those in adults.

Geriatrics (>65 years of age):
As reported in the literature and clinical studies, the administration of ATGAM 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 (see **DOSAGE AND ADMINISTRATION**) reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

Monitoring and Laboratory Tests

In patients with aplastic anaemia and other hematologic abnormalities who have received anti-thymocyte globulin (equine), abnormal tests of liver function and renal function have been observed.

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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

The primary clinical experience with ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) has been in renal allograft patients, who were also receiving concurrent standard immunosuppressive therapy (azathioprine, corticosteroids).

In controlled clinical trials, investigators have reported the following adverse reactions:

Incidence greater than 5%
chills (14%), fever (33%), leukopenia (14%), thrombocytopenia (11%) and dermatological reactions such as pruritus, rash, urticaria, wheal and flare (12.5%).

Incidence of 1 to 5%
arthralgia, chest and/or back pain, clotted A/V fistula, diarrhea, dyspnea, headache, hypotension, nausea and/or vomiting, night sweats, pain at the infusion site, peripheral thrombophlebitis and stomatitis.

The incidence of adverse reactions has been higher in patients being treated for aplastic anemia. Frequently reported adverse reactions among patients enrolled in aplastic anemia studies were arthralgia, chills, fever, skin rashes and thrombocytopenia. The high incidence of skin rashes and arthralgia was believed by investigators to represent serum sickness. In patients with aplastic anemia and other haematologic abnormalities who have received ATGAM, abnormal tests of liver function (SGOT, SGPT, alkaline phosphatase) and renal function (serum creatinine) have been observed. In some trials, clinical and laboratory findings of serum sickness have been seen in a majority of patients.
Other reactions reported in renal allograft or aplastic anemia patients receiving therapy have included: back pain, chest pain, clotted A/V fistula, diarrhea, dyspnea, headache, hypotension, nausea, night sweats, pain at the infusion site, peripheral thrombophlebitis, stomatitis and vomiting.

Reactions reported **rarely** have been: agitation, anaphylaxis, dizziness, edema, epigastric pain or hiccoughs, herpes simplex reactivation, hyperglycemia, hypertension, iliac vein obstruction, infection, laryngospasm, lymphadenopathy, malaise, paresthesia, periorbital edema, pleural effusions, possible encephalitis, proteinuria, pulmonary edema, renal artery thrombosis, seizure, tachycardia, toxic epidermal necrosis, weakness or faintness, and wound dehiscence.

Post-Market Adverse Drug Reactions

During approximately five years of post-approval marketing experience, the frequency of adverse reactions in voluntarily reported cases is as follows; chills (16%), fever (51%), leukopenia (14%), rashes (27%), systemic infection (13%), thrombocytopenia (30%).

Events reported with a frequency of 5 to 10% include; abnormal renal function tests, arthralgia, chest, back or flank pain, diarrhea, dyspnea/apnea, nausea and/or vomiting and serum sickness-like symptoms.

Events reported with a frequency of < 5% include; abnormal involuntary movement or tremor, abnormal liver function tests, abdominal pain, acute renal failure, anaphylaxis, anemia, aplasia or pancytopenia, bradycardia, confusion or disorientation, cough, deep vein thrombosis, dizziness, edema, enlarged or ruptured kidney, eosinophilia, epigastric or stomach pain, faintness, GI bleeding or perforation, haemolysis or haemolytic anemia, headache, Herpes Simplex infection, hyperglycemia, hypertension, hypotension, localized infection, lymphadenopathy, malaise, myalgias or leg pains, neutropenia or granulocytopenia, nosebleed, pain, swelling or redness at infusion site, paresthesias, pulmonary edema or congestive heart failure, renal artery thrombosis, rigidity, seizures, sore mouth-throat, sweating, laryngospasm/edema, tachycardia, thrombophlebitis, vasculitis, and viral hepatitis.

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 epinephrine (1:1,000 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, furosemide, 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 without 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, epinephrine, corticosteroid, 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 stabilized with pressors if necessary.

7. **CHILLS AND FEVER** occur frequently in patients receiving ATGAM. ATGAM may release endogenous leukocyte 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 arterialized 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.

10. **SERUM SICKNESS-LIKE SYMPTOMS** in aplastic anemia patients that have been treated with oral and IV corticosteroids. Resolution of symptoms has generally been prompt and long-term sequelae have not been observed. Prophylactic administration of corticosteroids may decrease the frequency of this reaction.

DRUG INTERACTIONS

Overview

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 AND ADMINISTRATION

Dosing Considerations

Before the first intravenous infusion of ATGAM, it is **strongly** recommended that skin testing potential recipients take place before commencing treatment. First the patient should receive an epicutaneous (prick) testing with undiluted ATGAM. If a wheal does not develop 10 minutes after pricking, then proceed to intradermal testing with 0.02 mL of a 1:1000 v/v saline dilution of

ATGAM with a separate saline control injection of similar volume. After 10 minutes read the results. A wheal at the ATGAM site of 3 mm or larger in diameter compared to the saline control site suggests clinical sensitivity and an increased possibility of a systemic allergic reaction.

Where an ATGAM skin test causes a locally positive reaction, serious consideration should be given to alternative forms of therapy. 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 generalized 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, as described above, skin testing will not predict for later development of serum sickness. (see **WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).**

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 and carefully observe patients for signs of allergic reactions.

Recommended Dose and Dosage Adjustment

Renal-Allograft Recipients

Adult renal allograft patients have received ATGAM at the dose of 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 [5,9,19,27] and at the time of the first rejection episode [7,14,18,21,25]. Most patients who received ATGAM for the treatment of acute rejection had not received it starting at the time of transplantation.

Delaying the Onset of Allograft Rejection: The recommended dose is 15 mg/kg daily for 14 days, then every other day 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 can be given.

Other Allograft Recipients
ATGAM has been used in liver transplant recipients[26] at daily doses of 8 to 15 mg/kg. The duration of therapy averaged 13 days. In heart transplant patients,[13,16,23] intermittent daily doses average 8 mg/kg (range: 5 to 11 mg/kg, duration of therapy averaged four months, and the number of doses averaged 29 (range: 7 to 49). In burn patients who have received temporary skin allografts,[3,4,8] ATGAM dosage ranged from 10 to 15 mg/kg for up to 24 doses. All patients received the first ATGAM dose in the 24-hour period immediately before or after the surgical procedure.

Bone Marrow Transplantation
Several different ATGAM dosage regimens have been used in patients receiving bone marrow transplants. [17,20,28,29] Generally, patients received ATGAM 7 to 20 mg/kg for 3 to 14 doses. The first dose was given 9 days before transplant for pre-conditioning, 7 to 30 days after transplant for prophylaxis of graft-versus-host disease or when graft-versus-host disease was diagnosed.

Aplastic Anemia
Patients with aplastic anemia [1,2,6,7,10,11,24] have received ATGAM in several regimens, generally 10 to 20 mg/kg for 8 to 21 doses.

Other Indications
ATGAM has also been used in patients with Sezary Syndrome, T-call leukemia,[12,15] and nephrotic syndrome. Although some patients have received multiple high doses intermittently over long periods, a standard dosage regimen has not been established.

Administration

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 faintly pink or brown, and may develop a slight granular of flaky deposit during storage. ATGAM (diluted or undiluted) should not be shaken because excessive foaming and/or denaturation of the protein may occur.

During the 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 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.

Using high-flow veins will minimize the occurrence of phlebitis and thrombosis.

Do not infuse a dose of ATGAM in less than 4 hours. Discard unused product or waste material.

Always keep a tray containing epinephrine, 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 **ADVERSE REACTIONS**).

Reconstitution:
ATGAM should be diluted for intravenous infusion in an inverted bottle of sterile vehicle, so that the undiluted ATGAM does not contact the air inside. Add the total daily dose of ATGAM to the sterile vehicle, with a concentration not exceeding 4 mg of ATGAM Sterile Solution per mL. The diluted solution should be gently rotated or swirled to effect complete mixing.
Once diluted, ATGAM has been shown to be physically and chemically stable for up to 24 hours at concentrations of up to 4 mg per mL in the following diluents:

- 0.9% Sodium Chloride Injection
- 5% Dextrose and 0.225 Sodium Chloride Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection

Adding ATGAM to dextrose injection 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). It is recommended that diluted ATGAM be stored in a refrigerator if it is prepared prior to the time of infusion. The diluted ATGAM solution should be allowed to reach room temperature before infusion.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Because of its mode of action and because it is a biologic substance, the maximum tolerated dose of ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) 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 of saline, seven times the recommended total dose and infusion concentration. In this

patient, the administration of ATGAM was not associated with any signs of acute intoxication or late sequelae.

Neither the maximum therapeutic dose nor the greatest number of doses (10 to 20 mg/kg dose) that can be administered to a single patient has been established. 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 regimens, but close monitoring of these patients is recommended.

ACTION AND CLINICAL PHARMACOLOGY

ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) is the purified concentrated, and sterile gamma globulin, primarily monomeric IgG, from hyperimmune plasma of horses immunized with human thymus lymphocytes. ATGAM is composed of antibodies that bind a wide variety of proteins on the surface of lymphocytes and in addition, binds to granulocytes, platelets and bone marrow cells.

ATGAM is a lymphocyte-selective immunosuppressant as is demonstrated by its ability to reduce the number of circulating, thymus-dependent 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 the 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. The mechanism of anti-thymocyte globulin (equine)-induced immunosuppression has not been determined. Published data indicate that the primary mechanism is the depletion of circulating lymphocytes, with greatest effect on T lymphocyte. Lymphocyte depletion may be caused by complement dependent lysis and/or activation-induced apoptosis. In addition, immunosuppression may be mediated by the binding of antibodies to lymphocytes which results in partial activation and induction of T lymphocyte anergy.

The mechanism of anti-thymocyte globulin (equine) therapy for aplastic anemia is attributed to its immunosuppressive actions. In addition, anti-thymocyte globulin (equine) directly stimulates the growth of hematopoietic stem cells and release of hematopoietic growth factors such as interleukin-3 and granulocyte/macrophage colony stimulating factor.

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.

Pharmacokinetics

In a small clinical study of 27 renal transplant patients, 10 to15 mg/kg/day i.v. of anti-thymocyte globulin (equine) was infused over 2 weeks. The mean peak concentration of plasma horse IgG was 727±310 μg/mL and the mean plasma half-life was of 5.7 ± 3 days (range: 1.5 – 13 days).

STORAGE AND STABILITY

Store ATGAM ampoules in the refrigerator at 2^{o} to 8^{o}C, **DO NOT FREEZE.** Protect ampoules from light by storing in the carton.

Once diluted, the solution is stable for up to 24 hours if stored in a refrigerator.

SPECIAL HANDLING INSTRUCTIONS

See **DOSAGE AND ADMINISTRATION**, **Administration.**

DOSAGE FORMS, COMPOSITION AND PACKAGING

ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) is supplied in 5 mL ampoules containing 250 mg protein per ampoule. Each mL of ATGAM contains 50 mg of horse gamma globulin stabilized in 0.3 molar glycine to a pH of approximately 6.8.
Cartons of 5 ampoules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

International non-proprietary name (INN): (lymphocyte immune globulin, anti-thymocyte globulin [equine])

Molecular weight: The molecular weight as determined by electrophoresis is approximately 150,000

Description: Lymphocyte immune globulin, anti-thymocyte globulin [equine] is a purified concentrated and sterile gamma globulin, primarily monomeric IgG, from hyperimmune serum of horses immunized with human thymus lymphocytes.

CLINICAL TRIALS

Clinical Trials have been performed on ATGAM.

TOXICOLOGY

Mutagenicity and carcinogenicity studies have not been conducted on ATGAM.

In animal studies, anti-thymocyte globulin (equine) was not detected at the limit of quantification in the milk of lactating cynomolgus monkeys.

Reproduction and Teratology

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

In monkey reproduction studies, maternal toxicity was observed with doses $\geq$ 20 mg/kg/day for 14 days. Maternal deaths occurred at a dose 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 last part of organogenesis. While the etiology of this toxicity is not known, it may possibly be attributed to haemolytic anemia due to cross-reactivity of anti-thymocyte globulin (equine) to a monkey red blood antigen. Humans do not share this antigen, thus this toxicity is not considered relevant to human development. Anti-thymocyte globulin (equine) was not teratogenic in rats or monkeys. At a dose of 100 mg/kg in rats during organogenesis, an increase in hypoplastic cervical vertebrae was observed.

REFERENCES

1. Amare M, Abdou NL, Robinson MG, Abdou NI. Aplastic anemia (AA) associated with bone marrow suppressor T-cell hyperactivity: Successful treatment with antithymocyte globulin (ATG). Am J Hematol 1978;5:25-32.

2. Bukowski RM, Hewlett JS, Hoffman GC, Rothman Hamburger SA. Antithymocyte globulin (ATG) therapy of severe aplastic anemia (AA). Meet Abstr Blood 1978;52(suppl 1):77.

3. Burke JF, Quinby WC, Bondoc CC. Early excision and prompt wound closure supplemented with immunosuppression. Surg Clin North Am 1978;58:1141-50.

4. Burke JF, Quinby WC, Bondoc CC, Cosimi AB, Russell PS, Szyfelbein SK. Immunosuppression and temporary skin transplantation in the treatment of massive third degree burns. Ann Surg 1975;182:183-97.

5. Butt KMH, Zielinski CM, Parsa I, Elberg AJ, Wechter WJ, Kountz SK. Trends in immunosuppression for kidney transplantation. Kidney Int 1978;13(suppl 8):S95-8.

6. Champlin R, Gale RP. Antithymocyte globulin (ATG) treatment of aplastic anemia (AA) -- a randomized controlled study. Meet Abstr Blood 1981;58(5)(suppl 1):40.

7. Cosimi AB. The clinical value of antilymphocyte antibodies. Transplant Proc 1981;13(1):462-8.

8. Cosimi AB, Burke JF, Russell PS. Transplantation of skin. Surg Clin North Am 1978;58:435-51.

9. Cosimi AB, Wortis HH, Delmonico FL, Russell PS. Randomized clinical trial of antithymocyte globulin in cadaver renal allograft recipients: Importance of T cell monitoring. Surgery 1976;80:155-63.

10. Doney KC, Torok-Storb B, Buckner CD, Weiden P, Storb R. Treatment of aplastic anemia (AA) with antithymocyte globulin (ATG) and androgens with or without mismatched bone marrow infusion. Meet Abstr Blood 1981;58(5)(suppl 1):40.

11. Doney KC, Weiden PL, Buckner CD, Storb R, Thomas ED. Treatment of severe aplastic anemia using antithymocyte globulin with or without an infusion of HCA haploidentical marrow. Exp Hematol 1981;9(8):829-34.

12. Edelson RL, Raafat J, Berger CL, Grossman M, Troyer C, Hardy M. Antithymocyte globulin in the management of cutaneous T-cell lymphoma. Cancer Treat Rep 1979;63:675-80.

13. English TAH, Cooper DKC, Cory-Pearce R. Recent experience with heart transplantation. Br Med J 1980;281:699-702.

14. Filo RS, Smith EJ, Leapman SB. Reversal of acute renal allograft rejection with adjunctive ATG therapy. Transplant Proc 1981;13(1):482-90.

15. Fisher RI, Kubota TT, Mandell GL, Broder S, Young RC. Regression of a T-cell lymphoma after administration of antithymocyte globulin. Ann Intern Med 1978;88:799-800.

16. Greipp RB, Stinson EB, Dong E Jr, Phillips RC, Morrell RM, Shumway NE. Use of antithymocyte globulin in human heart transplantation. Circulation 1972;45(suppl 1):147-53.

17. Gengozian N, Edward CL, Vodopick HA, Huebner RF. Bone marrow transplantation in a leukemic patient following immunosuppression with antithymocyte globulin and total body irradiation. Transplantation 1973;15:446-54.

18. Hardy MA, Nowygrod R, Elberg A, Appel G. Use of ATG in treatment of steroid-resistant rejection. Transplantation 1980;29:162-4.

19. Kountz SL, Butt KHM, Rao TKS, Zielinski CM, Rafi M, Schultz Jr. Antithymocyte globulin (ATG) dosage and graft survival in renal transplantation. Transplant Proc 1977;9:1023-5.

20. Meuwissen HJ, Moore EC, Strauss HS, Taft E, Britten A. Successful retransplantation of bone marrow following failure of initial engraftment in a patient with aplastic anemia. J Pediatr 1976;89:588-92.

21. Nowygrod R, Appel G, Hardy M. Use of ATG for reversal of acute allograft rejection. Transplant Proc 1981;13(1):469-72.

22. Pass RF, Whitley RJ, Drethelm AG, et al. Cytomegalovirus infection in patients with renal transplant: Potentiation by antithymocyte globulin and an incompatible graft. J Infect Dis 1980;142:9-17.

23. Reemstsma K, Bregman D, Drusin R, Dobelle W, Edie R, Hardy MA. Cardiac transplantation for patients requiring mechanical circulatory support. N Engl J Med 1978;298:670-1.

24. Shadduck RK, Winkelstein A, Zeigler A, et al. Aplastic anemia following infectious mononucleosis: Possible immune etiology. Exp Hematol 1979;7:264-71.

25. Shield CH, Cosimi AB, Tolkoff-Rubin N, Rubin R, Herrin J, Russell PS. Use of antithymocyte globulin for reversal of acute allograft rejection. Transplantation 1979;28(6):461-4.

26. Starzl TE, Koep LJ, Halgrimson CG, et al. Liver transplantation 1978. Transplant Proc II 1979;:240-6.

27. Wechter WJ, Brodie JA, Morrell RM, Rafi M, Schultz Jr. Antithymocute globulin (ATGAM) in renal allograft recipients. Transplantation 1979;28(4):294-302.

28. Weiden PL, Doney K, Storb R, Thomas ED. Antihuman thymocyte globulin (ATG) for prophylaxis and treatment of graft-versus host disease in recipients of allogenic marrow grafts. Transplant Proc 1978;10:213-6.

29. Weiden PL, Doney K, Storb R, Thomas ED. Antihuman thymocyte globulin for prophylaxis of graft-versus-host disease. Transplantation 1979;27:227-30.

PART III: CONSUMER INFORMATION

ATGAM* STERILE SOLUTION
(lymphocyte immune globulin, anti-thymocyte globulin [equine])

This leaflet is part III of a three-part "Product Monograph" published when ATGAM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ATGAM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) is indicated for any patient in whom reduction of peripheral T-lymphocyte function as measured by rosette-forming cell assay could be desirable. It is used at the time of kidney rejection as well as used with other therapies to delay the onset of a first rejection episode
It may also be used for other conditions in whom reduction of T-cell function could be desirable (ie: other allografts, bone marrow transplantation, aplastic anemia).

What it does:
ATGAM is an immune globulin and works by suppressing the body's immune system.

When it should not be used:
If you ever had an allergic reaction (for example rash, itchiness, or difficulty breathing) during prior administration of ATGAM or any other equine gamma globulin preparation.

What the medicinal ingredient is:
Each mL of ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) contains 50 mg of horse gamma globulin stabilized in 0.3 molar glycine to a pH of approximately 6.8.

What the important nonmedicinal ingredients are:
Glycine

What dosage forms it comes in:
ATGAM is supplied in cartons of 5 X 5 mL ampoules containing 250 mg protein per ampoule.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use ATGAM.
- Treatment with ATGAM should be discontinued if any of the following occurs:
  1. Anaphylaxis
  2. Severe and unremitting thrombocytopenia
  3. Severe and unremitting leukopenia
- This product is manufactured using components of human blood which may contain the causative agent of hepatitis and other viral diseases. Prescribed manufacturing procedures utilized in blood collection centres and the plasma testing laboratories are designed to reduce the risk of transmitting viral infection. However, the risk of viral infectivity from this product cannot be totally excluded.
- When you are receiving ATGAM, you will be monitored in a facility equipped and staffed with adequate laboratory and supportive medical resources.

BEFORE you are administered ATGAM talk to your doctor or pharmacist if:

- If you plan to drive or operate machinery
- If you have an acute viral illness.
- If you had severe or acute infections in the past.
- If you are pregnant or plan to become pregnant or are breast feeding
- If you plan to be vaccinated or have recently been vaccinated.
- If you have any allergies to this drug or its ingredients or components of the container.
- If you are taking other medications.

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, confusion, fainting), caution should be taken when driving or using machinery while on this medication.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ATGAM include:

- Live vaccines should not be administered when you are about to receive, receiving, or after treatment with ATGAM.
- Dilution of ATGAM in dextrose infusion solution is not recommended, as low salt concentration may result in precipitation. The use of highly acidic infusion solutions is also not recommended because of possible physical instability over time.
- When your dose of corticosteroids and other immunosuppressants is being reduced, some previously masked reactions to ATGAM may appear. Your healthcare professional will monitor you when ATGAM is being infused.

PROPER USE OF THIS MEDICATION

Usual dose:
ATGAM will always be prepared and given to you by your doctor or healthcare professional.

It is possible that skin testing will be done by a healthcare professional prior to your first infusion of ATGAM.

The recommended dose of ATGAM for renal-allograft patients is 10 to 30 mg/kg of body weight daily. The recommended dose for delaying the onset of allograft rejection is 15 mg/kg daily for 14 days, then every other day 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. The recommended dose for treatment of rejection is 10 to 15 mg/kg daily for 14 days. Additional alternate-day therapy up to a total of 21 doses can be given.

Other dosing regimens, depending on your condition, may be considered by your healthcare professional.

Missed Dose:
ATGAM will normally be administered by a health care professional in hospital. If you missed an ATGAM dose, contact your doctor

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Because of its mode of action and because it is a biologic substance, the maximum tolerated dose of ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) would be expected to vary from one person to another. The incidence of toxicologic manifestations did not increase with any regimens.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects occurred at an incidence greater than 5%: chills, fever, leucopenia, thrombocytopenia, dermatological reactions (pruritis, rash, urticaria, wheal and flare).

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom/Effect	Talk With Your Doctor or Pharmacist
Chills	√
Fever	√
Leukopenia (decrease in white blood cells)	√
Thrombocytopenia (decrease in platelets)	√
Skin reactions (itching, rash, hives, wheal and flare)	√
Arthralgia (joint pain)	√
Chest and/or back pain	√
Clotting of the dialysis access	√
Diarrhea	√
Shortness of breath	√
Headache	√
Decreased blood pressure	√
Nausea and/or vomiting	√
Night sweats	√
Pain at the infusion site	√
Blood clot	√
Swelling of the mouth	√
Abnormal tests of liver function (SGOT, SGPT, alkaline phosphatase)	√
Abnormal tests of kidney function (serum creatinine)	√
Tachycardia (increased heart rate)	√
Bradycardia (decreased heart rate)	√

This is not a complete list of side effects. For any unexpected effects while taking* ATGAM*, contact your doctor or pharmacist.

HOW TO STORE IT

Store ATGAM ampoules in the refrigerator at 2° to 8°C. Do not freeze. Protect the ampoules from light by storing in the carton.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.pfizer.ca or by contacting the sponsor, Pfizer Canada Inc., at: 1-800-463-6001 (Medical Information)

This leaflet was prepared by Pfizer Canada Inc.
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