PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]ATGAM®

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

Solution, 50 mg/mL, Intravenous

IMMUNOSUPPRESSANT

ATC code: L04AA03

Pfizer Canada ULC

17 300 Trans-Canada Highway
Kirkland, Quebec

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RECENT MAJOR LABEL CHANGES

3. SERIOUS WARNINGS AND PRECAUTIONS BOX	01/2025
4. DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	01/2025
4. DOSAGE AND ADMINISTRATION, 4.3 Reconstitution	01/2025
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ATGAM (lymphocyte immunoglobulin, 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. ATGAM is used for treatment of aplastic anemia, renal allograft rejection with conventional therapy for acute rejection episodes, or with other immunosuppressive therapies to delay the onset of a first rejection episode.

1.1 Pediatrics

Pediatrics *(< 18 years)*: Experience in children is limited (See 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics: 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 (see 7.1.4. Geriatrics).

2 CONTRAINDICATIONS

ATGAM is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

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

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Treatment with ATGAM should be discontinued if any of the following occurs (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS):
  - Anaphylaxis: Anaphylaxis has been reported with the use of ATGAM. ATGAM can cause potentially life-threatening anaphylaxis when injected intravenously. Monitor patients for signs and symptoms of anaphylaxis during infusion and for at least 24 hours after infusion.
  - Severe and unremitting thrombocytopenia
  - Severe and unremitting leukopenia

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

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

• A systemic reaction such as generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis precludes an additional administration of ATGAM.

Anaphylaxis/skin Testing: 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.

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 7 WARNINGS AND PRECAUTIONS)**.**

• 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.

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

- Anaphylaxis is uncommon but if this occurs during therapy with ATGAM, infusion of ATGAM should be discontinued immediately; and 0.3 mL aqueous epinephrine (1:1,000 dilution) should be administered intramuscularly along with steroids.

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

- 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. Respiration should be assisted and other resuscitative measures provided. DO NOT resume therapy with ATGAM.

- Pain in the chest, flank or back pain may indicate anaphylaxis or hemolysis. Treatment is the same as for respiratory distress.

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

- 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.
- 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.
- Itching and erythema probably result from the effect of ATGAM on blood elements. Antihistamines generally control the symptoms.
- Serum sickness-like symptoms may occur 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.
- 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.

4.2 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 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.

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 at daily doses of 8 to 15 mg/kg. The duration of therapy averaged 13 days. In heart transplant patients, 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, 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. 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 have received ATGAM in several regimens, generally 10 to 20 mg/kg for 8 to 21 doses. Because thrombocytopenia can be associated with the administration of ATGAM, patients receiving it for the treatment of aplastic anemia may need prophylactic platelet transfusions to maintain platelets at clinically acceptable levels.

Clinical experience in elderly patients has not identified differences in responses between the elderly and younger patients.

Treatment of aplastic anemia - concomitant immunosuppressive therapy and pre-medication

ATGAM is most commonly administered with ciclosporin.

It is recommended to administer pre-medication with corticosteroids and antihistamines prior to infusion of ATGAM in accordance with local treatment guidelines. Anti-pyretics may also increase the tolerability of ATGAM infusion.

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

4.3 Reconstitution

Parenteral Products:

ATGAM concentrate 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.

Add the total daily dose of ATGAM to an inverted bottle or bag of one of the following sterile vehicles below:

- 0.9 % sodium chloride solution,
- Glucose solution/sodium chloride solution:
    - 50 mg/mL (5%) glucose in 0.45% (4.5 mg/mL) sodium chloride solution
    - 50 mg/mL (5%) glucose in 0.225% (2.25 mg/mL) sodium chloride solution

Due to possible precipitation of ATGAM, it is not recommended to dilute with glucose solution alone.

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

The diluted solution should be gently rotated or swirled to effect thorough mixing.

Once diluted, ATGAM has been shown to be physically and chemically stable for up to 24 hours at 25°C, at concentrations of up to 4 mg/mL. 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 at room temperature.

From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately.

4.4 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, the ATGAM concentrate and diluted solution are transparent to slightly opalescent, colourless to light pink or light brown sterile aqueous solutions, which may develop a slight granular or flocculus deposit. 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 4.1 Dosing Considerations).

4.5 Missed Dose

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

5 OVERDOSAGE

Because of its mode of action and because it is a biologic substance, the maximum tolerated dose of ATGAM (lymphocyte immunoglobulin, anti-thymocyte globulin [equine]) would be expected to vary from patient to patient. To date, the largest single daily dose administered to one patient (renal transplant recipient) was 7,000 mg administered at a concentration of approximately 10 mg/mL of saline, seven times the recommended total dose and infusion concentration. In this patient, 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To ensure the traceability of biologic products, health professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Solution 50 mg/mL	Glycine Hydrochloric Acid Sodium Hydroxide Water for Injection

ATGAM (lymphocyte immunoglobulin, 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.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

This product is prepared from large pools of human plasma. Thus, there is a possibility it may contain causative agents of viral or other undetermined diseases.

General

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.

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.

Patients should be carefully monitored during and after therapy with ATGAM for adverse events.

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 live virus vaccines may not replicate successfully and the effectiveness of the vaccines could be reduced when it is administered after immunoglobulin infusion. The prescribing information for the respective vaccine should be consulted to determine the appropriate interval for vaccination in relation to immunosuppressive therapy.

Driving and Operating Machinery

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.

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.

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 4 DOSAGE AND ADMINISTRATION, Dosing Considerations).

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

Infection

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]). Monitor patients closely for concurrent infection. 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.

Monitoring and Laboratory Tests

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

Reproductive Health: Female and Male Potential

Women of childbearing potential should use effective contraception during and for at least 10 weeks after cessation of therapy (see 7.1.1. Pregnant Women).

- **Fertility**

No effects on fertility were observed in cynomolgus monkeys (*Macaca fascicularis)* with ATGAM at exposures similar to those obtained in humans at therapeutic doses.

- **Teratogenic Risk**

ATGAM was not teratogenic in rats or monkeys. Studies in animals have shown reproductive toxicity. These effects are not considered relevant to humans. (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicity)

Thrombocytopenia and neutropenia

Treatment with ATGAM may exacerbate thrombocytopenia and neutropenia. Consider discontinuing

therapy if severe and unremitting thrombocytopenia or leukopenia occurs.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies 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. ATGAM should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

7.1.2 Breast-feeding

It is not known if ATGAM is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk. Therefore, because of the potential for serious adverse reactions in breast-feeding neonates and infants, a decision should be made as to whether to discontinue breast-feeding or to discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

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.

7.1.4 Geriatrics

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 (see 4 **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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequent adverse events reported were chills (14%), fever (33%), leukopenia (14%), thrombocytopenia (11%) and skin reactions such as pruritus, rash, urticaria, wheal and flare (12.5%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The primary clinical experience with ATGAM (lymphocyte immunoglobulin, 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 (Table 2).

Table 2 – Clinical Trial Adverse Reactions ≥ 1 %

System Organ Class	Adverse Event
Blood and lymphatic system disorders	Leukopenia Thrombocytopenia
Gastrointestinal disorders	Diarrhea[a] Nausea[a] Stomatitis[a] Vomiting[a]
General disorders and administration site conditions	Chest pain[a] Chills[b] Infusion site pain[a] Pyrexia[a,b]
Immune system disorders	Serum sickness[b]
Injury, poisoning and procedural complications	Arteriovenous fistula thrombosis
Investigations	Liver function test abnormal[b] Renal function test abnormal[b]
Musculoskeletal and connective tissue disorders	Arthralgia Back pain[a]
Nervous system disorders	Headache
Respiratory, thoracic and mediastinal disorders	Dyspnea[a]
Skin and subcutaneous tissue disorders	Night Sweats[a] Pruritus Rash[b] Urticaria Wheal and flare
Vascular disorders	Hypotension[a] Thrombophlebitis[a,b]
a. Other reactions reported in renal allograft or aplastic anemia patients b. Frequently reported among patients with aplastic anemia	

The incidence of adverse reactions has been higher in patients being treated for aplastic anemia. The high incidence of skin rashes and arthralgia was believed by investigators to represent serum sickness.

8.3 Less Common Clinical Trial Adverse Reactions

Reactions reported rarely have been:

Blood and lymphatic system disorders: Lymphadenopathy
Cardiac disorders: Tachycardia
Eye Disorders: Periorbital edema
Gastrointestinal disorders: Abdominal pain upper
General disorders and administration site conditions: Edema, Malaise
Immune system disorders: Anaphylactic reaction

Infections and infestations: Encephalitis, Infection, Herpes simplex
Injury, poisoning and procedural complications: Wound dehiscence
Metabolism and nutrition disorders: Hyperglycemia
Nervous system disorders: Convulsion, Dizziness, Paresthesia, Syncope
Psychiatric disorders: Agitation
Renal and urinary disorders: Proteinuria, Renal artery thrombosis
Respiratory, thoracic and mediastinal disorders: Hiccups, Laryngospasm, Pleural effusion, Pulmonary edema
Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis
Vascular disorders: Hypertension, Iliac vein occlusion

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

In patients with aplastic anemia and other hematologic abnormalities who have received ATGAM, abnormal test results 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.

8.5 Post-Market Adverse Reactions

Refer below for the list of Post-Market Adverse Reactions.

Blood and lymphatic system disorders: Anemia, Eosinophilia, Granulocytopenia, Hemolysis, Hemolytic anemia, Neutropenia, Pancytopenia
Cardiac disorders: Bradycardia, Cardiac failure congestive
Congenital, familial and genetic disorders: Aplasia
Gastrointestinal disorders: Abdominal pain, Gastrointestinal hemorrhage, Gastrointestinal perforation, Oral pain
General disorders and administration site conditions: Infusion site erythema, Infusion site swelling, Pain
Infections and infestations: Cytomegalovirus infection, Epstein-Barr virus infection, Hepatitis viral, Localized infection, Sepsis, Systemic infection
Injury, poisoning and procedural complications: Kidney rupture
Musculoskeletal and connective tissue disorders: Flank pain, Muscle rigidity, Myalgia, Pain in extremity
Nervous system disorders: Dyskinesia, Tremor
Psychiatric disorders: Confusional state, Disorientation
Renal and urinary disorders: Kidney enlargement, Renal failure acute
Respiratory, thoracic and mediastinal disorders: Apnea, Cough, Epistaxis, Oropharyngeal pain
Skin and subcutaneous tissue disorders: Sweats
Vascular disorders: Deep vein thrombosis, Hypotension, Vasculitis

9 DRUG INTERACTIONS

9.2 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, monitor patients especially

closely during and after therapy with ATGAM.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ATGAM (lymphocyte immunoglobulin, 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.

10.2 Pharmacodynamics

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.

10.3 Pharmacokinetics

In a small clinical study of 27 renal transplant patients, 10 to 15 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).

Special Populations and Conditions

- **Hepatic and Renal Insufficiency**

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

- **Ethnic Origin**

A clinical study examined the pharmacokinetics of ATGAM in 6 adult Japanese patients with moderate or severe aplastic anemia. When administered via intravenous infusion at a dose of 10 mg/kg/day (N=3) or 20 mg/kg/day (N=3) for 8 days, the mean concentration was 1180 ± 240 µg/mL and 2060 ± 340 µg/mL, respectively at 1 hour after completion of infusion on Day 8. The apparent elimination half-life after the last dose varied from 1.3 to 6 days in these patients.

11 STORAGE, STABILITY AND DISPOSAL

Store ATGAM ampoules in the refrigerator at 2° to 8°C, **DO NOT FREEZE.** Keep ampoule in the carton in order to protect from light.

Diluted solution should be kept at room temperature. The solution should be used within 24 hours (including infusion time).

12 SPECIAL HANDLING INSTRUCTIONS

See 4 DOSAGE AND ADMINISTRATION, 4.4 Administration.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: lymphocyte immunoglobulin, anti-thymocyte globulin [equine]

Molecular formula and molecular mass: approximately 150 kD

Product Characteristics:

Lymphocyte immunoglobulin, 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. It is transparent to slightly opalescent, colorless to light pink or light brown sterile aqueous solution, which may develop a slight granular or flocculus deposit. For dilution prior to administration.

The concentrated solution pH is in the range of 6.4 - 7.2 and the osmolality is ≥240 mOsm/kg.

Viral Inactivation

Human blood products (red blood cells and plasma) are used in the manufacture of reagents used in the purification process of ATGAM. Throughout the product stream, standard measures are in place to prevent infections resulting from the use of biological products prepared using human components. In addition to screening of donors and individual donations for specific markers of infection collected using standard antiseptic techniques, effective manufacturing steps are included for inactivation/clearance of viruses.

Viral inactivation/clearance from equine plasma is effectively accomplished for each lot through 3 steps in the ATGAM manufacturing process: chemical treatment precipitates equine plasma proteins and has a high clearance of equine viruses, inactivation and further precipitation of equine viruses is achieved via immunoadsorption, and finally DEAE chromatography and virus filtration is performed to further purify the product. Despite this, encephalomyocarditis virus (EMCV) is the only virus evaluated to date that was not effectively removed by the last step. The possibility of transmitting infective agents cannot be totally excluded, including unknown or emerging viruses and other pathogens.

14 CLINICAL TRIALS

Controlled clinical trials

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.

Non-controlled clinical studies

ATGAM has been administered to other patients in whom reduction of T-lymphocyte 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, safety and efficacy have not been established in circumstances other than renal transplantation and aplastic anemia.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In animal studies, ATGAM was not detected at the limit of quantification in the milk of lactating cynomolgus monkeys (Macaca fascicularis).

Carcinogenicity: There was no evidence of genetic toxicity of ATGAM in a mutagenicity (Ames) assay and *in vitro* chromosome aberration assays.

Non-clinical data reveal no special hazard identified for humans based on conventional studies of repeated dose toxicity and genotoxicity. Carcinogenicity and pre-/post-natal development studies have

not been conducted on ATGAM.

Reproductive and Developmental Toxicology: 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 cynomolgus monkey (Macaca fascicularis) reproduction studies, ATGAM was embryotoxic and fetotoxic. Maternal toxicity was observed with ATGAM 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. The maternal and fetal deaths were attributed to maternal anemia due to red blood cell antigen that humans do not share. Therefore, this toxicity is not considered relevant to human fetal development. ATGAM was not embryotoxic, fetotoxic, or teratogenic in rats, after doses similar to doses used in humans. At a dose of 100 mg/kg in rats during organogenesis, an increase in hypoplastic cervical vertebrae was observed.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ATGAM (lymphocyte immunoglobulin, anti-thymocyte globulin [equine])

Read this carefully before you start taking **ATGAM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ATGAM**.

Serious Warnings and Precautions

- Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should use ATGAM.
- Treatment with ATGAM should be discontinued if any of the following occurs:
    - Serious allergic reactions (anaphylaxis)
    - Severe and unremitting deficiency in blood platelets (thrombocytopenia)
    - Severe and unremitting low white blood cells (leukopenia)
- When you are receiving ATGAM, you will be monitored in a facility equipped and staffed with adequate laboratory and supportive medical resources.

What is ATGAM used for?

ATGAM (lymphocyte immunoglobulin, anti-thymocyte globulin [equine]) is indicated for any patient in whom reduction of T-lymphocyte function (white blood cells) could be desirable.

ATGAM is used at the time of organ transplant rejection (such as renal-allograft) as well as used with other therapies to delay the onset of a first rejection episode. It may also be used for the treatment of aplastic anemia.

How does ATGAM work?

ATGAM is an immunoglobulin (antibody) from horses that were immunized with human thymus lymphocytes. ATGAM works by suppressing the body's immune system (T-lymphocyte function).

What are the ingredients in ATGAM?

Medicinal ingredients: lymphocyte immunoglobulin, anti-thymocyte globulin [equine]

Non-medicinal ingredients: Glycine, Hydrochloric Acid, Sodium Hydroxide, Water for Injection

ATGAM comes in the following dosage forms:

Solution, 50 mg/mL (5 X 5 mL ampoules containing 250 mg protein per ampoule.)

Do not use ATGAM 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.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ATGAM. Talk about any health conditions or problems you may have, including if you:

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

Other warnings you should know about:

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.

This product is manufactured using components of human blood which may contain the causative agent of hepatitis and other viral diseases. 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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ATGAM:

- Vaccination is not recommended in conjunction with ATGAM therapy as the effectiveness of the vaccines could be reduced.
- 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.

How to take ATGAM:

- ATGAM will be given to you by a healthcare professional in a healthcare setting.

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.

Overdose:

Because of its mode of action and because it is a biologic substance, the maximum tolerated dose of ATGAM (lymphocyte immunoglobulin, 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.

If you think you, or a person you are caring for, have taken too much ATGAM, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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

What are possible side effects from using ATGAM?

These are not all the possible side effects you may have when taking ATGAM. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects with ATGAM are: chills, fever, leukopenia, thrombocytopenia, skin reactions (itching, rash, hives, wheal and flare).

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Chills		√	
Fever		√	
Leukopenia (decrease in white blood cells)		√	
Thrombocytopenia (decrease in platelets)		√	
Skin reactions (itching, rash, hives, wheal and flare)		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Arthralgia (joint pain)		√	
Chest and/or back pain		√	
Clotting of the dialysis access		√	
Diarrhea		√	
Allergic reactions (shortness of breath, swelling of the mouth)		√	
Headache		√	
Decreased blood pressure		√	
Nausea and/or vomiting		√	
Night sweats		√	
Pain at the infusion site		√	
Blood clot		√	
Abnormal tests of liver function (SGOT, SGPT, alkaline phosphatase)		√	
Abnormal tests of kidney function (serum creatinine)		√	
Tachycardia (increased heart rate)		√	
Bradycardia (decreased heart rate)		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

Keep out of reach and sight of children.

If you want more information about ATGAM:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.pfizer.ca, or by calling 1-800-463-6001.

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