

# Lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution B.P.

## ATGAM<sup>®</sup> Sterile Solution



### **WARNING: ANAPHYLAXIS**

*See full prescribing information for complete boxed warning.*

Antithymocyte globulins can cause anaphylaxis when injected intravenously. Although ATGAM is processed to reduce the level of antibodies that will react to non-T cells, physicians should be prepared for the potential risk of anaphylaxis and monitor patients for signs and symptoms during infusion. Patients receiving ATGAM should be treated in facilities equipped and staffed with adequate laboratory and supportive medical resources.

### **1. GENERIC NAME**

Lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution B.P.

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 5 mL ampoules containing 50 mg lyphoillized ATG (Equine) per mL.

#### **List of excipients**

Glycine USP (stabilizer and tonicity regulator), 10% w/v Solution Sodium Hydroxide USP (pH adjustment), 10%v/v Solution Hydrochloric Acid USP (pH adjustment), Water for Injection USP

### **3. DOSAGE FORM AND STRENGTH**

Concentrate for solution for infusion.  
Strength: 50 mg / ml (250 mg antibody protein)

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## **Preparation and Administration**

### **Preparation of Solution**

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. However, because ATGAM is a gamma globulin product, it can be transparent to slightly opalescent, colorless to faintly pink or brown, and may develop a slight granular or flaky deposit during storage. Do not shake ATGAM (diluted or undiluted) because excessive foaming and/or denaturation of the protein may occur.

Dilute ATGAM for intravenous infusion in an inverted bottle of sterile vehicle so the undiluted ATGAM does not contact the air inside. Add the total daily dose of ATGAM to the sterile vehicle (see Compatibility and Stability). Do not exceed a concentration of 4 mg of ATGAM per mL. Gently rotate or swirl the diluted solution to effect thorough mixing.

### **Administration**

Allow the diluted ATGAM to reach room temperature before infusion. ATGAM is appropriately administered into a vascular shunt, arterial venous fistula, or a high-flow central vein using an in-line filter with a pore size of 0.2 to 1.0 micron. Use the in-line filter with all infusions of ATGAM to prevent the administration of any insoluble material that may develop in the product during storage. Use high-flow veins to minimize the occurrence of phlebitis and thrombosis. Do not infuse a dose of ATGAM in less than 4 hours. Always keep appropriate resuscitation equipment at the patient's bedside while ATGAM is being administered. Observe the patient continuously for possible allergic reactions throughout the infusions [see Warnings and Precautions (5.1) and Adverse Reactions (6)].

### **Compatibility and Stability**

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, and 5% Dextrose and 0.45% Sodium Chloride Injection.

Do not dilute ATGAM in Dextrose Injection, USP, as low salt concentrations may cause precipitation. Do not use highly acidic infusion solutions since these solutions may contribute to physical instability over time.

Store diluted ATGAM in a refrigerator if it is prepared prior to the time of infusion. Even if it is stored in a refrigerator, do not exceed a total time in dilution of 24 hours (including infusion time).

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

### **Renal Allograft Rejection**

ATGAM Sterile Solution is indicated for the management of allograft rejection in renal transplant patients. 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. Data accumulated to date have not consistently demonstrated improvement in functional graft survival associated with therapy to delay the onset of the first rejection episode.

### **Aplastic Anemia**

ATGAM is indicated for the treatment of moderate to severe aplastic anemia in patients who are unsuitable for bone marrow transplantation.

When administered with a regimen of supportive care, ATGAM may induce partial or complete hematologic remission. In a controlled trial, patients receiving ATGAM showed a statistically significantly higher improvement rate compared with standard supportive care at 3 months. Improvement was defined in terms of sustained increase in peripheral blood counts and reduced transfusion needs.

Clinical trials conducted at two centers evaluated the 1-year survival rate for patients with severe and moderate to severe aplastic anemia. Seventy-four of the 83 patients enrolled were evaluable based on response to treatment. The treatment groups studied consisted of 1) ATGAM and supportive care, 2) ATGAM administered following 3 months of supportive care alone, 3) ATGAM, mismatched marrow infusion, androgens, and supportive care, or 4) ATGAM, androgens, and supportive care. There were no statistically significant differences between the treatment groups. The 1-year survival rate for the pooled treatment groups was 69%. These survival results can be compared with a historical survival rate of about 25% for patients receiving standard supportive care alone.

The usefulness of ATGAM has not been demonstrated in patients with aplastic anemia who are suitable candidates for bone marrow transplantation or in patients with aplastic anemia secondary to neoplastic disease, storage disease, myelofibrosis, Fanconi's syndrome, or in patients known to have been exposed to myelotoxic agents or radiation.

To date, safety and efficacy have not been established in circumstances other than renal transplantation and aplastic anemia.

## **4.2 Posology and method of administration**

### **For Intravenous Use Only**

ATGAM is used with concomitant immunosuppressants. During repeat courses of ATGAM, observe patients for signs of allergic reactions

### **Renal Allograft Recipients**

Adult renal allograft patients have received ATGAM Sterile Solution at the dosage 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.

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.

*Delaying the Onset of Allograft Rejection:* Give a fixed dose of 15 mg/kg daily for 14 days, then every other day for 14 days for a total of 21 doses in 28 days. Administer the first dose within 24 hours before or after the transplant.

*Treatment of Rejection:* The first dose of ATGAM 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.

### **Aplastic Anemia**

The recommended dosage regimen is 10 to 20 mg/kg daily for 8 to 14 days. Additional alternate-day therapy up to a total of 21 doses can be administered. 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.

## **4.3 Contraindications**

Do not administer ATGAM Sterile Solution to a patient who has had a severe systemic reaction (e.g., anaphylactic reaction) during prior administration of ATGAM or any other equine gamma globulin preparation.

## **4.4 Special warnings and precautions for use**

Precise methods of determining the potency of ATGAM have not been established, thus activity may potentially vary from lot to lot. Discontinue treatment with ATGAM if any of the following occurs:

1. Symptoms of anaphylaxis (see section 4.8 **Undesirable effects**).
2. Severe and unremitting thrombocytopenia in renal transplant patients.
3. Severe and unremitting leukopenia in renal transplant patients.

### **Hypersensitivity**

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 has been reported.

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

### **Skin Testing**

To identify those at greatest risk of systemic anaphylaxis, Skin testing potential recipients is strongly recommended before commencing treatment. 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 1:1,000 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 dosed intravenously.

The predictive value of this test has not been proven clinically. Allergic reactions, such as anaphylaxis have occurred in patients whose skin test is negative. Also, skin testing done as described above will not predict for later development of serum sickness. 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.

### **Transmissible Infectious Agents**

Because this product is made using equine and human blood components, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

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

All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Pfizer, Inc. at 1-800-438-1985.

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

### **Immunizations**

Do not administer live vaccines to patients about to receive, receiving, or after treatment with ATGAM. Concomitant administration of ATGAM with live virus vaccines carries a potential of uncontrolled viral replication in the immunosuppressed patient. There is insufficient information to fully define the extent of the risk, or the period of time during which the risk exists. If administered, live viruses may interfere with ATGAM treatment.

### **Hepatic and Renal Function Tests**

In patients with aplastic anemia and other hematologic abnormalities who have received ATGAM, abnormal tests of liver function (SGOT, SGPT, alkaline phosphatase) and renal function (serum creatinine) have been observed.

## **PRECAUTIONS**

### **General**

Because ATGAM Sterile Solution is an immunosuppressive agent ordinarily given with corticosteroids and antimetabolites, monitor patients carefully for signs of leukopenia, thrombocytopenia, or concurrent infection. Several studies have suggested an increase in the incidence of cytomegalovirus infection in patients receiving ATGAM. In one study, it has been found that it may be possible to reduce this risk by decreasing the dosage of other immunosuppressive agents administered concomitantly with ATGAM. If infection occurs, institute appropriate adjunctive therapy promptly. On the basis of the clinical circumstances, a physician should decide whether or not therapy with ATGAM will continue.

The safety and effectiveness of ATGAM have been demonstrated only in renal transplant patients who received concomitant immunosuppressive therapy and in patients with aplastic anemia.

Dilution of ATGAM in dextrose injection 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.

### **4.5 Drugs 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.

### **4.6 Use in special population (such as pregnant women, Lactating women, Geriatric patients, Pediatric Patients)**

#### **Pregnancy**

Pregnancy category C - ATGAM was not teratogenic in rats or monkeys at a dose up to 20 mg/kg (see section 6.1 **Animal Toxicology or Pharmacology**). However, 20 mg/kg/day ATGAM for 16 days during organogenesis in cynomolgus monkeys was fetotoxic. No fetal or maternal toxicity was seen with 10 mg/kg/day ATGAM administered for 16 days during organogenesis. There are no adequate and well-controlled studies in pregnant women. It is also not known whether ATGAM can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ATGAM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Lactation**

In animal studies, a single dose of ATGAM up to 40 mg/kg was not detected at the limit of quantification in the milk of lactating cynomolgus monkeys. 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 neonates and infants from ATGAM, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

**Geriatric Use**

Clinical experience in a limited number of elderly patients ( $\geq 65$  years of age) has not identified differences in responses between the elderly and younger patients. In general, the dose for an elderly patient should be selected with caution, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

**Pediatric Use**

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

**4.7 Effects on ability to drive and use machine**

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.

**4.8 Undesirable effects**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of ATGAM has been evaluated in 367 patients with renal transplant and 109 patients with aplastic anemia.

The renal transplantation and aplastic anemia patients received a similar dosing regimen, and these data were pooled to obtain the frequencies listed in Tables 1 and 2 below.

The most commonly reported adverse reactions (occurring in greater than 10% of patients) are pyrexia, chills, rash, thrombocytopenia, leukopenia and arthralgia

Table 1. Adverse Reactions Occurring in  $\geq 1\%$  of Patients who Received ATGAM

| <b>Adverse Reaction<sup>a,b</sup></b>  | <b>ATGAM<br/>Frequency (%)<br/>(N = 476)</b> |
|--|--|
| Pyrexia  | 39.5   |
| Chills   | 26.5   |
| Rash   | 25.6   |
| Thrombocytopenia   | 21.6   |
| Leukopenia   | 17.9   |
| Arthralgia   | 17.2   |
| Urticaria  | 9.2  |
| Headache   | 5.3  |
| Pruritus   | 4.6  |
| Nausea   | 4.2  |
| Infection  | 3.4  |
| Vomiting   | 3.4  |
| Thrombophlebitis   | 3.2  |
| Hypertension   | 2.9  |
| Hypotension  | 2.9  |
| Diarrhea   | 2.9  |
| Abdominal pain upper   | 2.7  |
| Chest pain   | 2.7  |
| Infusion site pain   | 2.1  |
| Edema  | 2.1  |
| Bradycardia  | 1.5  |
| Back pain  | 1.5  |
| Lymphadenopathy  | 1.3  |
| Arteriovenous fistula thrombosis   | 1.3  |
| Dizziness  | 1.1  |
| Dyspnea  | 1.1  |
| Tachycardia  | 1.1  |
| Liver function test abnormal   | 1.0  |
| <sup>a</sup> Percentages are treatment-emergent all-causality events               |  |
| <sup>b</sup> Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms |  |

**Table 2. Adverse Reactions Occurring in <1% of Patients who Received ATGAM**

| <b>Adverse Reaction<sup>a,b</sup></b> | <b>ATGAM<br/>Frequency (%)<br/>(N = 476)</b> |
|---------------------------------------|--|
| Convulsion                            | 0.8  |
| Pleural effusion                      | 0.8  |
| Night sweats                          | 0.8  |
| Serum sickness                        | 0.6  |
| Hyperglycemia                         | 0.6  |
| Stomatitis                            | 0.6  |



| <b>Adverse Reaction<sup>a,b</sup></b>  | <b>ATGAM<br/>Frequency (%)<br/>(N = 476)</b> |
|--|--|
| Renal function test abnormal   | 0.6  |
| Herpes simplex   | 0.4  |
| Agitation  | 0.4  |
| Hiccups  | 0.4  |
| Proteinuria  | 0.4  |
| Asthenia   | 0.4  |
| Malaise  | 0.4  |
| Wound dehiscence   | 0.4  |
| Anaphylactic reaction  | 0.2  |
| Encephalitis   | 0.2  |
| Paresthesia  | 0.2  |
| Renal artery thrombosis  | 0.2  |
| Iliac vein occlusion   | 0.2  |
| Laryngospasm   | 0.2  |
| Pulmonary edema  | 0.2  |
| Dermatitis allergic  | 0.2  |
| Periorbital edema  | 0.2  |
| Toxic epidermal necrolysis   | 0.2  |
| <sup>a</sup> Percentages are treatment-emergent all-causality events               |  |
| <sup>b</sup> Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms |  |

### **Renal Transplantation**

The primary clinical experience with ATGAM Sterile Solution 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 1 patient in 3; chills in 1 patient in 7; leukopenia in 1 patient in 7; thrombocytopenia in 1 patient in 9; and dermatologic reactions, such as rash, pruritus, urticaria, wheal, and flare, in 1 patient in 8. 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; diarrhea; dyspnea; 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, weakness or faintness, edema, herpes simplex reactivation, hiccups or epigastric pain, hyperglycemia, hypertension, iliac vein obstruction, laryngospasm, localized infection, lymphadenopathy, malaise, myalgia, paresthesia, possible serum sickness, pulmonary edema, renal artery thrombosis, seizures, systemic infection, tachycardia, toxic epidermal necrosis, and wound dehiscence.

### **Aplastic Anemia**

In pre-marketing clinical trials with ATGAM in the treatment of aplastic anemia, patients were also being concurrently managed with support therapy (transfusions, steroids,

antibiotics, antihistamines). In these trials most patients experienced fever and skin reactions. Other frequently reported adverse reactions were chills, 1 patient in 2; arthralgia, 1 patient in 2; headache, 1 patient in 6; myalgia, 1 patient in 10; nausea, 1 patient in 15; chest pain, 1 patient in 15 and phlebitis, 1 patient in 20. The following reactions were reported by at least one patient and less than 5% of the total patients: diaphoresis, joint stiffness, periorbital edema, aches, edema, muscle ache, vomiting, agitation/lethargy, listlessness, light headedness, seizures, diarrhea, bradycardia, myocarditis, cardiac irregularity, hepatosplenomegaly, possible encephalitis or post-viral encephalopathy, hypotension, congestive heart failure, hypertension, burning soles/palms, foot sole pain, lymphadenopathy, post-cervical lymphadenopathy, tender lymph nodes, bilateral pleural effusion, respiratory distress, anaphylactic reaction, and proteinuria.

In some trials, clinical and laboratory findings of serum sickness were seen in a majority of patients.

### **Post-marketing Experience**

The following adverse reactions have been identified during post approval use of ATGAM. Because reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Infections and infestations:* Hepatitis viral, Localized infection, Systemic infection

*Blood and lymphatic system disorders:* Anemia, Eosinophilia, Granulocytopenia, Hemolysis, Hemolytic anemia, Neutropenia, Pancytopenia

*Psychiatric disorders:* Confusional state, Disorientation

*Nervous system disorders:* Dyskinesia, Syncope, Tremor

*Cardiac disorders:* Cardiac failure congestive

*Vascular disorders:* Deep vein thrombosis, Vasculitis

*Respiratory, thoracic and mediastinal disorders:* Apnea, Cough, Epistaxis, Oropharyngeal pain

*Gastrointestinal disorders:* Abdominal pain, Gastrointestinal hemorrhage, Gastrointestinal perforation, Oral pain

*Skin and subcutaneous tissue disorders:* Hyperhidrosis

*Musculoskeletal and connective tissue disorders:* Flank pain, Muscle rigidity, Myalgia, Pain in extremity

*Renal and urinary disorders:* Kidney enlargement, Kidney rupture, Renal failure acute

*Congenital, familial and genetic disorders:* Aplasia

*General disorders and administration site conditions:* Infusion site erythema, Infusion site swelling, Pain

During approximately 5 years of post-approval marketing experience, the frequency of adverse reactions in voluntarily reported cases is as follows: fever 51%; chills 16%; thrombocytopenia 30%; leukopenia 14%; rashes 27%; systemic infection 13%. Events reported in 5% to 10% of reported cases include abnormal renal function tests; serum sickness-like symptoms; dyspnea/apnea; arthralgia; chest, back, or flank pain; diarrhea and nausea and/or vomiting. Events 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, edema, 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, anemia, thrombophlebitis, dizziness, epigastric or stomach pain, lymphadenopathy, pulmonary edema or congestive heart failure, abdominal pain, nosebleed, vasculitis, aplasia or pancytopenia, abnormal involuntary movement or tremor, rigidity, sweating, laryngospasm/edema, hemolysis or hemolytic anemia, viral hepatitis, faintness, enlarged or ruptured kidney, paresthesias, and renal artery thrombosis.

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

**1. Anaphylaxis** is uncommon but serious and may occur at any time during therapy with ATGAM. Stop infusion of ATGAM immediately; administer 0.3 mL aqueous epinephrine (1:1,000 solution) intramuscularly. Administer steroids; assist respiration; and provide other resuscitative measures. **DO NOT** resume therapy with ATGAM.

**2. Hemolysis** can usually be detected only in the laboratory. Clinically significant hemolysis has been reported rarely. Appropriate treatment of hemolysis may include transfusion of erythrocytes; if necessary, administer intravenous mannitol, furosemide, sodium bicarbonate, and fluids. Severe and unremitting hemolysis may require discontinuation of therapy with ATGAM.

**3. Thrombocytopenia** is usually transient in renal transplant patients; platelet counts generally return to adequate levels without discontinuing therapy with ATGAM. Platelet transfusions may be necessary in patients with aplastic anemia (see sections 4.4 **Special warnings and precautions for use**, and 4.2 **Posology and method of administration**).

**4. Respiratory distress** may indicate an anaphylactoid reaction. Discontinue infusion of ATGAM. If distress persists, administer an antihistamine, epinephrine, corticosteroids, or some combination of the three.

**5. Pain in chest, flank, or back** may indicate anaphylaxis or hemolysis. Treatment is that indicated above for those conditions.

**6. Hypotension** may indicate anaphylaxis. Stop infusion of ATGAM and stabilize blood pressure 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, antipyretics, or corticosteroids generally controls this reaction.

**8. Chemical phlebitis** can be caused by infusion of ATGAM through peripheral veins. This can often 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 have been treated with oral or 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.

#### **4.9 Overdose**

The maximum tolerated dose of ATGAM Sterile Solution would be expected to vary from patient to patient due to the biological nature of the product. The largest single daily dose known to be administered to a patient (renal transplant recipient) was 7,000 mg administered at a concentration of approximately 10 mg/mL Sodium Chloride Injection, 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.

A maximum therapeutic dose has not been established therefore the definition of overdose for ATGAM has not been clearly defined. 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; however, close monitoring of the patient is recommended.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Mechanism of Action**

ATGAM is composed of antibodies that bind a wide variety of proteins on the surface of lymphocytes. In addition, ATGAM binds to granulocytes, platelets, bone marrow cells, and other cell types. The mechanism of ATGAM-induced immunosuppression has not been determined. Published data indicate that the primary mechanism is the depletion of circulating lymphocytes, with greatest effect on T lymphocytes. 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 ATGAM therapy for aplastic anemia is attributed to its immunosuppressive actions. In addition, ATGAM directly stimulates the growth of hematopoietic stem cells and release of hematopoietic growth factors such as interleukin-3 and granulocyte/macrophage colony stimulating factor.

## **5.2. Pharmacodynamic Properties**

ATGAM Sterile Solution 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 antilymphocytic 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 antilymphocytic 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 ordinarily 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.

## **5.3 Pharmacokinetic Properties**

Distribution:

During infusion of 10 to 15 mg/kg/day, the mean peak value (n = 27 renal transplant patients) was found to be  $727 \pm 310$   $\mu\text{g/mL}$ .

In a small clinical study, ATGAM administered with other immunosuppressive therapy and measured as horse IgG had a serum half-life of  $5.7 \pm 3$  days. The range for half-life was 1.5 to 13 days

## **6. NONCLINICAL PROPERTIES**

### **6.1. Animal Toxicology or Pharmacology**

## **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Mutagenicity and carcinogenicity studies have not been conducted on ATGAM.

In fertility studies, ATGAM at doses 10, 20 and 40 mg/kg/day was administered to cynomolgus monkeys (*Macaca fascicularis*) for 14 days either before (male monkeys) or before and after (female monkeys) cohabitation with untreated mates. ATGAM treatment was not associated with male or female hormonal or copulation behavior changes. A decrease in fertility index in female monkeys receiving ATGAM was seen. Female toxicity including death, was observed with ATGAM doses of  $\geq 20$  mg/kg/day. While the etiology of this toxicity is uncertain, it may be attributed to hemolytic anemia due to cross-reactivity of ATGAM to a monkey red blood antigen.

In embryo-fetal toxicity studies, ATGAM was administered to rats and cynomolgus monkeys for 11 and 16 days, respectively during organogenesis. In rats, hypoplastic cervical vertebrae, a finding consistent with delayed skeletal development, were observed in fetuses whose dams received ATGAM at doses of 100 mg/kg/day during organogenesis. In monkey reproduction studies, maternal toxicity (vaginal bleeding, decreased body weight and loss of appetite) was observed with ATGAM doses  $\geq 20$  mg/kg/day after 16 days of dosing. Fetal deaths occurred in dams treated with 20 mg/kg/day ATGAM earlier in organogenesis (days 20-35), but not when treatment was given at a later part of organogenesis (days 35-50). 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.

## **7. DESCRIPTION**

Atgam is a transparent to slightly opalescent aqueous protein solution, colorless to faintly pink or brown, and nearly odorless. It may develop a slight granular or flaky deposit during storage, which does not influence the activity

## **8. PHARMACEUTICAL PARTICULARS**

### **8.1 Incompatibilities**

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.

### **8.2 Shelf-life**

24 months

### **8.3. Packaging information**

It is supplied in a set of 5 ampoules. Each ampoule contains 5 mL of ATGAM Sterile Solution, having 50 mg of lyophilized ATG (Equine) per mL.

#### **8.4 Storage and handling instructions**

Store at 2°C to 8°C. Do not freeze. Protect from light.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. However, because ATGAM is a gamma globulin product, it can be transparent to slightly opalescent colorless to faintly pink or brown, and may develop a slight granular or flaky deposit during storage. ATGAM (diluted or undiluted) should not be shaken because excessive foaming and/or denaturation of the protein may occur.

Dilute ATGAM for intravenous infusion in an inverted bottle of sterile vehicle so the undiluted ATGAM does not contact the air inside. Add the total daily dose of ATGAM to the sterile vehicle (see section 8.1 **Incompatibilities**). The concentration should not exceed 4 mg of ATGAM per mL. The diluted solution should be gently rotated or swirled to effect thorough mixing.

The diluted ATGAM should be allowed to reach room temperature before infusion. ATGAM is appropriately administered 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 infusions of ATGAM to prevent the administration of any insoluble material that may develop in the product during storage. The use of high-flow veins will minimize the occurrence of phlebitis and thrombosis. Do not infuse a dose of ATGAM in less than 4 hours. Always keep appropriate resuscitation equipment at the patient's bedside while ATGAM is being administered. Observe the patient continuously for possible allergic reactions throughout the infusions (see section 4.8 **Undesirable effects**).

ATGAM, once diluted, 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, and 5% dextrose and 0.45% sodium chloride injection. It is recommended that diluted ATGAM be stored in a refrigerator if it is prepared prior to the time of infusion. Even if it is stored in a refrigerator, the total time in dilution should not exceed 24 hours (including infusion time).

#### **9. Manufactured by**

Pharmacia & Upjohn Company LLC, 7000 Portage Road,  
Kalamazoo, Michigan; 49001, USA

**Imported and Marketed in India by**

Pfizer Products India Private Limited,  
The Capital- B Wing, 1802, 18<sup>th</sup> Floor, Plot No. C-70, G Block, Bandra Kurla Complex,  
Bandra (East), Mumbai 400 051

**10. Permission or license number with date:**

No. 4-35/95-DC dated 09-Jun-1995 and supplemented by 28-Jun-2012

Subsequent approval for change in specification to B.P. and shelf-life update received on  
21-Dec -2020

**11. Date of revision**

Jan 2021