Atgam®

lymphocyte immune globulin,
anti-thymocyte globulin [equine] sterile solution

For Intravenous Use only

DESCRIPTION

ATGAM Sterile Solution contains lymphocyte immune globulin, anti-thymocyte globulin [equine]. It is the purified, concentrated, and sterile gamma globulin, primarily monomeric IgG, from hyperimmune serum of horses immunized with human thymus lymphocytes. Anti-thymocyte globulin (equine) is a transparent to slightly opalescent aqueous protein solution. It may appear colorless to faintly pink or brown and is nearly odorless. It may develop a slight granular or flaky deposit during storage. (For information about in-line filters, see Infusion Instructions in the POSOLOGY AND METHOD OF ADMINISTRATION.)

Before release for clinical use, each lot of anti-thymocyte globulin (equine) is tested to assure its ability to inhibit rosette formation between human peripheral lymphocytes and sheep red blood cells *in vitro*. In each lot, antibody activity against human red blood cells and platelets is also measured and determined to be within acceptable limits. Only lots that test negative for antihuman serum protein antibody, antiglomerular basement membrane antibody and pyrogens are released.

Each milliliter of anti-thymocyte globulin (equine) contains 50 mg of horse gamma globulin stabilized in 0.3 molar glycine to a pH of approximately 6.8.

PHARMACOLOGICAL PROPERTIES

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.

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 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 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.

Clinical Studies
Renal Transplant Rejection

The use of anti-thymocyte globulin (equine) for acute allograft rejection was evaluated in three different treatment applications:

1. In one randomized controlled trial, anti-thymocyte globulin (equine) treatment was substituted for standard therapy (i.e., bolus doses of intravenous steroids) in living related transplant recipients experiencing their first rejection episode and was proven effective in reversing the rejection episodes in all treated subjects.

2. Results from randomized controlled trials in the United States in patients with steroid resistant rejection episodes showed that anti-thymocyte globulin (equine), when administered in conjunction with standard therapy, yielded efficacy results superior to those of standard therapy alone.

3. The effect of anti-thymocyte globulin (equine) when administered in conjunction with standard therapy at the time of diagnosis of the first rejection episode was studied under two different protocols with living donors and cadaveric transplants. The results from these studies showed a statistically significant improvement in rejection resolution and functional graft survival associated with anti-thymocyte globulin (equine) therapy.

The effectiveness of anti-thymocyte globulin (equine) in acute renal allograft rejection was also demonstrated in other controlled and non-controlled studies performed in various medical centers. In these studies, anti-thymocyte globulin (equine) was administered at time of diagnosis of the first rejection episode at a range of 10 to 15 mg/kg per day for 14 days, followed by alternate day therapy for a total of 21 doses in 28 days.

Aplastic Anemia

Anti-thymocyte globulin (equine) was administered with standard supportive care and/or various other conventional therapies. Anti-thymocyte globulin (equine)-treated patients showed a statistically significantly higher improvement rate compared with standard supportive care at 3 months. Anti-thymocyte globulin (equine) administered at a dose range of 10 to 20 mg/kg/day for 8 to 14 days has been beneficial, with the

majority of clinical studies employing 15-20 mg/kg/day. Additional alternate day therapy for another 14 days may also be given for a total of up to 21 doses.

A variety of published studies reported the use of anti-thymocyte globulin (equine) at doses 15 to 20 mg/kg/day for 4 to 10 days or for 14 days of daily therapy and another 14 days of alternate-day therapy for a total of up to 21 doses.

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) anti-thymocyte globulin (equine) and supportive care, 2) anti thymocyte globulin (equine) administered following 3 months of supportive care alone, 3) anti-thymocyte globulin (equine), mismatched marrow infusion, androgens, and supportive care, or 4) anti-thymocyte globulin (equine), 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.

Pharmacokinetic Properties

Distribution

During infusion of 10-15 mg/kg/day, the mean peak value (n = 27 renal transplant patients) was found to be 727 ± 310 µg/mL.

Metabolism and elimination

The half-life of equine immunoglobulin after anti-thymocyte globulin (equine) infusion was found to be 5.7 ± 3.0 days in one group of recipients. The range for half-life was 1.5 to 13 days.

THERAPEUTIC INDICATIONS

Renal Transplantation

Anti-thymocyte globulin (equine) 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

Anti-thymocyte globulin (equine) 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, anti-thymocyte globulin (equine) may induce partial or complete hematologic remission. In a controlled trial, patients receiving anti-thymocyte globulin (equine) 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.

The usefulness of anti-thymocyte globulin (equine) 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.

CONTRAINDICATIONS

Do not administer anti-thymocyte globulin (equine) sterile solution to a patient who has had a severe systemic reaction (e.g., anaphylactic reaction) during prior administration of anti-thymocyte globulin (equine) or any other equine gamma globulin preparation.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Only physicians experienced in immunosuppressive therapy in the treatment of renal transplant or aplastic anemia patients should use anti-thymocyte globulin (equine).

Patients receiving anti-thymocyte globulin (equine) should be treated in facilities equipped and staffed with adequate laboratory and supportive medical resources.

Precise methods of determining the potency of anti-thymocyte globulin (equine) have not been established, thus activity may potentially vary from lot to lot.

Discontinue treatment with anti-thymocyte globulin (equine) if any of the following occurs,

1. Symptoms of anaphylaxis (see UNDESIRABLE EFFECTS).
2. Severe and unremitting thrombocytopenia in renal transplant patients.
3. Severe and unremitting leukopenia in renal transplant patients.

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.

Immune-mediated reactions

In rare instances, serious immune-mediated reactions have been reported with the use of anti-thymocyte globulin (equine). Clinical signs associated with anaphylaxis, other infusion associated reactions, and serum sickness have been reported (see UNDESIRABLE EFFECTS). Based on the mechanism of action of anti-thymocyte globulin (equine), there is a potential risk of cytokine release syndrome.

A systemic reaction such as a generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis precludes any additional administration of anti-thymocyte globulin (equine).

Skin Testing

To identify those at greatest risk of systemic anaphylaxis, skin testing potential recipients before commencing treatment is strongly recommended (see POSOLOGY AND METHOD OF ADMINISTRATION).

General
Because anti-thymocyte globulin (equine) Sterile Solution is an immunosuppressive agent ordinarily given with corticosteroids and antimetabolites, watch patients carefully for signs of leukopenia, thrombocytopenia, or concurrent infection.

Infection
Monitor patients carefully for concurrent infection. Several studies have suggested an increase in the incidence of cytomegalovirus Infection in patients receiving anti-thymocyte globulin (equine) . 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 anti-thymocyte globulin (equine). If infection occurs, institute appropriate adjunctive therapy promptly. On the basis of the clinical circumstances, a physician should decide whether or not therapy with anti-thymocyte globulin (equine) will continue.

In common with products derived from, or purified with human blood components, the possibility of transmission of some infectious diseases should be borne in mind.

The safety and effectiveness of anti-thymocyte globulin (equine) have been demonstrated only in renal transplant patients who received concomitant immunosuppressive therapy and in patients with aplastic anemia.

Dilution of anti-thymocyte globulin (equine) in dextrose injection, USP, 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.

Renal or hepatic impairment
In other support studies in patients with aplastic anemia and other hematologic abnormalities who have received anti-thymocyte globulin (equine), 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 were seen in a majority of patients.

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

Pediatric population
Experience with children has been limited. Anti-thymocyte globulin (equine) 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.

Elderly population

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 POSOLOGY AND METHOD OF ADMINISTRATION), reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

When the dose of corticosteroids and other immunosuppressants is being reduced, some previously masked reactions to anti-thymocyte globulin (equine) may appear. Under these circumstances, observe patients especially carefully during therapy with anti-thymocyte globulin (equine).

FERTILITY, PREGNANCY AND LACTATION

Fertility

Administration of anti-thymocyte globulin (equine) to cynomolgus monkeys (Macaca fascicularis) at doses comparable to those used in clinical trials was not associated with impairment of male or female fertility (see PRECLINICAL SAFETY DATA).

Pregnancy

Pregnancy category C - Anti-thymocyte globulin (equine) was not teratogenic in rats or monkeys (see PRECLINICAL SAFETY DATA).

There are no adequate and well-controlled studies in pregnant women. Anti-thymocyte globulin (equine) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

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

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.

UNDESIRABLE EFFECTS

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

The adverse drug reactions (ADR) reported with anti-thymocyte globulin (equine) during clinical studies or through post-marketing experience are presented in the table below. Adverse reactions are listed by MedDRA System Organ Class and Preferred Term, and frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse Reactions Table

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Frequency not known (cannot be estimated from available data)
Infections and Infestations		Infection	Herpes simplex			Hepatitis viral,* Systemic infection,* Localised infection*
Blood and Lymphatic System Disorders	Thrombocytopenia, Leucopenia	Lymphadenopathy				Anaemia,* Aplasia,* Granulocytopenia,* Haemolysis,* Haemolytic anaemia,* Neutropenia,* Pancytopenia,* Eosinophilia*
Immune System Disorders			Serum sickness, Anaphylactic reaction			Vasculitis*
Metabolism and Nutrition Disorders			Hyperglycaemia			
Psychiatric Disorders			Agitation			
Nervous System Disorders		Headache, Dizziness	Convulsion, Encephalitis, Paraesthesia			Confusional state,* Disorientation,* Dyskinesia,* Tremor,* Syncope*
Cardiac Disorders		Bradycardia, Tachycardia				Cardiac failure congestive*
Vascular Disorders		Thrombophlebitis, Hypertension, Hypotension	Renal artery thrombosis, Iliac vein occlusion			Deep vein thrombosis,* Gastrointestinal haemorrhage*
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea	Pleural effusion, Laryngospasm, Pulmonary oedema			Apnoea,* Cough,* Epistaxis*

Adverse Reactions Table

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Frequency not known (cannot be estimated from available data)
Gastrointestinal Disorders		Nausea,[§] Vomiting,[§] Diarrhoea, Abdominal pain upper	Stomatitis, Hiccups[§]			Abdominal pain,[*] Gastrointestinal perforation,[*] Oral pain,[*] Oropharyngeal pain[*]
Skin and Subcutaneous Tissue Disorders	Rash	Urticaria,[§] Pruritus	Night sweats, Dermatitis allergic, Periorbital oedema, Toxic epidermal necrolysis			
Musculoskeletal, Connective Tissue and Bone Disorders	Arthralgia	Back pain[§]				Flank pain,[*] Muscle rigidity,[*] Myalgia,[*] Pain in extremity[*]
Renal and Urinary Disorders			Proteinuria			Kidney enlargement,[*] Renal failure acute,[*] Ruptured kidney[*]
General Disorders and Administration Site Conditions	Pyrexia, Chills	Chest pain,[§] Infusion site pain, Oedema	Asthenia, Malaise			Infusion site erythema,[*] Infusion site swelling,[*] Hyperhidrosis,[*] Pain[*]
Investigations			Renal function test abnormal, Liver function test abnormal			
Injury, Poisoning and Procedural Complications		Arteriovenous fistula thrombosis	Wound dehiscence			

*Frequency not known (cannot be estimated from the available data).
[§]For those ADR terms when accounted in the source dataset as a single reaction with a related ADR term (e.g., nausea/vomiting), the total number of occurrences was assumed to be the same for each individual ADR term.

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 anti-thymocyte globulin (equine). 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 anti-thymocyte globulin (equine).

2. **Haemolysis** can usually be detected only in the laboratory. Clinically significant haemolysis has been reported rarely. Appropriate treatment of haemolysis may

include transfusion of erythrocytes; if necessary, administer intravenous mannitol, furosemide, sodium bicarbonate, and fluids. Severe and unremitting haemolysis may require discontinuation of therapy with anti-thymocyte globulin (equine).

3. **Thrombocytopenia** is usually transient in renal transplant patients; platelet counts generally return to adequate levels without discontinuing therapy with anti-thymocyte globulin (equine). Platelet transfusions may be necessary in patients with aplastic anemia (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and POSOLOGY AND METHOD OF ADMINISTRATION).

4. **Respiratory distress** may indicate an anaphylactoid reaction. Discontinue infusion of anti-thymocyte globulin (equine). 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 haemolysis. Treatment is that indicated above for those conditions.

6. **Hypotension** may indicate anaphylaxis. Stop infusion of anti-thymocyte globulin (equine) and stabilize blood pressure with pressors if necessary.

7. **Chills and fever** occur frequently in patients receiving anti-thymocyte globulin (equine). Anti-thymocyte globulin (equine) 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 anti-thymocyte globulin (equine) 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 anti-thymocyte globulin (equine) 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.

OVERDOSE

Because of its mode of action and because it is a biologic substance, the maximal tolerated dose of anti-thymocyte globulin (equine) Sterile Solution would be expected to vary from patient to patient. To date, the largest single daily dose administered to a patient, a renal transplant recipient, was 7,000 mg administered at a concentration of approximately 10 mg/mL Sodium Chloride Injection, USP, approximately seven times the recommended total dose and infusion concentration. In this patient, administration of anti-thymocyte globulin (equine) 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 anti-thymocyte globulin (equine) 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 three 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.

POSOLOGY AND METHOD OF ADMINISTRATION

Adult patients

Renal Allograft Recipients

Adult renal allograft patients have received anti-thymocyte globulin (equine) 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. Anti-thymocyte globulin (equine) 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 anti-thymocyte globulin (equine) for the treatment of acute rejection had not received it starting at the time of transplantation.

Usually, anti-thymocyte globulin (equine) is used concomitantly with azathioprine and corticosteroids, which are commonly used to suppress the immune response. Exercise caution during repeat courses of anti-thymocyte globulin (equine); 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 anti-thymocyte globulin (equine) 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 anti-thymocyte globulin (equine), patients receiving it for the treatment of aplastic anemia may need prophylactic platelet transfusions to maintain platelets at clinically acceptable levels.

Elderly population (≥65 years of age)

In general, the dose for an elderly patient should be selected with caution, usually starting at the low end of the dosage range (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Skin Testing

Before the first infusion of ATGAM, it is strongly recommended that patients be tested with an intradermal injection of 0.1 mL of a 1:1,000 dilution (5 µg horse IgG) of anti-thymocyte globulin (equine) in sodium chloride injection, USP and a contralateral sodium chloride injection control. Use only freshly diluted anti-thymocyte globulin (equine) for skin testing. The patient, and specifically the skin test, should be

observed every 15 to 20 minutes over the first hour after intradermal injection. A local reaction of 10 mm or greater with a wheal or erythema, or both, with or without pseudopod formation and itching or a marked local swelling should be considered a positive test.

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. In the presence of a locally positive skin test to anti-thymocyte globulin (equine), serious consideration to alternative forms of therapy should be given. The risk to benefit ratio must be carefully weighed. If therapy with anti-thymocyte globulin (equine) 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 with a physician familiar with the treatment of potentially life threatening allergic reactions is in attendance.

A systemic reaction such as a generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis precludes any additional administration of anti-thymocyte globulin (equine) see SPECIAL WARNINGS AND PRECAUTIONS FOR USE and UNDESIRABLE EFFECTS.

Preparation of Solution
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. However, because anti-thymocyte globulin (equine) 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. Anti-thymocyte globulin (equine) (diluted or undiluted) should not be shaken because excessive foaming and/or denaturation of the protein may occur.

Dilute anti-thymocyte globulin (equine) for intravenous infusion in an inverted bottle of sterile vehicle so that the undiluted anti-thymocyte globulin (equine) does not contact the air inside. Add the total daily dose of anti-thymocyte globulin (equine) to the sterile vehicle (see Incompatibilities and Shelf Life). The concentration should not exceed 4 mg of anti-thymocyte globulin (equine) per ml. The diluted solution should be gently rotated or swirled to effect thorough mixing.

Administration
The diluted anti-thymocyte globulin (equine) should be allowed to reach room temperature before infusion. Anti-thymocyte globulin (equine) 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 anti-thymocyte globulin (equine) 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 anti-thymocyte globulin (equine) in less than 4 hours. Always keep appropriate resuscitation equipment at the patient's bedside while anti-thymocyte globulin (equine) is being administered. Observe the patient continuously for possible allergic reactions throughout the infusions (see UNDESIRABLE EFFECTS).

It is recommended that diluted anti-thymocyte globulin (equine) be stored in a refrigerator, if it is prepared prior to the time of infusion. Even if stored in a refrigerator, the total time in dilution should not exceed 24 hours (including infusion time).

Any unused product or waste material should be disposed of in accordance with local requirements.

Incompatibilities and Shelf Life
Anti-thymocyte globulin (equine), 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.

Adding anti-thymocyte globulin (equine) 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. It is recommended that diluted anti-thymocyte globulin (equine) 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).

QUALITATIVE AND QUANTITATIVE COMPOSITION
Anti-thymocyte globulin (equine) Sterile Solution, containing 50 mg of horse gamma globulin/ml, is supplied as follows: 5 – 5 ml ampoules NDC 0009-7224-02

SPECIAL PRECAUTIONS FOR STORAGE
Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). **DO NOT FREEZE.**

For storage conditions of diluted solution, see Incompatibilities and Shelf Life.

Rx only

PRECLINICAL SAFETY DATA
Mutagenicity and carcinogenicity studies have not been conducted on anti-thymocyte globulin (equine).

Fertility

In monkey reproduction studies, maternal toxicity was observed with anti-thymocyte globulin (equine) doses of ⩾20 mg/kg/day. While the etiology of this toxicity is uncertain, it may be attributed to hemolytic anemia due to cross-reactivity of a Anti-thymocyte globulin (equine) to a monkey red blood antigen.

Pregnancy

Anti-thymocyte globulin (equine) was not teratogenic in rats or monkeys. An increase in hypoplastic cervical vertebrae was observed in rat fetuses at doses of 100 mg/kg/day administered anti-thymocyte globulin (equine) during organogenesis.

In monkey reproduction studies, maternal toxicity was observed with Anti-thymocyte globulin (equine) doses of 20 mg/kg/day after 14 days of dosing with maternal deaths occurring at doses 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 latter 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.

PRODUCT OWNER

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