SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

Atgam 50 mg/ml **concentrate** for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of **concentrate** for solution for infusion contains 50 mg of immunoglobulin against T lymphocytes for use in human medicine, of animal origin (equine).

5 ml of **concentrate** for solution for infusion (1 ampoule) contain 250 mg of immunoglobulin against T lymphocytes for use in human medicine, of animal origin (equine).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

Transparent to slightly opalescent, colourless to light pink or light brown sterile aqueous solution intended for dilution prior to administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Immunosuppression. Atgam is indicated for the concomitant use in immunosuppression of patients who have undergone renal transplant, for the postponement of first rejection reaction and/or at the time of rejection, to increase frequency of resolution of acute rejection episode.

Atgam as an addition to regimen of standard supportive care has induced instances of partial or complete hematologic recovery and improved survival in patients with aplastic anaemia of known or suspected immunologic etiology. Reports from non-controlled clinical studies have shown benefit from concomitant immunosuppression with Atgam in cases of T-cell malignancies, graft-versus-host disease, or patients who have received skin, cardiac, liver or bone-marrow transplants.

4.2 Posology and method of administration

Posology
The diluted solution should be allowed to reach room temperature before infusion.

Renal allograft recipients
In combination with azathioprine and corticosteroids it is recommended that Atgam is administered at 10 to 15 mg/kg per day for 14 days, followed by alternate day therapy for a total of 21 doses in 28 days.

When given to delay the onset of the first rejection episode, initiate therapy within 24 hours before or after transplant. When given to treat rejection, initiate therapy at time of diagnosis of the first rejection episode.

Aplastic anaemia patients
In conjunction with standard supportive therapy administration of Atgam at 15 to 20 mg/kg per day for 8 to 14 days has been beneficial. Additional alternate therapy for another 14 days may also be given for a total of up to 21 doses.

Paediatric population
No data are available.
The safety and efficacy of Atgam in children aged less than 18 years have not yet been established.

Method of administration
Atgam is intended for intravenous use.

To minimize the incidence of phlebitis and thrombosis, infusion should be administered into a high flow central vein or vascular anastomosis or arterial venous anastomosis through an in line-filter (0.2-1.0 micron). All the doses should be given under constant medical surveillance. A dose of Atgam should not be infused in less than 4 hours. Diluted solution should be refrigerated until use and used within 24 hours (including infusion time).

For information on dilution, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients.

Hypersensitivity to any other equine gamma globulin preparation.

4.4 Special warnings and special precautions for use

Only physicians experienced in immunosuppressive therapy should use Atgam. Facilities equipped and staffed with adequate laboratory and supportive medical resources should be used.

Treatment with Atgam should be discontinued if anaphylaxis or severe and unremitting thrombocytopenia or leukopenia occur.

The manufacture of Atgam employs tissue of human and animal origin. When such medicinal products are administered, the possibility of transmission of certain infectious diseases due to transmission of infective agents cannot be totally excluded. The risk of transmission is, however, reduced by selection and testing of tissue and by virus inactivation/removal procedures included in the production process.

Monitor patients carefully for concurrent infection. Some studies have suggested an increase in the incidence of cytomegalovirus infection in patients receiving Atgam. Some physicians have found it may be possible to reduce this risk by decreasing the dosage of other immunosuppressive agents which might be administered concomitantly with Atgam.

To identify those at greatest risk of systemic anaphylaxis, especially if the patient is atopic, skin testing of potential recipients before commencing treatment is **strongly** recommended. A conservative, conventional approach would first employ epicutaneous testing with undiluted Atgam. If the subject does not show a pomphus ten minutes after pricking, proceed to intradermal testing with 0.02 ml of a saline dilution (1:1000 v/v) of Atgam with a separate saline control injection of similar volume. Read the result at 10 minutes. A pomphus 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 in case the drug is given intravenously.

The predictive value of this test has not been proven clinically. Allergic reactions can also occur 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 assessed. If therapy with Atgam is deemed appropriate following a locally positive skin test, treatment should be administered in a setting where intensive life support facilities are immediately available and a physician familiar with the treatment of potentially life threatening allergic reactions is in attendance.

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

Although anaphylaxis is rare, remedial facilities such as adrenalin should always be available during infusion and vaccination.

Paediatric population
Experience with use in children is limited.

4.5 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 Atgam may appear. Under these circumstances, patients should be especially carefully observed during treatment with Atgam.

4.6 Fertility, pregnancy and lactation

The use of Atgam has not been evaluated in pregnant or lactating women. Animal reproduction studies have not been conducted with Atgam. It is not known whether Atgam can cause fetal harm when administered to a pregnant woman or can affect reproduction capability. Administration of Atgam to pregnant women is not recommended and should be considered only under exceptional circumstances.

It is not known whether Atgam is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, caution should be exercised when Atgam is administered to nursing women.

4.7 Effects on ability to drive and use machines

It is not known whether Atgam influences the ability to drive and use machines.

4.8 Undesirable effects

Renal transplantation: The primary clinical experience with Atgam has been in renal allograft patients who were also receiving azathioprine and corticosteroids. In these patients, most frequently reported undesirable effects are the following: fever, chills, leucopenia, thrombocytopenia, arthralgia and dermatological reactions such as rash, urticaria, pomphus and erythema and pruritus.

Aplastic anemia: The incidence of adverse reactions has been higher in patients being treated for aplastic anaemia. Frequently reported adverse reactions among patients enrolled in aplastic anaemia studies were fever, chills, skin rash, arthralgia and thrombocytopenia. The high incidence of skin rash and arthralgia was believed by investigators to represent serum sickness. In patients with aplastic anaemia 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. In some trials, clinical and laboratory findings of serum sickness have been observed in a majority of patients.

Incidence of undesirable effects observed in use of Atgam is not known, since it cannot be estimated from the available data.

Organ class	**Undesirable effects**
Infections and infestations	

Not known	infection, encephalitis, reactivation of Herpes Simplex virus
Blood and lymphatic system disorders	
Not known	leucopoenia, thrombocytopenia, lymphadenopathy
Immune system disorders	
Not known	serum sickness, anaphylaxis
Psychiatric disorders	
Not known	agitation
Nervous system disorders	
Not known	headache, dizziness, paresthesia, convulsions
Cardiac disorders	
Not known	chest pain, tachycardia
Vascular disorders	
Not known	hypotension, peripheral thrombophlebitis, clotted arteriovenous fistula, hypertension, oedema, iliac vein obstruction, renal artery thrombosis
Respiratory, thoracic and mediastinal disorders	
Not known	dyspnoea, pulmonary oedema, pleural effusions
Gastrointestinal disorders	
Not known	nausea, vomiting, diarrhoea, stomatitis, epigastric pain or hiccoughs, laryngospasm
Skin and subcutaneous disorders	
Not known	rash, urticaria, pomphus, pruritus, night sweats, periorbital oedema, wound dehiscence, toxic epidermal necrosis
Musculoskeletal and connective tissue disorders	
Not known	arthralgia, back pain
General disorders and administration site conditions	
Not known	fewer, chills, pain at the site of infusion, weakness or faintness, malaise
Investigations	
Not known	abnormal liver function tests (SGOT, SGPT, alkaline phosphatase) and abnormal kidney function tests (serum creatinine), hyperglycaemia, proteinuria

4.9 Overdose

Because of its mode of action and because it is a biologic substance, the maximum tolerated dose of Atgam would be expected to vary from patient to patient. To date, the largest single daily dose administered to a patient, was 7.000 mg administered at a concentration of approximately 10 mg/ml in saline solution, approximately 7-times the recommended total daily dose and infusion concentration. In this patient, the administration of Atgam was not associated with any signs of acute intoxication.

The greatest number of doses (10 to 20 mg/kg/dose) that can be administered to a single patient has not yet been determined. Some renal transplant patients 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.

No known antidote. Treatment should be symptomatic.

Shock (anaphylaxis and allergy)
Inject 1 ml (0.5 ml in children) of adrenaline 1:1.000 intramuscularly; and repeat injection of the same dose every 30 minutes until blood pressure has returned to normal. At the same time, inject 50-100 mg prednisolone intravenously and antihistamines intramuscularly. In case of extremely severe collapse, 0.2–0.5 ml of adrenaline 1:10.000 can be slowly injected intravenously. Oral treatment with antihistamines should be continued for 10 days in order to prevent the possible appearance of delayed allergic complications.

Serum sickness
Antihistamines should be administered orally. Intensive pruritis can be alleviated immediately, but only temporarily, and can be alleviated by a subcutanous injection of 1.0 ml adrenaline 1:1.000.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodymanic properties

Pharmacotherapeutical group: immunosuppressants (immunosuppressive agents); selective immunosuppressants (immunosuppressive agents)
ATC code: L04AA03

The immunosuppressive action of Atgam is apparently due to its interactions with T lymphocytes. Binding of the equine immunoglobulin to surface molecules of human T lymphocytes allows the IgG to interfere with the action of these cells. A major consequence is clearance of the cells, manifested by loss of CD3+ and CD2+ lymphocytes from the circulating blood. The mechanism for this clearance probably includes both cytotoxicity of the antibody mediated by complement and clearing in the reticuloendothelial system due to macrophage extraction of the opsonized T lymphocytes. The T cells are apparently killed by Atgam. Renewal of these cells then requires repopulation from the bone marrow and thymic processing.

5.2 Pharmacokinetic properties

Distribution
During infusion of 10 mg/kg/day, the peak plasma level of equine immunoglobulin was seen after 5 days of treatment. The mean peak value (n = 27 patients) was found to be 727 ± 310 µg/ml.

Metabolism and elimination
The half-life of equine immunoglobulin after Atgam infusion was found to be 5.7± 3.0 days in one group of recipients. The range for half-life was 1.5 to 12 days.

5.3 Preclinical safety data

Few data are available from animal studies that assist in evaluating the toxicity of Atgam. Such data as do exist do not indicate a particular hazard.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- glycine
- water for injection

Medicine may contain sodium hydroxide (E524) and hydrochloric acid (E507) for pH adjustment.

6.2 Incompatibilities

Dextrose injection (precipitation).
Highly acidic infusions (physical instability over time).

6.3 Shelf-life

3 years
reconstituted solution: 24 hours

Once diluted, Atgam has been shown to be physically and chemically stable for up to 24 hours at concentrations of up to 4 mg/ml in sodium chloride (9 mg/ml) injection.

6.4 Special precautions for storage

Store the product in a refrigerator (2°C - 8°C). Do not freeze.

For storage conditions of reconstituted solution, see section 6.3.

6.5 Nature and contents of container

Carton with five 5 ml ampoules made out of colourless class I glass, containing 250 mg (50 mg/ml) of immunoglobulin against T lymphocytes for use in human medicine, of animal origin (equine).

6.6 Special precautions for disposal and other handling

The total daily dose of Atgam should be added to an inverted bottle of one of the following sterile solutions:

- 9 mg/ml sodium chloride,
- 50 mg/ml dextrose and 4.5 mg/ml sodium chloride or
- 50 mg/ml dextrose and 2.25 mg/ml sodium chloride

Dose should not exceed 4 mg of Atgam per ml.
The diluted solution should be gently rotated or swirled to effect thorough mixing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Atgam can be transparent to slightly opalescent, colourless to light pink or light brown and may develop a slight granular or flocculus deposit during storage.

Atgam (diluted or undiluted) should not be shaken as this could cause excessive foaming and/or the denaturalization of the protein. Atgam should be diluted prior to infusion by inverting the container of the sterile vehicle, in such a manner that the diluted Atgam does not come in contact with the air inside. Add the total daily dose of Atgam to the sterile vehicle with concentration not to exceed 4 mg of Atgam Sterile Solution per ml. The diluted solution should be gently rotated or shaked to effect thorough mixing.

The diluted Atgam should be allowed to reach room temperature prior to its infusion. Atgam should be administered into a high flow central vein or vascular anastomosis or arterial venous anastomosis

through an in line-filter (0.2-1.0 micron).The in-line filter must 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 incidence of phlebitis and thrombosis. A dose of Atgam should not be infused in less than 4 hours. Keep the patient under continuous observation throughout the infusion for possible allergic reactions (see section 4.8).

It is recommended that diluted Atgam 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).

7. MARKETING AUTHORISATION HOLDER

Pfizer Luxembourg SARL, 51, Avenue J. F. Kennedy, L-1855 Luxembourg

8. MARKETING AUHTORISATION NUMBER

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