Summary of Product Characteristics

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Atgam 50 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains horse anti-human T lymphocyte immunoglobulin (eATG) 50 mg.

Each 5 ml ampoule contains 250 mg of eATG.

Purified, concentrated, sterile gamma globulin, primarily monomeric IgG, from hyperimmune serum of horses immunised with human thymus lymphocytes.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Transparent to slightly opalescent, colourless to light pink or light brown sterile aqueous solution which may develop a slight granular or flocculus deposit. For dilution prior to administration.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Atgam is indicated for use in adults and in children aged 2 years and older for the treatment of acquired moderate to severe aplastic anaemia of known or suspected immunologic aetiology as part of standard immunosuppressive therapy in patients who are unsuitable for haematopoietic stem cell transplantation (HSCT) or for whom a suitable HSC donor is not available.

4.2 Posology and method of administration

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

Posology

Adult patients and children aged 2 years and older
Dosage recommendations are based on body weight (bw).

The recommended total dose is 160 mg/kg bw, administered as part of standard immunosuppressive therapy, as follows (see sections 4.4, 4.8 and 5.1):

- 16 mg/kg bw/day over 10 days or
- 20 mg/kg bw/day over 8 days or
- 40 mg/kg bw/day over 4 days

Monitoring and management of adverse events
Patients should be carefully monitored during and after treatment for adverse events. Recommendations for monitoring and management of adverse events are included in Table 1. Treatment of the adverse events should be instituted in accordance with local guidelines.

Table 1. Recommendations for Monitoring and Management of Adverse Events

Adverse Event	**Recommendations for Monitoring and Management**
Anaphylaxis, including respiratory distress	To identify those at greatest risk of systemic anaphylaxis, skin testing of potential recipients before commencing treatment is strongly recommended, especially if the patient is atopic. Patients should be carefully monitored for anaphylaxis, including respiratory distress, and treatment should be discontinued if anaphylaxis occurs (see section 4.4).
Cytokine Release Syndrome (CRS)	If CRS occurs, discontinuation of treatment should be considered (see section 4.4).
Thrombocytopenia and neutropenia	If there is evidence of severe and unremitting thrombocytopenia or neutropenia, discontinuation of treatment should be considered (see section 4.4).

Special populations

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

Paediatric population
Currently available data in children less than 18 years of age are described in sections 4.8 and 5.1.

Elderly (> 65 years)
Clinical experience in elderly patients has not identified differences in responses between the elderly and younger patients. Therefore, no dose adjustment is recommended for elderly patients.

Method of administration

Atgam is intended for intravenous use and should be administered preferably, via a high flow central vein.

Pre-medication
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 (see section 4.4).

Administration
Atgam should be diluted prior to infusion and administered using appropriate aseptic technique (see sections 6.3 and 6.6).

Diluted Atgam should be at room temperature (20°C - 25°C) prior to infusion. Atgam should be administered into a high flow central vein through an in-line filter (0.2-1.0 micron). An in-line filter (not supplied) must be used with all infusions of Atgam to prevent the administration of any insoluble material that may develop during storage. The use of high flow veins will minimize the incidence of phlebitis and thrombosis.

The recommended infusion duration for the 40 mg/kg dose regimen is 12 to 18 hours. Atgam should not be infused in less than 4 hours. Increasing the infusion duration may minimize adverse reactions. The patient should be kept under continuous observation during and after the infusion for possible allergic reactions (see sections 4.4 and 4.8). Following administration, it is recommended to flush the intravenous line.

The infusion volume of the diluted solution should take into consideration factors such as patient's haemodynamic status, age and weight.

Concomitant immunosuppressive therapy
Atgam is most commonly administered with ciclosporin A.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to any other horse gamma globulin preparation.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Special considerations for Atgam infusion

Atgam should be administered into a high flow central vein through an in-line filter (not supplied). Atgam should not be infused in less than 4 hours. Increasing the infusion duration may minimize adverse reactions. The patient should be kept under continuous observation during and after the infusion for possible allergic reactions (see section 4.8).

Infection

Due to the nature of the disease and the immunosuppressive effects of Atgam, opportunistic infections (bacterial and fungal) are very common. Sepsis has also been reported. The risk of infections is increased when Atgam is combined with other immunosuppressants. There is an increased risk of viral reactivation (e.g., cytomegalovirus [CMV], Epstein–Barr virus [EBV], herpes simplex virus [HSV]). Patients should be carefully monitored for evidence of infection and treatment should be instituted in accordance with local guidelines.

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, serum sickness and associated symptoms such as rash, arthralgia, pyrexia, chills, and pain have been reported (see section 4.8).

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

It is recommended to administer corticosteroids and antihistamines prior to infusion of Atgam (see sections 4.2 and 4.5). Antipyretics may also be administered to increase the tolerability of Atgam infusion.

Cytokine release syndrome

There is a potential risk of cytokine release syndrome, which can be fatal (see section 4.2).

Anaphylaxis/skin testing

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 wheal 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 wheal at the Atgam site of 3 millimetres or 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.

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 is not predictive of future 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 benefit-risk

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 (see section 4.2).

Thrombocytopenia and neutropenia

Treatment with Atgam may exacerbate thrombocytopenia and neutropenia (see section 4.2).

Renal and liver function tests

In patients with aplastic anaemia and other haematologic abnormalities who have received Atgam abnormal test results of liver function and renal function have been observed.

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 the effectiveness of the vaccines could be reduced. The prescribing information for the respective vaccine should be consulted to determine the appropriate interval for vaccination in relation to immunosuppressive therapy.

Excipients

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per total dose, that is to say is essentially 'sodium-free'.

Atgam may be further prepared for administration with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total daily intake from all sources that will be administered to the patient.

Transmissible Agents

Atgam is made from horse plasma and also employs human blood-derived reagents in the process.

Effective manufacturing steps for the inactivation/removal of viruses are employed in the Atgam process and these steps have been validated to clear a wide range of both human blood-borne and horse viruses, using a virus panel approach. This covers the complete virus spectrum from small, non-enveloped viruses such as parvoviruses and Hepatitis A to large enveloped viruses like Herpes Simplex Virus. Despite this, when medicinal products prepared from horse and human blood are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

When tapering corticosteroids and other immunosuppressants, some previously masked reactions to Atgam may appear. Under these circumstances, patients should be observed carefully during and after treatment with Atgam.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of horse anti-human T lymphocyte immunoglobulin in pregnant women. The outcome of pregnancies cannot be determined. Studies in animals have shown reproductive toxicity (see section 5.3). These effects are not considered relevant to humans.

As a precautionary measure, it is preferable to avoid the use of Atgam during pregnancy.
Women of childbearing potential should use effective contraception during and up to 10 weeks after cessation of therapy.

Breast-feeding

It is unknown whether horse anti-human T lymphocyte immunoglobulin is excreted in human milk. Available toxicological data in animals have not shown excretion of horse anti-human T lymphocyte immunoglobulin in milk (see section 5.3). As a risk to the breast-fed child cannot be excluded, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Atgam therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Administration of horse anti-human T lymphocyte immunoglobulin to cynomolgus monkeys (*Macaca fascicularis*) at doses comparable to those used in clinical studies was not associated with impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect or ability to drive or use machines have been performed. Horse anti-human T lymphocyte immunoglobulin has a moderate influence on the ability to drive and use machines. 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.

4.8 Undesirable effects

The most commonly reported adverse reactions from clinical studies (occurring in greater than 10% of patients) are infections, neutropenia, serum sickness, headache, hypertension, diarrhoea, rash, arthralgia, pyrexia, chills, pain, oedema and abnormal liver function test (see section 4.4). Adverse reactions listed as frequency unknown are from post-marketing experience.

For safety information with respect to transmissible agents, see section 4.4.

Tabulated list of adverse reactions

In the following table, adverse reactions are listed by MedDRA system organ class and preferred term.

Note: 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), very rare (< 1/10,000), and not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2. Adverse Reactions

System Organ Class	Very Common	Common	Uncommon	Frequency Not Known
Infections and infestations	Infection, Localized Infection	Sepsis, Herpes simplex		Hepatitis viral, Epstein–Barr Virus Cytomegalovirus infection
Blood and lymphatic system disorders	Neutropenia	Haemolysis, Leukopenia, Lymphadenopathy	Thrombocytopenia	Pancytopenia, Granulocytopenia, Haemolytic anaemia, Anaemia, Eosinophilia
Immune system disorders	Serum sickness		Anaphylactic reaction	
Metabolism and nutrition disorders		Hyperglycaemia		
Psychiatric disorders			Agitation	Confusional state, Disorientation
Nervous system disorders	Headache	Convulsion, Syncope, Paraesthesia, Dizziness		Encephalitis, Dyskinesia, Tremor
Eye disorders			Periorbital oedema	

Cardiac disorders		Bradycardia, Tachycardia		Cardiac failure congestive
Vascular disorders	Hypertension	Hypotension, Thrombophlebitis		Vasculitis, Iliac vein occlusion, Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders		Pleural effusion, Dyspnoea, Epistaxis, Cough		Laryngospasm, Pulmonary oedema, Apnoea, Oropharyngeal pain, Hiccups
Gastrointestinal disorders	Diarrhoea	Gastrointestinal haemorrhage, Abdominal pain, Abdominal pain upper, Vomiting, Stomatitis, Nausea		Gastrointestinal perforation, Oral pain
Skin and subcutaneous tissue disorders	Rash	Pruritus, Urticaria	Dermatitis allergic	Toxic epidermal necrolysis, Night sweats, Hyperhidrosis
Musculoskeletal and connective tissue disorders	Arthralgia	Myalgia, Back pain		Muscle rigidity, Flank pain, Pain in extremity
Renal and urinary disorders		Proteinuria		Renal failure acute, Renal artery thrombosis, Kidney enlargement
Congenital, familial and genetic disorders				Aplasia
General disorders and administration site conditions	Oedema, Pyrexia, Pain, Chills	Chest pain, Malaise	Infusion site erythema	Infusion site swelling, Infusion site pain, Asthenia
Investigations	Liver function test abnormal	Renal function test abnormal		
Injury, poisoning and procedural complications				Kidney rupture, Arteriovenous fistula thrombosis, Wound dehiscence

Paediatric population

Data from published studies of differing designs suggest that the safety of Atgam in paediatric patients with aplastic anaemia is similar to that of adults, when treated with dosages comparable to those used in adults over similar treatment durations.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance.
Website: www.hpra.ie.

4.9 Overdose

The maximum tolerated dose of Atgam would be expected to vary from patient to patient due to the biological nature of the product.

A maximum therapeutic dose has not been established therefore the definition of overdose for Atgam has not been clearly defined. Some aplastic anaemia patients have received up to 21 doses as additional alternate day therapy for another 14 days. The incidence of toxicologic manifestations did not increase with any of these regimens; however close monitoring of the patient is recommended.

No signs of acute intoxication or late sequelae have been observed at a single dose 7,000 mg in one renal transplant recipient treated with Atgam.

There is no known antidote. Treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressants, ATC code: L04AA03.

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 and bone marrow cells. 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 anaemia is attributed to its immunosuppressive actions. In addition, Atgam directly stimulates the growth of haematopoietic stem cells and release of haematopoietic growth factors such as interleukin-3 and granulocyte/macrophage colony stimulating factor.

Clinical efficacy and safety

The use of Atgam for the treatment of moderate to severe aplastic anaemia is based on five clinical studies, and published reports.

Atgam was evaluated in 5 clinical studies that enrolled a total of 332 patients with aplastic anaemia who were evaluable for efficacy, including patients who had aplastic anaemia of idiopathic or presumed immunologic aetiology, secondary aetiology including post-hepatitis, pregnancy, paroxysmal nocturnal haemoglobinuria (PNH), and other causes. Of these, 252 patients were treated with Atgam 160 mg/kg which was administered in equally-divided doses over 4 or 8 or 10 days; 115 patients (46%) received Atgam as the only immunosuppressive agent while CsA was co-administered to 137 patients (54%).

The response rate in individual studies ranged from 39% to 68%, with the higher rates seen in the more recent studies that included CsA (see Table 3). Atgam has induced instances of partial or complete haematologic recovery and improved survival in patients with aplastic anaemia of known or suspected immunologic aetiology in patients who are unsuitable for bone marrow transplant.

160 mg/kg (total dose) administered over 8 or 10 days

Study 3-197, Study 3-198, Study 5000
In three controlled clinical studies completed in the 1980's, 115 evaluable patients with moderate (Study 3-197 and Study 5000) to severe (all 3 studies) aplastic anaemia who were not candidates for bone marrow transplantation were administered eATG at 160 mg/kg bw over 8 days or 10 days; patient ages ranged from 1 to 76 years. Haematologic response rates for eATG-treated patients ranged from 39% to 52% in these three studies, and survival rates were 50% or more. See Table 3 for more details.

160 mg/kg (total dose) administered over 4 days

(Scheinberg 2009)
A total of 77 patients with severe aplastic anaemia, 4 to 78 years of age, participated in a prospective, randomised study comparing eATG/ciclosporin (CsA)/sirolimus with standard eATG/CsA immunosuppressive therapy. Thirty-five patients received eATG/CsA/sirolimus and 42 patients received standard eATG/CsA. Intravenous eATG was administered at a dose of 40 mg/kg

bw/day for 4 days and CsA was given at 10 mg/kg/day (15 mg/kg/day for children under 12 years old) for 6 months. Based on randomisation, oral sirolimus was given at 2 mg/day in adults or 1 mg/m^2/day in children under 40 kg for 6 months. The primary endpoint of the study was haematologic response rate at 3 months, defined as no longer meeting the criteria for SAA.

After a planned interim analysis of 30 evaluable patients in each arm, accrual to the eATG/CsA/sirolimus arm was closed, as the conditional power for rejecting the null hypothesis was less than 1%. The overall response rate at 3 months was 37% for eATG/CsA/sirolimus and 57% for eATG/CsA, and at 6 months was 51% for eATG/CsA/sirolimus and 62% for eATG/CsA. The overall survival at 3 years for patients in the eATG/CsA/sirolimus arm was 97%, and was 90% in the eATG/CsA arm. See Table 3 for more details.

(Scheinberg 2011)
A total of 120 treatment-naïve patients (60 per arm), with severe aplastic anaemia, 2 to 77 years of age, were randomised to receive either eATG at 40 mg/kg bw/day for 4 days or rabbit anti-thymocyte globulin (rATG) at 3.5 mg/kg/day for 5 days. Each treatment arm also included CsA at 10 mg/kg/day (15 mg/kg/day for children under 12) given in divided doses every 12 hours for at least 6 months, with the dose adjusted to maintain trough blood levels of 200 to 400 ng/mL. The primary endpoint was haematologic response at 6 months, defined as no longer meeting the criteria for severe aplastic anaemia.

The observed rate of haematologic response at 6 months was in favour of eATG compared with rATG (68% vs 37%, respectively [p< 0.001]). The overall survival rate at 3 years differed significantly between the two regimens: 96% in the eATG group compared with 76% in the rATG group (p=0.04) when data were censored at the time of stem cell transplantation, and 94% compared with 70% (p=0.008) in the respective groups when stem cell transplantation events were not censored. See Table 3 for more details.

Table 3. Key Clinical Studies with Atgam for the Treatment of Aplastic Anaemia*

Study	**eATG+ comparator or other therapy**	**No. of subjects analysed**	**Response rate (endpoint)[a]**	***P* Value**	**Survival rate (time point)**	***P* Value**
160 mg/kg (total dose) administered over 8 days or 10 days						
Study 3-197 (20 mg/kg for 8 days)	eATG	21	47%[b]/ 52%[c] (3 mo)	<0.01[b]/<0.01[c]	62%[d] (12 mo)	NA
	Supportive care only	20	6%[b] / 0%[c]			

Table 3. Key Clinical Studies with Atgam for the Treatment of Aplastic Anaemia*

Study	eATG+ comparator or other therapy	No. of subjects analysed	Response rate (endpoint)[a]	*P* Value	Survival rate (time point)	*P* Value
Study 3-198 (16 mg/kg for 10 days)	eATG + OXY + Bone marrow infusion	23	43%[b]/ 39%[c] (3 mo)	Not reported	83% (12 mo)	=0.14
	eATG + OXY	18	44%[b]/ 39%[c] (3 mo)		59% (12 mo)	
Study 5000 (20 mg/kg for 8 days)	eATG + Androgen	26	42% (6 mo)	>0.9	55%[e] (24 mo)	=0.65
	eATG + Placebo	27	44% (6 mo)		50%[e] (24 mo)	
160 mg/kg (total dose) administered over 4 days						
Scheinberg 2009	eATG+ CsA + sirolimus	35	51% (6 mo)	Not reported	97% (36 mo)	=0.30 (log-rank)
	eATG + CsA	42	62% (6 mo)		90% (36 mo)	
Scheinberg 2011	eATG + CsA	60	68% (6 mo)	<0.001	96%[g]/94%[h] (36 mo)	=0.04[g]/=0.008[h]
	rATG[f] + CsA	60	37% (6 mo)		76%[g]/70%[h] (36 mo)	

Abbreviation: OXY: oxymetholone.

* These clinical studies were conducted from 1979 to 2010.

[a] Haematologic response was defined differently in different studies, confidence intervals added where available.

[b] Sponsor's evaluation of response.

[c] Investigator's evaluation of response.

[d] This survival estimate includes the 21 subjects who were randomised to receive eATG, plus another 11 subjects who received eATG after crossing over from the control group.

[e] Patients with severe aplastic anaemia only.

[f] CsA was discontinued at 6 months in the rATG group.

[g] Subjects who had stem cell transplantation were censored.

[h] Subjects who had stem cell transplantation were not censored.

Antibody against horse IgG was assessed in two clinical studies performed in renal transplant patients treated with Atgam; 9% to 37% of treated patients show detectable levels of anti-horse IgG antibodies. The incidence of anti-horse antibody formation in aplastic anaemia patients and of their neutralizing potential is unknown and its clinical significance has not been established.

Paediatric population

Data from published studies of differing designs suggest that the efficacy of Atgam in paediatric patients with aplastic anaemia is similar to that of adults, when treated with dosages comparable to those used in adults over similar treatment durations.

However, based on data from a compassionate use program, achieving haematological response could be less successful in children between the ages of 2 and 11 years in the subgroup of very severe aplastic anaemia paediatric patients compared with older children or adult patients with very severe aplastic anaemia.

5.2 Pharmacokinetic properties

Distribution

During infusion of Atgam at 10 to 15 mg/kg bw/day, the mean peak plasma horse immunoglobulin level (n = 27 renal transplant patients) was found to be 727 ± 310 µg/ml.

Elimination

The half-life of horse anti-human T lymphocyte immunoglobulin after infusion was found to be 5.7 ± 3.0 days in renal transplant patients. The range for half-life was 1.5 to 13 days.

Special populations

Ethnicity
A clinical study examined the pharmacokinetics of Atgam in 6 adult Japanese patients with moderate or severe aplastic anaemia. When administered via intravenous infusion at a dose of 10 mg/kg bw/day (n=3) or 20 mg/kg bw/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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard identified for humans based on conventional studies of repeated dose toxicity, genotoxicity, and fertility.

Carcinogenicity, and pre-/post-natal development studies have not been conducted with horse anti-human T lymphocyte immunoglobulin.

Pregnancy

Atgam was not embryotoxic, fetotoxic, or teratogenic in rats, after doses similar to doses used in humans. In monkey reproduction studies, Atgam was embryotoxic and fetotoxic. These effects occurred in the presence of maternal toxicity (observed with Atgam doses of 20 mg/kg/day, with maternal deaths occurring at doses of 40 mg/kg/day). Foetal deaths occurred following maternal treatment during the first part of organogenesis, but not during the latter part of organogenesis. The maternal and foetal deaths were attributed to maternal anaemia due to a red blood cell antigen that humans do not share. Therefore, this toxicity is not considered relevant to human foetal development.

Lactation

In animal studies, Atgam was not detected at the limit of quantification in the milk of lactating cynomolgus monkeys.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine

Water for Injections
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened ampoules

2 years.

Chemical and physical in-use stability been demonstrated for 24 hours at 25°C. From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination,the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Unopened ampoules

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the ampoules in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3 and 6.6.

6.5 Nature and contents of container

5 ml of concentrate for solution in an ampoule (Type 1 glass).
Pack size: 5 ampoules.

6.6 Special precautions for disposal and other handling

Preparation of infusion solution

As Atgam is a gammaglobulin, both the concentrate and diluted solution should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. The concentrate and diluted solution are transparent to slightly opalescent, colourless to light pink or light brown and both 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 denaturation of the protein. Atgam concentrate should be diluted prior to infusion by inverting the container of the sterile diluent in such a manner that the undiluted Atgam does not come in contact with the air inside.

Add the total daily dose of Atgam to an inverted bottle or bag of one of the following sterile diluents below:
- 0.9% sodium chloride,
- 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 (see section 6.2).

The recommended concentration of the diluted Atgam is 1 mg/mL in the chosen diluent. The concentration should not exceed 4 mg/mL of Atgam.

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

Once diluted, for intravenous administration only.

Diluted Atgam should be allowed to reach room temperature (20°C - 25°C) before infusion. Infusion volumes of 250 ml to 500 ml may be used. Atgam should be administered into a high flow central vein through an in-line filter (0.2-1.0 micron).

An in-line filter (not supplied) must be used with all infusions of Atgam to prevent the administration of any insoluble material that may develop in the product during storage.

It is recommended that once diluted, the solution be used immediately. Diluted Atgam should be stored at room temperature (20°C - 25°C) if not used immediately. The total time in dilution should not exceed 24 hours (including infusion time).

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

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

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/238/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th March 2022

10 DATE OF REVISION OF THE TEXT

January 2024