SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ATGAM® solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of solution contains antithymocyte immunoglobulin (equine) 50 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

ATGAM is a transparent to slightly opalescent aqueous protein solution. It may appear colourless to faintly pink or brown and is nearly odourless. It may develop a slight granular or flaky deposit during storage.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renal transplantation

ATGAM is indicated in combination with concomitant immunosuppressive therapy for the management of allograft rejection in renal patients.

Aplastic anaemia

ATGAM is indicated for the treatment of moderate to severe aplastic anaemia in patients who are unsuitable

for bone marrow transplantation.

4.2 Posology and method of administration

Skin testing

Before the first infusion of ATGAM, skin testing of potential recipients is **strongly** recommended before commencing treatment. A conservative, conventional approach would first employ epicutaneous (prick) testing with undiluted ATGAM. If the patient does not show a wheal 10 minutes after pricking, proceed to intradermal injection of 0,02 mL of a 1:1000 v/v dilution of ATGAM in saline and a separate saline control injection of similar volume.

Use only freshly diluted ATGAM for skin testing.

Read the result at 10 minutes: A wheal of 3 mm or greater than that of the saline control site, with erythema or both with or without pseudopod formation and itching or a marked local swelling, should be considered a positive test, and an increased possibility of a systemic allergic reaction should the medicine be dosed intravenously.

Note: The predictive value of this test has not been proven clinically.

Posology

Renal allograft recipients

Delaying the onset of allograft rejection: 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 anaemia

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.

Special populations

Use in the elderly (≥ 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 section 4.4).

Method of administration

For intravenous infusion.

Administration

The diluted ATGAM solution should be at 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 ATGAM 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).

4.3 Contraindications

ATGAM is contraindicated in patients with a known hypersensitivity to antithymocyte immunoglobulin (equine) or to any of the excipients of ATGAM listed in section 6.1.

Do not administer ATGAM 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.

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

Safety in pregnancy and lactation has not been established.

Experience in children has been limited.

4.4 Special warnings and precautions for use

Only medical practitioners experienced in immunosuppressive therapy in the management of renal transplant or aplastic anaemia patients should use ATGAM**.**

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

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:

- Anaphylaxis
- Severe and unremitting thrombocytopenia
- Severe and unremitting leukopenia

Anaphylaxis

Anaphylaxis may occur at any time during therapy with ATGAM. Stop infusion immediately and do not resume therapy with ATGAM. Respiratory distress and hypotension may indicate an anaphylactoid reaction. Discontinue infusion of ATGAM if this occurs. Pain in the chest, flank, or back may indicate anaphylaxis or haemolysis.

Immune-mediated reactions

In rare instances, serious immune-mediated reactions have been reported with the use of ATGAM. Clinical signs associated with anaphylaxis, other infusion associated reactions, and serum sickness have been reported (see section 4.8). Based on the mechanism of action of ATGAM, there is a potential risk of cytokine release syndrome.

A systemic reaction such as generalised rash, tachycardia, dyspnoea, hypotension or anaphylaxis precludes any additional administration of ATGAM.

Skin testing

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 with a medical practitioner familiar with the treatment of potentially life threatening allergic reactions in attendance.

Allergic reactions such as anaphylaxis have occurred in patients whose skin test is negative.

Positive skin testing will not predict later development of serum sickness.

Infection

Monitor patients carefully for signs of leukopenia, thrombocytopenia or concurrent infection. An increase in the incidence of cytomegalovirus infection in patients receiving ATGAM has been observed. Severe and unremitting haemolysis may require discontinuation of therapy with ATGAM.

Because thrombocytopenia can be associated with the administration of ATGAM, patients receiving it for the treatment of aplastic anaemia may need prophylactic platelet transfusions to maintain platelets at clinically acceptable levels.

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.

Renal or hepatic impairment

In patients with aplastic anaemia and other haematologic abnormalities who have received ATGAM, abnormal tests of liver function and renal function have been observed.

Live-virus vaccines

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

Use in the elderly

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 section 4.2), reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicine therapy in this age group.

Paediatric population

Experience with children has been limited (see section 4.3).

4.5 Interaction with other medicines 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, observe patients especially carefully during therapy with ATGAM.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

4.7 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 ATGAM.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated summary of adverse reactions

The adverse drug reactions (ADR) reported with ATGAM during clinical studies or through post-marketing experience are presented in the tables 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.

MedDRA system organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Common	Infection
	Uncommon	Herpes simplex
Blood and lymphatic system disorders	Very common	Thrombocytopenia, leukopenia
	Common	Lymphadenopathy
Immune system disorders	Uncommon	Serum sickness, anaphylactic reaction
Metabolism and nutrition disorders	Uncommon	Hyperglycaemia
Psychiatric disorders	Uncommon	Agitation
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Convulsion, encephalitis, paraesthesia
Cardiac disorders	Common	Bradycardia, tachycardia
Vascular disorders	Common	Thrombophlebitis, hypertension, hypotension
	Uncommon	Renal artery thrombosis, iliac vein occlusion
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Pleural effusion, laryngospasm, pulmonary oedema

Gastrointestinal disorders	Common	Nausea*, vomiting*, diarrhoea, upper abdominal pain
	Uncommon	Stomatitis, hiccups*
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Urticaria*, pruritus
	Uncommon	Night sweats, allergic dermatitis, periorbital oedema, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
	Common	Back pain*
Renal and urinary disorders	Uncommon	Proteinuria
General disorders and administration site conditions	Very common	Pyrexia, chills
	Common	Chest pain*, infusion site pain, oedema
	Uncommon	Asthenia, malaise
Investigations	Uncommon	Abnormal renal function test, abnormal liver function test
Injury, poisoning and procedural complications	Common	Arteriovenous fistula thrombosis
	Uncommon	Wound dehiscence
* 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.		

Post-marketing experience

The following adverse reactions were reported during post-marketing experience with ATGAM:

MedDRA system organ class	**Adverse reaction***
Infections and infestations	Viral hepatitis, systemic infection, localised infection
Blood and lymphatic system disorders	Anaemia, aplasia, granulocytopenia, haemolysis, haemolytic anaemia, neutropenia, pancytopenia, eosinophilia
Immune system disorders	Vasculitis
Nervous system disorders	Confusional state, disorientation, dyskinesia, tremor, syncope
Cardiac disorders	Congestive cardiac failure
Vascular disorders	Deep vein thrombosis, gastrointestinal haemorrhage
Respiratory, thoracic and mediastinal disorders	Apnoea, cough, epistaxis
Gastrointestinal disorders	Abdominal pain, gastrointestinal perforation, oral pain, oropharyngeal pain
Musculoskeletal and connective tissue disorders	Flank pain, muscle rigidity, myalgia, pain in extremity
Renal and urinary disorders	Kidney enlargement, acute renal failure, ruptured kidney

General disorders and administration site conditions	Infusion site erythema, infusion site swelling, hyperhidrosis, pain

* Frequency not known (cannot be estimated from the available data)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See section 4.8. Treatment is symptomatic and supportive.

The maximum tolerated dose of ATGAM would be expected to vary from patient to patient due 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 of saline, seven times the recommended total dose and infusion concentration. In this patient, the administration of ATGAM was not associated with any signs of acute intoxication or late sequelae.

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 Pharmacodynamic properties

Category and class: A 30.4 Other

Antithymocyte immunoglobulin (equine) is composed of antibodies that bind a wide variety of proteins on the surface of lymphocytes. In addition, antithymocyte immunoglobulin (equine) binds to granulocytes, platelets and bone marrow cells. The mechanism of antithymocyte immunoglobulin (equine) induced immune suppression 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 antithymocyte immunoglobulin (equine) therapy for aplastic anaemia is attributed to its immunosuppressive actions. In addition, antithymocyte immunoglobulin (equine) directly stimulates the growth of haematopoietic stem cells and release of haematopoietic growth factors such as interleukin-3 and granulocyte/macrophage colony stimulating factor.

5.2 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.

Biotransformation and elimination

The half-life of equine immunoglobulin after antithymocyte immunoglobulin (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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine

Water for injection

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

The dilution of ATGAM in Dextrose Injection is not recommended, as low salt concentrations may cause precipitation. The use of highly acidic infusion solutions is also not recommended because of possible physical instability over time.

6.3 Shelf life

36 months.

Diluted solution

Diluted solution should be kept at room temperature (20 - 25 °C). The solution should be used within 24 hours (including infusion time).

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).

Do not freeze.

Keep the ampoule in the outer carton in order to protect from light.

For storage conditions of diluted solution, see section 6.3.

6.5 Nature and contents of container

ATGAM solution for infusion is available in 5 mL ampoules in cartons of 5 ampoules.

6.6 Special precautions for disposal and other handling

Preparation of solution

Inspect visually for particulate matter and discolouration prior to administration. ATGAM can be transparent to slightly opalescent, colourless 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 *Compatibility and stability*). The concentration should not exceed 4 mg of ATGAM per mL. The diluted solution should be gently rotated or swirled to effect thorough mixing.

Compatibility and stability

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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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10. DATE OF REVISION OF THE TEXT

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