SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal product:

Thymogam - Equine Anti-Thymocyte globulin (Equine ATG)

The Product is of equine origin derived from the blood hyper immunized against human thymocytes for ponies.

1.1 Strength

250 mg / 5ml

1.2 Pharmaceutical form:

Liquid Injection for Intravenous use

2. Qualitative and quantitative compositions :

2.1 Qualitative Declaration :

Each 5 ml of the solution contains 250.0 mg of Equine ATG. Additionally, it contains Glycine B.P., Sodium chloride B.P. and Water for Injection USP.

2.2 Quantitative Declaration

Qualitative and quantitative composition of Thymogam 250.

Pack Size: 5ml

Names of Ingredients	Unit and/or Percentage Formula	Function	Reference to Standards
Active Substance(s)a			
Equine ATG produced from Animal Plasma.	50 mg/ml	Active ingredient	I.H.
Excipient(s)			
Glycine	3.75mg/ml	Stabilizer	B.P.
Sodium Chloride	2.92mg/ml	pH adjustment	B.P.
Water for Injection	q.s.	Aqueous vehicle	U.S.P.

3. Pharmaceutical form:

Liquid Injection for Intravenous use.

Thymogam is clear or slightly opalescent and colourless or pale yellow coloured liquid, free from suspended particles in 5 ml vial.

4. Clinical particulars:

4.1 Therapeutic Indications:

Renal transplantation: **Thymogam** is indicated for the management of allograft rejection, including delay of onset of first rejection episode, in patients who have undergone renal transplantation.

Aplastic Anaemia: **Thymogam** is indicated in the treatment of moderate to severe aplastic anaemia in patients not suitable for bone marrow transplant.

4.2 Dosage and Administration:

Following are the recommended dosages for Equine ATG:

Renal Allograft Recipients: 10 to 15mg/kg daily for 14 days (14 doses) followed by alternate day therapy for further 14 days (7 doses) bringing the total doses to 21 in 28 days.

In children, doses in the range of 5 to 25mg/kg daily have been administered. **In adult** renal allograft recipient's doses of 10 to 30mg/kg daily have been administered. When given to delay onset of first rejection episode, start therapy within 24 hours before or after transplant. When given to treat rejection, start therapy at time of diagnosis of the first rejection episode. Equine ATG can also be used concomitantly with azathioprine and corticosteriods which are also used to suppress the immune response.

Aplastic Anaemia Recipients: 10 to 20mg/kg daily for 8-14 days followed by alternate day therapy for a total of 21 doses. These patients are to be monitored continuously for thrombocytopenia. When administered with a regime of supportive care, it may induce partial to complete haematological remission.

British Committee for Standards in Haematology states 'The dose of horse ATG (ATGAM) is 40 mg/kg/d for 4 d. It is given as an intravenous infusion over 12-18 h.'

https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.13853

Many studies from literature including studies on Indian pediatric population have used 40mg/kg/day for four days regimen in treatment of aplastic anaemia. This dose was found to be effective and well tolerated.

Special population

Paediatric Use:

Experience with children has been limited. Equine ATG has been administered at dosage levels comparable to those in adults.

Use in Elderly Patients:

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. The dose for an elderly patient should be selected with caution, starting

at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

For pregnant and nursing women – see section 4.7

Renal impairment

Equine ATG is used in patient who require renal transplantation. This has been detailed above. Abnormal renal function tests have been observed after administration of Equine ATG.

Hepatic impairment

No data on patients with hepatic impairment is available. However, abnormal hepatic function tests have been observed after administration of Equine ATG. Hence these patients should be closely monitored.

4.3 Method of Administration

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

Thymogam should be diluted before use in 0.9% Sodium Chloride Injection, 5% Dextrose and 0.225% Sodium Chloride, or 5% Dextrose and 0.45% Sodium Chloride Injection to a concentration not to exceed 4mg of Equine ATG per ml. The diluted solution should be gently rotated or swirled to effect thorough mixing and allowed to reach room temperature before infusion.

4.4 Contra-indications

Thymogam should not be administered to a patient who has previous history of severe systemic reaction to this preparation or any other equine globulin preparations.

4.5 Special Warnings and precautions for use:

Only physicians experienced in immunosuppressive therapy should use Equine ATG**.** Use Equine ATG only in facilities equipped and staffed with adequate laboratory and supportive medical resources. Discontinue therapy if anaphylaxis or severe and unremitting thrombocytopenia or leucopenia occurs.

As observed with products derived from or purified with human blood components, the possibility of transmission of some infectious diseases should be borne in mind. Monitor patients carefully for concurrent infection. Several studies have suggested and increase in the incidence of cytomegalovirus infection in patients receiving ATG. To identify those at greatest risk of systemic anaphylaxis, physician should strongly recommend skin testing before commencing treatment.

The skin test is described as below:

Before the first infusion of Thymogam, it is strongly recommended that patients be tested with an intradermal testing with 0.02 mL of a 1:1000 dilution of Thymogam in sodium chloride solution with a separate Sodium chloride injection control of similar volume. Observe the results every 10 minutes over the first hour after intradermal injection. A wheal of 3mm or greater in diameter at the site of Thymogam injection than that at the Sodium chloride injection control site (or a positive prick test) shows clinical sensitivity and an increased possibility of systemic allergic reactions.

Note: The predictive value of this test has not been proved 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 Thymogam, serious consideration to alternative forms of therapy should be given.

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

4.6 Interaction with other drugs , other forms of interactions:

When the dose of corticosteroids and other immunosuppressants is being reduced, some previously masked reactions to Equine ATG may appear. Under these circumstances, observe patients carefully during therapy with Equine ATG.

4.7 Use in pregnancy and lactation:

Equine ATG has not been evaluated in either pregnant or lactating women. Animal reproduction studies have not been conducted with Equine ATG. It is also not known whether Equine ATG can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Equine ATG administration to pregnant women is not recommended and should be considered only under exceptional circumstances. It is not known whether Equine ATG is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Equine ATG , caution should be exercised when Thymogam is administered to a nursing woman.

4.8 Effects :on ability to drive and use machines

Equine ATG is unlikely to affect the ability of an individual to drive or use machines, since adverse reactions are usually infusion-related. However, the

clinical condition of patients who require Equine ATG generally precludes driving or operating machinery.

4.9 Undesirable effects :

Based on the published literature on Thymogam following are adverse events identified-

In study conducted Shah S et al, in 2018 (n=91), the most common side effects observed with Thymogam were Febrile neutropenia (57.1%), Gum Hypertrophy (15.4%), Hypertension (14.3%), Pneumonia (5.5%), Intracranial haemorrhage (5.5%) and Renal failure (2.2%).

Clinical trial (BSV_ATG-AA_1211) conducted in patients of Aplastic anaemia, it was reported that Fever (20%) was the most common adverse event observed followed by rashes (10%) and anorexia (10%).
Following list of adverse events on Equine ATG-

Adverse events	Frequency
Allergic urticaria, Papular rash/ patches, Wheal and flare, Pruritus, Fever, Leukopenia, Thrombocytopenia, Arthralgia	Very common
Back pain, Night sweats, Pain at infusion site, Diarrhoea, Oral ulcer, Vomiting, Chest pain, Bilateral pleural effusion, Hypotension, Clotted AV fistula, Peripheral thrombophlebitis, Headache	Common
Swelling on the face, Lymphadenopathy, Wound dehiscence, Toxic epidermal necrolysis, Weakness Bilateral pedal oedema, Poisoning and procedural complications, Epigastric pain, Hiccoughs, Laryngospasm, Pulmonary oedema, Tachycardia, Hypertension, Iliac vein obstruction, Renal artery, thrombosis, Anaphylaxis, Serum sickness, Urinary tract infection, Ventilator associated pneumonia, Septicaemia, Proteinuria, Seizure, Agitation, Dizziness, Paraesthesia, Deranged liver function tests, Deranged renal function tests,	Rare
Erythema, Body ache, Mucositis, Shivering, Constipation, Acidity, Oral bleeding, Mild per rectal bleeding, Dyspnoea, Cough, Pain in nostrils, Acute parotitis, Acute suppurative otitis media, Gingivitis, Abscess in neck, Typhoid, Unspecified infections and infestations, Anorexia, Hyperglycaemia, Acute renal failure, Kidney dysfunction, Febrile neutropenia, Blurred vision, Burning of eye, Muscle pain, Weight gain, Elevated serum ferritin levels	Unknown frequency

Other adverse events seen are

From literature data-

Very common- leucopenia

Common- night sweats; pain at the infusion site, stomatitis, diaphoresis, joint stiffness, periorbital oedema, aches, oedema, muscle ache, agitation/lethargy, listlessness, light-headedness, diarrhoea, bradycardia, myocarditis, cardiac irregularity, hepatosplenomegaly, possible encephalitis or post viral encephalopathy, congestive heart failure, burning soles/palms, foot sole pain, lymphadenopathy, post-cervical lymphadenopathy, tender lymph nodes, respiratory distress.

Rare - faintness, oedema, herpes simplex reactivation, localized infection, , malaise, myalgia, systemic infection, toxic epidermal necrosis.

In patients with aplastic anaemia and other haematologic abnormalities who have received ATG, 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 in majority of patients.

4.10 Overdose

Maximal tolerated dose of Equine ATG vary from patient to patient because of its mode of action and because it is a biological substance.

From literature data, the largest single daily dose administered to a patient, a renal transplant recipient, was 7000mg administered at a concentration of approximately 10mg/ml diluted with Sodium Chloride Injection, USP, approximately 7 times the recommended total dose and infusion concentration and was not associated with any signs of acute intoxication.

The maximum 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 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 toxicological manifestations did not increase with any of these regimens.

If an overdosage is suspected, discontinue the therapy. Monitor the patient closely for renal and hepatic functions. Administer supportive therapy as required.

5. Pharmacological properties :

5.1. Clinical and Animal Pharmacology:

Pharmacodynamic properties

ATG is a 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 anti-lymphocytic 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 anti-lymphocytic activity, ATG contains low concentrations of antibodies against other formed elements of the blood. In rhesus and cynomolgus monkeys, ATG 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 ATG does not cause severe lymphopenia.

In general, when ATG is given with other immunosuppressive therapy, such as antimetabolites and corticosteroids, the patient's own antibody response to horse gamma globulin is minimal.

The mechanism of Equine ATG induced immunosuppression has not been determined. Published data indicate that the primary mechanism is the depletion of circulating lymphocytes, with greatest effect on T lymphocyte. 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 Equine ATG therapy for aplastic anemia is attributed to its immunosuppressive actions. In addition, Equine ATG 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 ATG is given with other immunosuppressive therapy, such as antimetabolites and corticosteroids, the patient's own antibody response to horse gamma globulin is minimal.

Clinical data on Thymogam.

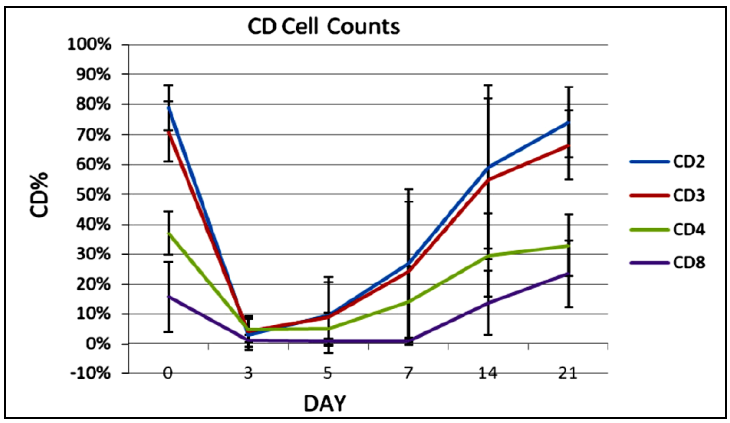
1. Safety and efficacy of indigenous equine antithymocyte globulin along with cyclosporine in subjects with acquired aplastic anemia. (BSV_ATG-AA_1211) (Agarwal, 2015)

30 subjects enrolled 19 completed day 90 and 18 completed day 180 visit.

On day 90, 12 of 30 subjects responded (CR 1, PR 11) and 15 of 30 (CR 2, PR 13) on day 180. The most common adverse event was fever related to eATG infusion. There were two serious adverse events (acute renal failure, febrile neutropenia) and both recovered with treatment. There were no unusual adverse events noted during the study period. Blood T lymphocytes showed a mean decrease of 91 % from baseline that recovered by day 21.

Lymphocyte subset (CD2, CD3, CD4 and CD8) counts tested in this study were seen to fall to minimum between days 3 and 5 after Thymogam administration and recover between days 7 and 14, confirming the action on T cell-mediated immunity and this result was seen in all the subjects irrespective of the clinical response on day 180.

Figure 1. Blood T lymphocyte counts at baseline and 3, 5, 7, 14 and 21 days after Thymogam administration



It was concluded that eATG is safe and in combination with cyclosporine showed overall response in 50% of enrolled subjects.

2. Immunosuppressive therapy for aplastic anaemia: a single-centre experience from western India (Shah, 2018)

This study evaluated a large cohort of aplastic anaemia patients who received and indigenous preparation of Equine ATG along with cyclosporine as first line treatment. At 2 years 23.5% adults and 31% children showed complete response and an overall of 68.1% cases became transfusion independent. Mortality rate was calculated to be 31% and common cause of death were infection and intracranial haemorrhage.

3. Thymogam in prevention of rejection in subjects undergoing renal transplantation surgery (BSV/ATG-SD/04)

This was a prospective single-centre phase IV post-marketing study to prevent rejection in subjects undergoing renal transplantation surgery. Thirteen patients (4 females) with mean age of 44 years, and weight 56.7 kg, received Thymogam as a single dose administered at a dose of 25mg/kg body weight over 4 to 6 hours. All 13 patients showed recovery of T-lymphocyte subset counts towards normalcy within 14 days of transplantation. At six months completion, serum creatinine levels have been seen to return to normalcy as other haematological parameters. There

has been no incidence of rejection. No serious adverse events were encountered and the CD3 counts started falling in the 48-hour post-transplant assay, remaining for a week, before rising to pre-treatment values. There was no rejection in small group of renal transplantation patients.

4. Efficacy and Safety in renal transplant patients after single bolus intravenous Thymogam (BSV/ATG-SD/0604)

A total of 46 patients enrolled in the study. 6 patients showed biopsy confirmed acute rejection of the 44 patients who underwent renal transplant surgery. The serum creatinine levels from baseline mean value of 7.04 mg/dl to mean level of 1.5 mg/dl at visit 4. The mean change from baseline to the visit 4 was 5.17 ($p > 0.0001$). 39 patients survived six months after surgery. A total of 13 patients had at least one AE. Treatment related AEs were seen in 5 patients. There were 4 deaths and 2 of these were related to Thymogam. Thymogam was well tolerated by patients and there were no clinically significant abnormalities observed in laoboratory tests. There was low responsiveness of T cells depicted by decreased cell count in first visit and gradual increase in fourth visit. At six months, 92.3% of graft survival was seen. This study showed use of induction therapy reduced acute rejection of kidney transplant.

The immunosuppressive action of Thymogam is apparently due to its by loss of CD3+ and CD2+ lymphocytes from the circulating blood. The mechanisms for this clearance probably include both cytotoxicity of the antibody mediated by complement and clearing in the reticuloendothelial system due to macrophage extraction of the opsonized T lymphocytes.

Published reports have revealed a serum half-life of 1.5 - 12 days. A study evaluating the pharmacokinetics of equine ATG at a dose of 40 mg/kg/day for 4 days, in 43 patients with severe aplastic anemia using ELISA, reported that ATG reached high plasma concentrations, 2 days after the first infusion, peaking at week 1 (237.6±12.7 µg/mL), and then gradually decreased. The ATG concentration decreased by 18%, 46%, and 74% from peak values when assessed at week 2, week 3, and 1 month, respectively. When patients' serial plasma samples were assayed by western blotting, the peak levels occurred on day 4 and the levels gradually decreased by day 14 and were barely detectable on days 21 and 28.

5.2. Pre-clinical safety data

The product Equine ATG Injection is well-known and well established in international literature.

Carcinogenicity, mutagenicity, reproduction and teratology

Mutagenicity and carcinogenicity studies have not been conducted on Equine ATG.

From literature data, in animal studies, Equine ATG was not detected at the limit of quantification in the milk of lactating cynomolgus monkeys.

From literature data, the administration of Equine ATG to cynomolgus monkeys (Macaca fascicularis) at doses comparable to those used in clinical trials was not associated with impairment of male or female fertility.

In monkey reproduction studies, maternal toxicity was observed with doses > 20 mg/kg/day for 14 days. Maternal deaths occurred at a dose of 40 mg/kg/day. Foetal deaths occurred in dams treated with 20 mg/kg/day during the first part of organogenesis, but not in dams treated during the last part of organogenesis. While the etiology of this toxicity is not known, it may possibly be attributed to haemolytic anemia due to cross-reactivity of Equine ATG to a monkey red blood antigen. Humans do not share this antigen; thus this toxicity is not considered relevant to human development.

Equine ATG was not teratogenic in rats or monkeys. At a dose of 100 mg/kg in rats during organogenesis, an increase in hypoplastic cervical vertebrae was observed.

6. Pharmaceutical particulars :

6.1. List of excipients:

- Glycine
- Sodium Chloride
- Water for Injection

6.2. Incompatibility:

When the dose of corticosteroids and other immunosuppressants is being reduced, some previously masked reactions to Equine ATG may appear. Under these circumstances, observe patients carefully during therapy with Thymogam.

From literature data - adding ATG 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 ATG 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).

6.3. Shelf-life:

24 months from the date of manufacturing.

6.4. Special precaution for storage

Store between 2°C – 8°C. Do not freeze.

6.5. Nature and contents of container:

This product is packed in 5ml USP Type I, moulded, narrow mouth, transparent, colorless flint glass vial, bunged with rubber bung 20 mm chlorobutyl and sealed with aluminium flip-of seal 20 mm Bio Green. Each such vial is labeled and packed in a carton along with the insert. The carton is sealed with the help of cello tape.

6.6. Special precautions for disposal and other handling

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

7. Marketing authorization holder

Bharat Serums & Vaccines Ltd'
17th Floor, Hoechst House,
lot No. 193, Vinay K Shah Marg,
Nariman Point, Mumbai – 400 021 India.

Manufacturer (Name, Address, Country):
Bharat Serums and Vaccines Limited
Plot No. K-27,
Anand Nagar, Additional M.I.D.C.
Ambernath (East), India

8. Marketing Authorization Number

9. Date of first authorization / renewal of the authorization:

10. Date of final revision of the documents:

12-November-19