WELLMED Doctors helping patients for more than 25 years	**Effective Date:** 08/02/24	**Revision Date(s):** 02/25/19, 02/18/22, 08/02/23, 07/31/24
Department: PHARMACY	**MMC Review/ Approval Date(s):** 03/15/22, 08/04/23, 08/01/24	**Page(s): 14**

Policy Number: 047.004

Title: Coverage Determination Policy for Antithymocyte Globulins

- **Atgam (Antithymocyte globulin equine) and Thymoglobulin (Antithymocyte globulin rabbit)**

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

☒ Network Management/Provider Services	☒ Utilization Management
☐ Member services	☐ Case management
☐ Quality Management	☐ Disease management
☐ Credentialing	☒ Claims
☐ IT	☐ Human resources
☐ Administration	☐ Finance
☐ Compliance/delegation	☒ Pharmacy
	☐ ALL

Approved by: Megan Ortiz, MD FACOG Senior Medical Director	Megan Lenhart Ortiz MD Digitally signed by Megan Lenhart Ortiz MD Date: 2024.08.02 09:44:16 -05'00'	**Date:** 08/02/2024
Reviewed by: Pathik Tripathi, Pharm.D, MS Director, Clinical Pharmacy	Pathik Tripathi Digitally signed by Pathik Tripathi Date: 2024.08.02 08:59:13 -05'00'	**Date:** 08/02/2024

Available LCD/NCD/LCA:

CMS Local Coverage Determination for Texas (LCD): Immunosuppressive Drugs (L33824)
CMS National Coverage Determination (NCD): Lymphocyte Immune Globulin, Anti-Thymocyte Globulin (Equine) (260.7)

Disclaimer:

WellMed Coverage Determination Policies are developed as needed, are regularly reviewed and updated, and are subject to change. They represent a portion of the resources used to support WellMed coverage decision making. WellMed may modify these Policy Guidelines at any time. Medicare source materials used to develop these guidelines include, but are not limited to, CMS National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Medicare Benefit Policy Manual, Medicare Claims Processing Manual, Medicare Program Integrity Manual, Medicare Managed Care Manual, etc. The information presented in the WellMed Coverage Determination Policies is believed to be accurate and current as of the date of publication, and is provided on an "AS IS" basis. Where there is a conflict between this document and Medicare source materials, the Medicare source materials will apply.

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Coverage Policy Number: 047.004

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Initial/New Requests

Note: *For all requests, patient should not be receiving any live vaccines prior to, during, or after treatment with Atgam. In addition, live vaccines should not be given to patients who have been recently treated with Thymoglobulin.*

Atgam and Thymoglobulin should be prescribed by or in consultation with nephrologist, transplant specialist, hematologist and/or oncologist.

WellMed Medical Management will cover **Atgam (Antithymocyte Globulin Equine)** as medically necessary when the following diagnosis specific criteria are met:

1. Treatment of Allograft rejection in patients who have received a renal transplant: **ALL** of the following must be met:
   A. Patient has received a kidney transplant
   B. Atgam will be administered with conventional therapy/immunosuppressants*
   C. Dosing does not exceed FDA approved dosing: 10 to 15 mg/kg daily intravenously for 14 days; additional alternate-day therapy up to a total of 21 doses may be given.

2. Treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation: **ALL** of the following criteria must be met:
   A. Provider has indicated patient is not suitable for a bone marrow transplant
   B. Diagnosis of aplastic anemia is NOT secondary to any of the following: neoplastic disease, storage disease, myelofibrosis, Fanconi syndrome, exposure to myelotoxic agents or radiation.
   C. Dosing does not exceed FDA approved dosing: 10 to 20 mg/kg daily intravenously for 8 to 14 days; additional alternate-day therapy up to a total of 21 doses may be given.

NOTE: The usefulness of Atgam has not been demonstrated in patients with aplastic anemia who are suitable candidates for bone marrow transplantation

WellMed Medical Management will cover **Thymoglobulin** (**Antithymocyte Globulin Rabbit)** as medically necessary when the following diagnosis specific criteria are met:

1. Prophylaxis of acute rejection in patients receiving a kidney transplant **ALL** of the following must be met:
   A. Thymoglobulin will be administered with immunosuppressants*
   B. Patient does NOT have any active acute or chronic infections
   C. WBC or Platelet count has been provided
      i. If WBC count is between 2,000- 3,000 cells/mm^3 or platelet count is between 50,000-75,000 cells/mm^3 Thymoglobulin dose should be reduced by one-half. Provider should consider stopping Thymoglobulin if WBC count falls below 2000 cells/mm^3 or if platelet count falls below 50,000 cells/mm^3 .
   D. Dose does NOT exceed 1.5 mg/kg of body weight administered daily for 4 to 7 days

2. Treatment of acute rejection in patients following a kidney transplant **ALL** of the following must be met:
   A. Thymoglobulin will be administered with immunosuppressants*
   B. Patient does NOT have any active acute or chronic infections
   C. WBC or Platelet count has been provided
      i. If WBC count is between 2,000- 3,000 cells/mm^3 or platelet count is between 50,000-75,000 cells/mm^3 Thymoglobulin dose should be reduced by one-half. Provider should consider stopping Thymoglobulin if WBC count falls below 2000 cells/mm^3 or if platelet count falls below 50,000 cells/mm^3 .
   D. Dose does NOT exceed 1.5 mg/kg of body weight administered daily for 7 to 14 days

Renewal/Continuation of Therapy Requests

WellMed Medical Management will cover **Atgam (Antithymocyte Globulin Equine)** for renewal as medically necessary when the following diagnosis- specific criteria are met:

1. Treatment of Allograft rejection in Renal Transplant patients OR Treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation**, ALL** of the following must be met:
   A. Patient must meet initial coverage criteria
   B. Patient has NOT experienced any allergic reactions during any prior ATGAM or equine gamma globulin administration
   C. Request is for a max of 21 doses at FDA approved dosing

WellMed Medical Management will cover **Thymoglobulin** (**Antithymocyte Globulin Rabbit)** for renewal as medically necessary when the following criteria are met:

1. Prophylaxis or Treatment of acute rejection in patients following a kidney transplant, **ALL** of the following must be met:
   A. Patient must meet initial coverage criteria
   B. WBC or platelet count has been provided
      i. If WBC count is between 2,000- 3,000 cells/mm^3 or platelet count is between 50,000-75,000 cells/mm^3 Thymoglobulin dose should be reduced by one-half. Provider should consider stopping Thymoglobulin if WBC count falls below 2000 cells/mm^3 or if platelet count falls below 50,000 cells/mm^3 .
   C. Request does NOT exceed 1.5 mg/kg daily AND 1 one of the following
      i. Duration does not exceed 7 days for prophylaxis
      ii. Duration does not exceed 14 days for treatment

FDA Approved Dose and Indication

Drug	Indication	Dosing
Atgam®	• Treatment of Allograft rejection in patients who have received a renal transplant (administered with conventional therapy)	• 10 to 15 mg/kg daily intravenously for 14 days*
	• Moderate to Severe Aplastic Anemia in patient's unsuitable for bone marrow transplant	• 10 to 20 mg/kg daily intravenously for 8 to 14 days*
	*Additional alternate-day therapy up to a total of 21 doses may be given for both indications	
Thymoglobulin®	• Prophylaxis of acute rejection in patients following a kidney transplant (In combination with other immunosuppressive agents)	• 1.5 mg/kg of body weight administered daily for 4 to 7 days
	• Treatment of acute rejection in patients following a kidney transplant (In combination with other immunosuppressive agents)	• 1.5 mg/kg of body weight administered daily for 7 to 14 days **Dose Adjustment:** • WBC count 2,000-3,000 cells/mm^3 or platelet count is 50,000-75,000 cells/mm^3 : <u>Reduce dose by 50%.</u> • WBC count below 2000 cells/mm^3 or platelet count below 50,000 cells/mm^3: <u>Consider discontinuing therapy</u>.

General Background

Antithymocyte globulins (ATG) are polyclonal antibodies, which appear to cause immunosuppression through the elimination of antigen-reactive T lymphocytes. ATG is used to treat and prevent organ rejection in renal transplant patients and to treat severe aplastic anemia.

Since ATG is an immunosuppressant, patients should be monitored closely for infections, including cytomegalovirus (CMV). ATG can also cause hematologic toxicity including leukopenia and thrombocytopenia, which may necessitate dose reduction or discontinuation. Other common side effects include chills, headache, arthralgia, and dermatological reactions. Anaphylaxis and hypersensitivity has occurred rarely with ATG, so skin testing is recommended prior to the first dose. All patients receiving ATG should be monitored closely for adverse reactions to include at a minimum: Lymphocyte count (total lymphocyte and/or T-cell subset), CBC with differential and platelet count; vital signs during administration; and signs and symptoms of infection.

There are two ATG products on the market Atgam and Thymoglobulin, which are used for different indications. Antithymocyte globulin products are **NOT** interchangeable. Doses vary for each product due to differences in protein composition and concentration.

Atgam® has a US Boxed warning that it may cause anaphylaxis when injected intravenously. Although antithymocyte globulin (equine) is processed to reduce the level of antibodies that will react to non-T cells, health care providers should be prepared for the potential risk of anaphylaxis and monitor for signs/symptoms during infusion and for at least 24 hours after infusion.

Thymoglobulin® has a US Boxed warning that it should only be used by physicians experienced in immunosuppressive therapy in transplantation.

***Examples of conventional therapy/immunosuppressants used in renal transplant patients**
• Tacrolimus (Prograf) • Cyclosporine (SandImmune) • Cyclosporine, modified (Neoral) • Mycophenolate mofetil (Cellcept) • Mycophenolic acid (Myfortic) • Azathioprine (Imuran) • Sirolimus (Rapamune) • Steroids: Prednisone, methylprednisolone

Clinical Evidence

In a multicenter, double-blind, randomized trial, antithymocyte globulin (rabbit) was shown to be superior to antithymocyte globulin (equine) in reversing acute rejection and preventing subsequent episodes (Gaber 1998). Based on data from studies (including 10 years follow up) comparing ATG (rabbit) to ATG (equine) for induction, ATG (rabbit) has emerged as the T-cell lymphocyte depleting induction therapy of choice over ATG (equine) in adult kidney transplantation due to its improved efficacy and lower incidence of acute rejection (Brennan 1999; Hardinger 2008).

A randomized controlled trial of the use of Atgam as a substitute for standard therapy for treatment of the first acute rejection episode was conducted at one transplant center in recipients of living related renal allografts. A total of 22 patients were studied; 11 in each of the two treatment groups [Atgam versus standard therapy (bolus doses of Solu-Medrol)]. Patients randomized to the Atgam group received 14–21 doses of Atgam therapy, starting on the day the rejection was diagnosed. Atgam was administered daily according to a dose-by-rosette regimen, which resulted in a mean daily dose of approximately 15 mg/kg. Patients randomized to the control group received Solu-Medrol at a dosage of 15 mg/kg starting on the day the rejection was diagnosed, administered either daily or on alternate days for 3 to 7 doses to complete a maximum total dose of 5,000 mg for the course of the rejection episode. In this study, Atgam was at least effective as standard therapy for treatment of acute allograft rejection.

Results from randomized controlled trials in patients with first acute renal allograft rejection episodes refractory to conventional steroid therapy have demonstrated that Atgam, when administered in conjunction with standard therapy, yields efficacy results superior to those of standard therapy alone.

The use of Atgam for the treatment of moderate to severe aplastic anemia in patients who are unsuitable for bone marrow transplantation is based on data from three controlled studies. Please see package insert for detailed description of all three clinical studies.

In a randomized trial in cadaveric recipients with a first acute renal allograft rejection episode at the time of diagnosis, antithymocyte globulin equine administered with standard therapy resulted in significant improvements in rejection resolution and functional graft survival with no significant difference seen in patient survival. In another study in living, related renal transplant recipients, there was no significant difference seen in rate of rejection resolution, functional graft survival, or patient survival. In a study of patients with first renal allograft rejection episode refractory to conventional steroid therapy, when antithymocyte globulin equine was administered with standard therapy, there was significant improvements in functional graft survival and patient's survival.

In a systematic review and meta-analysis of 6 randomized trials in 568 patients, there was no significant benefit with rabbit or equine antithymocyte globulin (ATG) for overall survival (496 patients in 5 studies) or the incidence of relapse (255 patients in 2 studies) when used for prophylaxis of graft-versus-host disease following allogeneic stem cell or bone marrow transplantation for hematological diseases. In a subgroup analysis, prophylaxis with equine ATG did not significantly reduce the incidence of all grades or grades II to IV acute graft-versus-host disease

HCPCS Code

HCPCS Code	Description
J7504	**Atgam** (Antithymocyte globulin equine) Intravenous Solution, 250mg
J7511	**Thymoglobulin** (Antithymocyte globulin rabbit) Intravenous Powder for Solution, 25 MG

Acronyms

ATG = Antithymocyte Globulin

CMV = Cytomegalovirus

SAA = Severe Aplastic Anemia

HSCT = Hematopoietic Stem Cell Transplant

NCD = National Coverage Determination

LCD = Local Coverage Determination

WBC= White Blood Cell Count

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Policy History/Revision Information

Date Revised	Type of Changes (Significant or Minor)	List Significant Changes and/or Status of policy
07/07/17	Significant	New coverage criteria created.
02/25/19	Minor	Deleted off-label indication and dosing for Thymoglobulin. Added Wellmed disclaimer and CMS LCD/NCD statement. Updated references-Eric McDermott, PharmD
02/18/22	Significant	Created criteria for initial and renewal requests for Atgam and Thymoglobulin's FDA approved indications. Added FDA Dosing table and chart of conventional immunosuppressive therapies. Updated General Background, Clinical Evidence, and References. MVader, PharmD.
08/02/23	Minor	Updated the FDA Approved Dose table, updated HCPCS Code table and References. C. Osidele, Pharm.D.
07/31/2024	Minor	Annual revision, LCD (33824) hyperlink updated – Pathik Tripathi, PharmD