CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immune Globulin – Atgam Utilization Management Medical Policy

- Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] intravenous infusion – Pfizer)

REVIEW DATE: 01/22/2025

OVERVIEW

Atgam, an immune globulin, is indicated for the following uses:[1]

- **Allograft rejection**, for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection, Atgam increases the frequency of resolution of the acute rejection episode.
- **Aplastic anemia,** for the treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation. The usefulness of Atgam has not been demonstrated in patients with aplastic anemia who are suitable candidates for bone marrow transplantation or in patients with aplastic anemia secondary to neoplastic disease, storage disease, myelofibrosis, Fanconi's syndrome, or in patients known to have been exposed to myelotoxic agents or radiation.

Dosing Information

- **Aplastic anemia.** A more common high dose regimen used for aplastic anemia is 40 mg/kg/day for 4 days in combination with cyclosporine.[16] It is noted that when given over longer timeframes, such as 8 to 14 days, the incidence and severity of serum sickness is greater.[17] A recent study investigating eltrombopag added to standard immunosuppressive therapy used Atgam administered at a dose of 40 mg/kg on 4 consecutive days.[18] British guidelines also support this dosage.[3]
- **Acute Graft-Versus-Host Disease.** Atgam has been used for steroid-resistant acute graft-versus-host disease at a dose of 15 mg/kg per dose over 3 hours twice daily for 5 days for a total of 10 doses.[19]
- **Immunotherapy-related cardiovascular toxicity.** One case report has been published which summarized the use of equine ATG for the treatment of a patient with fulminant myocarditis secondary to Opdivo® (nivolumab intravenous infusion) therapy.[10] Equine ATG was administered according to the local protocol for acute cellular rejection and consisted of 500 mg on Day 1 and the dose was titrated by 250 mg daily to maintain a CD2/3 level of 50 – 100/µL for a total of 5 days of treatment. Resolution of ventricular arrhythmias occurred within 3 days of beginning ATG and cardiac enzymes normalized by Day 5. Cardiac biopsy 10 days after beginning ATG treatment revealed histologic improvement with significantly less myocyte necrosis.
- **Myelodysplastic syndrome.** In one study in patients with myelodysplastic syndrome to improve cytopenia, horse anti-thymocyte globulin was given at a dose of 15 mg/kg for 5 days.[20] Another older study dosed Atgam at 40 mg/kg/day intravenously for 4 days.[21]

Guidelines

The use of Atgam is supported in a number of clinical guidelines.[2-9]

- **Acute cellular rejection**: The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Care of Kidney Transplant Recipients (2009) recommends anti-thymocyte globulin (ATG) as a treatment option for induction therapy, given prior to, at the time of, or immediately after transplant.[2] The KDIGO guidelines recommend ATG for the treatment of

acute cellular rejection unresponsive to corticosteroids, recurrent acute cellular rejection, and for acute antibody-mediated rejection.

- **Aplastic anemia**: The British Society of Haematology guidelines for the diagnosis and management of aplastic anemia (2024) recommend anti-thymocyte globulin (ATG) [horse ATG {i.e., Atgam} is the preferred source] plus cyclosporine for the first-line treatment of patients with non-severe aplastic anemia (also known as moderate aplastic anemia) who are transfusion dependent, bleeding, encountering infections, or for lifestyle.[3] ATG with cyclosporine and eltrombopag is indicated in severe or very severe aplastic anemia. Generally, patients under 40 years of age would be assessed for the availability of an HLA-matched sibling donor prior to ATG. A second course of ATG may be indicated for failure to respond or relapse after a first course. For pediatric patients, the use of a matched sibling donor stem cell transplant is first line therapy for severe aplastic anemia.[4] ATG and cyclosporine or recommended for patients with an available sibling match. In some instances, a matched unrelated donor stem cell transplant may be a reasonable alternative to ATG plus cyclosporine. The results of additional clinical trials are pending. In addition, Atgam is included in conditioning regimens for bone marrow transplantation.[5]
- National Comprehensive Cancer Network (NCCN) guidelines:[6-9]
  - **Graft-vs-host disease:** The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines (version 2.2024 – August 30, 2024) recommend ATG as additional therapy in conjunction with corticosteroids for the management of acute steroid-refractory disease.[7,9]
  - **Hematopoietic Stem Cell Transplantation:** The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines (version 2.2024 – August 30, 2024) also note that ATG can be used for conditioning as part of a reduced-intensity regimen in combination with cladribine and busulfan.[7,9]
  - **Immunotherapy-related toxicity:** The NCCN Guidelines for the Management of Immunotherapy-Related Toxicities (version 1.2025 – December 20, 2024), recommend ATG as additional treatment for life-threatening cardiac immune-related adverse events (mycarditis) if there is no improvement within 24 to 48 hours of starting high-dose methylprednisolone.[6,7] ATG can also be considered for elevated liver transaminases if there is worsening or no improvement after use with corticosteroids, such as prednisone or methylprednisolone. ATG can also be given for Grade 4 hemolytic anemia in the management of immune checkpoint inhibitor-related toxicities.[6]
  - **Myelodysplastic syndrome:** The NCCN Clinical Practice Guidelines (version 1.2025 – November 15, 2024) recommend ATG as a treatment option for the management of lower risk disease.[7,8] Treatment with ATG alone or in combination with cyclosporine and/or Promacta® (eltrombopag olamine tablets) is recommended for select patients with clinically relevant thrombocytopenia or neutropenia; or for select patients with symptomatic anemia.

Other Uses With Supportive Evidence

- **Induction Therapy.** Atgam has been utilized as a component of induction therapy for heart and lung transplantation.[11-15]
- **Graft-vs-host disease (prevention).** A report from the European Society for Blood and Marrow Transplantation working group (2024) propose that the combination of ATG and post-transplant cyclophosphamide is superior to either monotherapy for graft-vs-host disease prophylaxis.[22]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Atgam. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if

the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Atgam as well as the monitoring required for adverse events and long-term efficacy, approval requires Atgam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Atgam is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Allograft Rejection in Solid Organ Transplant.** Approve for 1 month if the patient meets the following (A and B):
   - **A)** Patient meets ONE of the following (i or ii):
     - **i.** Atgam is used for induction therapy, prior to, at the time of, or immediately following transplantation; OR
     - **ii.** Atgam is used for the treatment of acute rejection; AND
   - **B)** The medication is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   - **A)** Up to 15 mg/kg administered intravenously daily for up to 14 days with an additional alternate-day therapy up to a total of 21 doses, if needed; OR
   - **B)** The dosing regimen is based on a transplant center's protocol.

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2. **Aplastic Anemia.** Approve for 1 month if the patient meets the following (A and B):
   - **A)** Patient has moderate to severe disease; AND
   - **B)** The medication is prescribed by or in consultation with a hematologist or a physician who specializes in the treatment of aplastic anemia.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   - **A)** Up to 20 mg/kg administered intravenously daily for up to 14 days with an additional alternate-day therapy up to a total of 21 doses, if needed; OR
   - **B)** Up to 40 mg/kg intravenously daily for up to 4 consecutive days.
     Note: The course may be repeated, if needed.

Other Uses with Supportive Evidence

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3. **Hematopoietic Stem Cell Transplantation or Umbilical Cord Transplantation**. Approve for 1 month if the patient meets the following (A and B):
   - **A)** Atgam is used as part of a conditioning regimen beginning prior to hematopoietic stem cell transplantation or umbilical cord transplantation; AND

B) The medication is prescribed by or consultation with an oncologist or a physician who specializes in stem cell or umbilical cord transplantation.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 40 mg/kg administered intravenously daily as a single dose, or divided and given twice daily for up to 4 days; OR
B) The dosing regimen is based on a transplant center's protocol.

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4. Graft-Versus-Host Disease (Prevention or Treatment). Approve for 1 month if the medication is prescribed by or consultation with an oncologist or a physician who specializes in transplantation.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 40 mg/kg/day administered intravenously daily or twice daily for up to 10 doses; OR
B) The dosing regimen is based on a transplant center's protocol.

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5. Immune Checkpoint Inhibitor-Related Toxicities. Approve for 1 month if the patient meets the following (A, B, C, and D):
A) Patient has received at least one immune checkpoint inhibitor; AND
Note: Immune checkpoint inhibitors include Opdivo (nivolumab intravenous infusion), Keytruda (pembrolizumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Libtayo (cemiplimab intravenous infusion), Jemperli (dostarlimab intravenous infusion).
B) Patient meets ONE of the following (i, ii, or iii):
i. Patient has cardiac immune-related adverse events; OR
Note: Examples of cardiac immune-related adverse events are myocarditis, pericarditis, arrhythmias, impaired ventricular function, large vessel vasculitis.
ii. Patient has elevated liver enzymes or toxic liver disease; OR
iii. Patient has hemolytic anemia; AND
C) Patient has not improved after therapy with corticosteroids; AND
Note: Examples of corticosteroids include prednisone, dexamethasone, methylprednisolone.
D) The medication is prescribed by or consultation with a cardiologist, oncologist, gastroenterologist, immunologist, or a physician who specializes in the treatment of immune checkpoint inhibitor-related toxicity.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 15 mg/kg administered intravenously daily for 14 days with an additional alternate-day therapy up to a total of 21 doses, if needed; OR
B) Up to 30 mg/kg/day administered intravenously.

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6. Myelodysplastic Syndrome. Approve for 1 month if the patient meets the following (A and B):
A) Patient has lower risk disease; AND
Note: Lower risk disease is defined as International Prognostic Scoring System (IPSS) risk of low or intermediate-1; IPSS-Revised (IPSS-R) risk of very low, low, or intermediate; IPSS-Molecular (IPSS-M) risk of very low, low, moderate low. Other risk stratification models may also be used

(e.g., the MD Anderson Cancer Center or the World Health Organization Prognostic Scoring System).

B) The medication is prescribed by or in consultation with an oncologist or a physician who specializes in the treatment of myelodysplastic syndromes.

Dosing. Approve ONE of the following dosing regimens (A or B)

A) Up to 40 mg/kg/day administered intravenously for up to 4 days; OR

B) Up to 15 mg/kg administered intravenously daily for 5 days

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Atgam is not recommended in the following situations.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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14. Mullen JC, Kuurstra EJ, Oreopoulos A, et al. A randomized controlled trial of daclizumab versus anti-thymocyte globulin induction for heart transplantation. *Transplant Res*. 2014;3:14.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Allograft Rejection in Solid Organ Transplant**. Updated dosing to up to 15 mg/kg administered intravenously daily for up to 14 days with additional alternate-day therapy up to a total of 21 doses, if needed; previously was up to 15 mg/kg administered intravenously daily for up to 14 days AND up to seven additional doses can be administered intravenously every other day for a maximum total of 21 doses in 28 days. Added a dosing regimen based on a transplant center's protocol. **Aplastic Anemia**. Removed the requirement that the patient is unsuitable for bone marrow transplantation. Added a dosing regimen of up to 40 mg/kg intravenously daily for up to 4 consecutive days. **Hematopoietic Stem Cell Transplantation or Umbilical Cord Transplantation**. Updated condition of approval, previously was Allogeneic Hematopoietic Stem Cell Transplantation. Removed allogeneic wording and added umbilical cord transplantation wording throughout the criteria. Added a dosing regimen based on a transplant center's protocol. **Graft-Versus-Host Disease**. Removed 'allogeneic hematopoietic stem cell' wording from prescriber's or consultant prescriber's specialty. Added 'daily or twice daily' wording to the dosing regimen of 40 mg/kg/day. Added a dosing regimen based on a transplant center's protocol. **Immune Checkpoint Inhibitor-Related Toxicities**. Added additional examples of immune checkpoint inhibitors. Added option for approval that a patient has elevated liver enzymes or toxic liver disease. The option for approval that the patient has life-threatening myocarditis, pericarditis, arrhythmias, impaired ventricular function criterion was updated to patient has cardiac immune-related adverse events and examples of these events were listed in a note. The requirement that the patient has not improved within 24 hours of starting pulse dose methylprednisolone was updated to patient has not improved after therapy with corticosteroids and examples of corticosteroids were listed in a note. Gastroenterologist was added to the list of prescribers or consultant prescribers. Updated dosing to up to 15 mg/kg administered intravenously daily for 14 days with an additional alternate-day therapy up to a total of 21 doses, if needed; previously was up to 15 mg/kg administered intravenously daily for 14 days and up to seven additional doses can be administered intravenously every other day for maximum total of 21 doses in 28 days. Added a new dosing regimen of up to 30 mg/kg/day administered intravenously. **Myelodysplastic Syndrome**. Added International Prognostic Scoring System-Molecular risk of very low, low, moderate low to the note. Additionally, added in the note that other risk stratification models may also be used (e.g., the MD Anderson Cancer Center or the World Health Organization Prognostic Scoring System). Removed the following requirement: Patient has one of the following according to the prescriber: (i) Clinically relevant thrombocytopenia (ii) Clinically relevant neutropenia (iii) Increased marrow blasts (iv) Symptomatic anemia. A physician who specializes in the treatment of myelodysplastic syndromes was added to the list of prescribers or consultant prescribers. Added a new dosing regimen of up to 15 mg/kg administered intravenously daily for 5 days.	01/03/2024
Annual Revision	**Aplastic Anemia.** Added the following note to dosing B) Up to 40 mg/kg intravenously daily for up to 4 consecutive days: The course may be repeated, if needed.	01/22/2025

	Graft-Versus-Host Disease (Prevention or Treatment). Updated condition of approval, previously was Graft-Versus-Host Disease. Removed criteria related to acute disease and refractory or resistant to corticosteroid therapy. **Immune Checkpoint Inhibitor-Related Toxicities.** Added hemolytic anemia as one of the immune checkpoint inhibitor-related toxicities. Also added immunologist as one of the prescriber's specialties.	