

## Lymphocyte immune globulin, anti-thymocyte globulin [equine] (Atgam®)

### Medicare Advantage Medical Policy #MA-201

Original Effective Date: 04/01/2026

Current Effective Date: 04/01/2026

<b>Policy:</b>	<b>Immune Globulin – Atgam Utilization Management Medical Policy</b> <ul style="list-style-type: none"><li>Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] intravenous infusion – Pfizer)</li></ul>
<b>DATE:</b>	03/12/2025
<b>Applicable Lines of Business:</b>	Medicare Advantage - Medical
<b>Applicable States:</b>	All States
<b>Applicable NCDs, LCDs, and/or LCAs</b>	NCD 260.7

## SUMMARY OF EVIDENCE

Atgam, an immune globulin, is indicated for the following uses:<sup>1</sup>

- 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.<sup>16</sup> It is noted that when given over longer timeframes, such as 8 to 14 days, the incidence and severity of serum sickness is greater.<sup>17</sup> A recent study investigating eltrombopag added to standard immunosuppressive therapy used Atgam administered at a dose of 40 mg/kg on 4 consecutive days.<sup>18</sup> British guidelines also support this dosage.<sup>3</sup>
- 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.<sup>19</sup>
- 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.<sup>10</sup> 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.<sup>20</sup> Another older study dosed Atgam at 40 mg/kg/day intravenously for 4 days.<sup>21</sup>

## Guidelines

The use of Atgam is supported in a number of clinical guidelines.<sup>2-9</sup>

- **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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup>
- National Comprehensive Cancer Network (NCCN) guidelines:<sup>6-9</sup>
  - **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.<sup>7,9</sup>
  - **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.<sup>7,9</sup>
  - **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 (myocarditis) if there is no improvement within 24 to 48 hours of starting high-dose methylprednisolone.<sup>6,7</sup> 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.<sup>6</sup>
  - **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.<sup>7,8</sup> 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.<sup>11-15</sup>

**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.<sup>22</sup>

## ANALYSIS OF EVIDENCE

The information provided in the summary of evidence is supported by labeled indications, CMS-approved compendia, published clinical literature, clinical practice guidelines, and/or applicable National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs). Refer to the Sources of Information section of this policy for additional information.

## 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 indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. 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.

This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the Sources of Information section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Sources of Information section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage.

**Note:** Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles.

*Indications with a ^ below are referenced in both the corresponding Standard Medical Utilization Management Internal Policy AND applicable National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and/or Local Coverage Articles (LCAs). Coverage criteria for these indications may be internally developed and/or referenced in applicable NCDs, LCDs, and/or LCAs. For these indications, internally developed coverage criteria is denoted throughout the policy in the following manner: 1) IC-L (internal criteria supported by the labeled indication), 2) IC-COMP (internal criteria supported by CMS-approved compendia), 3) IC-ISGP (internal criteria intended to interpret or supplement general provisions outlined in applicable NCDs, LCDs, and/or LCAs), or 4) IC-EC (internal criteria intended to expand coverage beyond the coverage outlined in applicable NCDs, LCDs, and/or LCAs). For these indications, coverage criteria that is NOT denoted with one of the above indicators is referenced in*

*applicable NCDs, LCDs, and/or LCAs. Additional information supporting the rationale for determination of internal coverage criteria can be found via the Sources of Information section.*

*Indications with a @ below are referenced in the corresponding Standard Medical Utilization Management Internal Policy, but are NOT directly referenced in applicable National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and/or Local Coverage Articles (LCAs). Coverage criteria for these indications is internally developed. These indications and their respective coverage criteria represent expanded coverage beyond the coverage outlined in applicable NCDs, LCDs, and/or LCAs.*

*Indications with a # below are supported and referenced in applicable National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and/or Local Coverage Articles (LCAs), but are NOT directly referenced in the corresponding Standard Medical Utilization Management Internal Policy. Coverage criteria for these indications is referenced in applicable NCDs, LCDs, and/or LCAs.*

## **RECOMMENDED AUTHORIZATION CRITERIA**

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

### **FDA-Approved Indications**

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#### **1. Allograft Rejection in Solid Organ Transplant. ^**

**Criteria.** Approve for 1 month if the patient meets the following criteria (A or B):

- A) Atgam is used for induction therapy, prior to, at the time of, or immediately following transplantation; <sup>IC-EC</sup> OR
- B) Atgam is used for the treatment of acute rejection. <sup>IC-L</sup>

**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. @**

**Criteria.** Approve for 1 month if the patient has moderate to severe disease.

**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.

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### **Other Uses with Supportive Evidence**

#### **3. Myelodysplastic Syndrome. @**

**Criteria.** Approve for 1 month if the patient has lower risk disease.

**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).

**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

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#### 4. Immune Checkpoint Inhibitor-Related Toxicities. <sup>®</sup>

**Criteria.** Approve for 1 month if the patient meets the following criteria (A, B, and C):

- A) The patient has received at least one immune checkpoint inhibitor; AND
  - Note: Immune checkpoint inhibitors include Opdivo® (nivolumab injection for intravenous use), Keytruda® (pembrolizumab injection for intravenous use), Tecentriq® (atezolizumab injection for intravenous use), Bavencio® (avelumab injection for intravenous use), Imfinzi® (durvalumab injection for intravenous use), Yervoy® (ipilimumab injection for intravenous use), 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.
  - Note: Examples of corticosteroids include prednisone, dexamethasone, methylprednisolone.

**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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#### 5. Hematopoietic Stem Cell Transplantation or Umbilical Cord Transplantation. <sup>®</sup>

**Criteria.** Approve for 1 month if Atgam is used as part of a conditioning regimen beginning prior to hematopoietic stem cell transplantation 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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#### 6. Graft-vs.-Host Disease (Prevention or Treatment). <sup>®</sup>

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**Criteria.** Approve for 1 month.

**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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## 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.

## SOURCES OF INFORMATION

1. Atgam® intravenous infusion [prescribing information]. New York, NY: Pfizer; September 2023.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guidelines for the care of kidney transplant recipients. *Am J Transplant.* 2009;9:S1-S157.
3. Kulasekararaj A, Cavenagh J, Dokal I, et al. Guidelines for the diagnosis and management of adult aplastic anaemia: A British Society for Haematology Guideline. *Br J Haematol.* 2024;204:784-804.
4. Shimano KA, Rothman JA, Allen S, et al. Treatment of newly diagnosed severe aplastic anemia in children: Evidence-based recommendations. *Pediatr Blood Cancer.* 2024;71(8):e31070.
5. Peslak SA, Olson T, Babushok DV. Diagnosis and treatment of aplastic anemia. *Curr Treat Options Oncol.* 2017;18:70.
6. The NCCN Management of Immunotherapy-Related Toxicities Clinical Practice Guidelines in Oncology (version 1.2025 – December 20, 2024). © 2024 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed January 10, 2025.
7. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on January 10, 2025. Search term: antithymocyte globulin, equine.
8. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 1.2025 – November 15, 2024). © 2024 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed January 10, 2025.
9. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines in Oncology (version 2.2024 – August 30, 2024). © 2024 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed January 10, 2025.
10. Tay RY, Blackley E, McLean C, et al. Successful use of equine anti-thymocyte globulin (ATGAM) for fulminant myocarditis secondary to nivolumab therapy. *Br J Cancer.* 2017;117:921-924.
11. Ailawadi G, Smith PW, Oka T, et al. Effects of induction immunosuppression regimen on acute rejection, bronchiolitis obliterans, and survival after lung transplantation. *J Thorac Cardiovasc Surg.* 2008;135:594-602.
12. Hayes D, Kirkby S, Wehr AM, et al. A contemporary analysis of induction immunosuppression in pediatric lung transplant recipients. *Transpl Int.* 2014;27:211-218.
13. Scheffert JL, Raza K. Immunosuppression in lung transplantation. *J Thorac Dis.* 2014;6:1039-1053.
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.
15. MacDonald PS, Mundy J, Keogh AM, et al. A prospective randomized study of prophylactic OKT3 versus equine antithymocyte globulin after heart transplantation – increased morbidity with OKT3. *Transplantation.* 1993;55:110-116.
16. Rosenfeld SJ, Kimball J, Vining D, et al. Intensive immunosuppression with antithymocyte globulin and cyclosporine as treatment for severe acquired aplastic anemia. *Blood.* 1995;85(11): 3058-3065.
17. Aplastic anemia: management in adults. UpToDate 2025. Available at: [Evidence-Based Clinical Decision Support System | UpToDate | Wolters Kluwer](https://www.uptodate.com). Accessed on January 10, 2025.
18. Peffault de Latour R, Kulasekararaj A, Iacobelli S, et al. Eltrombopag added to immunosuppression in severe aplastic anemia. *N Engl J Med.* 2022;386(1):11-23.
19. MacMillan ML, Weisdorf DF, Davies SM, et al. Early antithymocyte globulin therapy improves survival in patients with steroid-resistant acute graft-versus-host disease. *Biol Blood Marrow Transplant.* 2002;8:40-46.
20. Passweg JR, Aristoteles AN, Giagounidis MS, et al. Immunosuppressive therapy for patients with myelodysplastic syndrome: A prospective randomized multicenter Phase III trial comparing antithymocyte globulin plus cyclosporine with best supportive care. *J Clin Oncol.* 2010;29(3):303-9.

21. Molldrem JJ, Caples M, Mavroudis D, et al. Antithymocyte globulin for patients with myelodysplastic syndrome. *Br J Haematol.* 1997;99(3):699-705.
22. Bazarbachi A, Labopin M, Raiola A, et al. Posttransplant cyclophosphamide versus anti-thymocyte globulin versus combination for graft-versus-host disease prevention in haploidentical transplantation for adult acute myeloid leukemia: A report from the European Society of Blood and Marrow Transplantation Acute Leukemia Working Party. *Cancer.* 2024;130(18):3123-3136.
23. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for Lymphocyte Immune Globulin, Anti-Thymocyte Globulin (Equine) (260.7). [Version Number 1, Effective date: "not posted." Accessed March 12, 2025].

## HISTORY

Type of Revision	Summary of Changes	Date
Policy created	New Medicare Advantage Medical Policy	02/05/2020
Policy revision	Added the following to the Policy Statement <u>Note</u> : Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles."	04/03/2020
Policy review	No criteria changes.	12/08/2021
Policy review	No criteria changes.	12/14/2022
Policy revision	<b>Allograft Rejection in Solid Organ Transplant.</b> 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. <b>Aplastic Anemia.</b> 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. <b>Hematopoietic Stem Cell Transplantation or Umbilical Cord Transplantation.</b> 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. <b>Graft-Versus-Host Disease.</b> 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. <b>Immune Checkpoint Inhibitor-Related Toxicities.</b> 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. Updated dosing to up to 15 mg/kg	02/20/2024

	<p>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.</p> <p><b>Myelodysplastic Syndrome.</b> 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. Added a new dosing regimen of up to 15 mg/kg administered intravenously daily for 5 days.</p>	
Policy revision	<p><b>Aplastic Anemia.</b> 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.</p> <p><b>Graft-Versus-Host Disease (Prevention or Treatment).</b> Updated condition of approval, previously was Graft-Versus-Host Disease. Removed criteria related to acute disease and refractory or resistant to corticosteroid therapy.</p> <p><b>Immune Checkpoint Inhibitor-Related Toxicities.</b> Added hemolytic anemia as one of the immune checkpoint inhibitor-related toxicities. Also added immunologist as one of the prescriber's specialties.</p> <p>Revision based on commercial policy update.</p>	01/30/2025
Policy revision	No criteria changes. Formatting and notation updates.	03/12/2025

*This policy was prepared and managed by CareContinuum and henceforth adopted by Blue Advantage effective 04/01/2026. Reviews are to be executed on behalf of Blue Advantage in accordance with applicable guidelines.*