



# CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Lymphocyte Immune Globulin,  
Anti-Thymocyte Globulin  
[Equine] (Atgam®)**

**Effective Date..... 12/15/2008  
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Coverage Policy Number ..... 5004**

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## Hyperlink to Related Coverage Policies

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

## Coverage Policy

**CIGNA HealthCare covers lymphocyte immune globulin, anti-thymocyte globulin [equine] (Atgam®) as medically necessary for ANY of the following indications:**

- management of allograft rejection in renal transplant patients
- treatment of moderate-to-severe aplastic anemia in patients who are unsuitable for bone marrow transplantation
- use as an immunosuppressant in liver, bone-marrow, heart, skin, and other organ transplants

## General Background

### FDA Approved Indications

Renal Transplantation - Atgam sterile solution is indicated for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection, it increases the frequency of resolution of the acute rejection episode. The drug has also been administered as an adjunct to other immunosuppressive therapy to delay the onset of the first rejection episode.

Aplastic Anemia – Atgam is indicated for the treatment of moderate to severe aplastic anemia in patients who are unsuitable for bone marrow transplantation.

Lymphocyte immune globulin, Anti-thymocyte globulin (ATG [equine]) is an immunoglobulin-containing immunosuppressive agent used in both the management of transplant rejection and the treatment of aplastic anemia. ATG [equine] is a sterile solution of primarily monomeric Immunoglobulin G (IgG) derived from equine sources immunized with human thymus lymphocytes.

ATG [equine] mainly exhibits immunosuppressive activity inhibiting cell-mediated immune responses such as allograft rejection and delayed hypersensitivity reactions. Antilymphocyte preparations may also have activity inhibiting humoral immune responses. The exact mechanism(s) of immunosuppressive action of ATG [equine], though not fully elucidated, may involve elimination of antigen-reactive T cells (T-lymphocytes) in peripheral blood and/or alteration of T-cell function. The effects of antilymphocyte preparations, including ATG [equine], on T cells are variable and complex, and may depend on the condition being treated such as allograft rejection or aplastic anemia.

In addition to its antilymphocytic activity, ATG [equine] preparations contain antibodies to blood components resulting in leukopenia, thrombocytopenia, or hemolysis. The effects of ATG [equine] on bone marrow cells are variable and complex and remain to be fully elucidated, and it may have antineoplastic activity against certain malignant lymphomas.

Peak plasma levels of equine Immunoglobulin G (IgG) following intravenous (IV) administration of ATG [equine] vary, depending on the patient's individual processing of foreign IgG. After IV infusion of ATG [equine] 10 mg/kg daily for five days, mean peak plasma levels of equine IgG averaged  $727 \pm 310$  mcg/mL. ATG [equine] is poorly distributed into lymphoid tissues, including spleen and lymph nodes. The plasma half-life of equine IgG reportedly averages about six days (range: 1.5–12 days). Approximately 1% of a dose of ATG [equine] is excreted in urine, principally as unchanged equine IgG.

ATG [equine] is used for the treatment and prevention of acute rejection in renal allograft recipients, usually as an adjunct to other immunosuppressive therapy such as azathioprine, corticosteroids, or graft irradiation. Immunosuppressive therapy that includes ATG [equine] generally appears to reverse initial episodes of acute rejection an average of 2–3 days earlier than immunosuppressive therapy that does not include ATG [equine]. Adjunctive therapy with ATG [equine] for the treatment of initial episodes of acute rejection also appears to reduce the incidence of recurrent rejection and is generally associated with a reduced cumulative corticosteroid dosage in the post-transplantation period. Immunosuppressive therapy that includes ATG [equine] for the treatment of acute rejection also appears to increase long-term graft survival rates compared with immunosuppressive therapy that does not include ATG [equine].

Prophylactic immunosuppressive therapy that includes ATG [equine] may reduce the incidence and delay the onset of initial episodes of acute rejection, but improved renal allograft survival with such therapy has not been consistently demonstrated. Further study is needed to determine the optimum dosage and duration of prophylactic ATG [equine] therapy. Many factors, including variability among individual lots of ATG [equine], the number of patients studied and type of allograft received, and low dosage regimens used in early studies have made evaluation difficult, and the effect of prophylactic ATG [equine] on long-term graft survival remains to be clearly determined. Prophylactic immunosuppressive therapy that includes ATG [equine] does not appear to increase long-term patient survival rates compared to immunosuppressive therapy that does not include ATG [equine].

ATG [equine] is used for the treatment of moderate to severe aplastic anemia in patients not considered suitable candidates for bone marrow transplantation. When combined with conventional supportive therapy in patients with aplastic anemia, ATG [equine] may induce a partial or complete hematologic remission. In a well-controlled study, ATG [equine] produced a substantially higher hematologic response rate (as determined by sustained increases in peripheral blood cell counts and decreased transfusion requirements) at three months when compared with conventional supportive therapy alone. The usefulness of ATG [equine] 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 myelofibrosis, Fanconi's syndrome, neoplastic disease, storage disease, or in patients known to have been exposed to myelotoxic agents or radiation.

Fever and chills are the most common side effects of ATG [equine], occurring in 51% and 16% of patients, respectively. Febrile reactions will decrease in severity after the first few doses and are

managed with antipyretics, antihistamines, corticosteroids, or a combination of these agents. Leukopenia and thrombocytopenia occur in 14 and 30% of patients, respectively, receiving ATG [equine] or potentially more frequently in patients with aplastic anemia. The effects are generally transient and may respond to dosage reduction without platelet transfusion. Anaphylaxis, though rare, could occur at any time during treatment. Serum sickness reactions have been reported in as many as 10% of renal allograft recipients receiving ATG [equine]; however, this may be confounded by the difficulty in diagnosing serum sickness reactions in these patients.

ATG [equine] should not be administered to patients who have had severe systemic reactions (e.g., generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis) during prior administration of ATG [equine] or any other equine gamma globulin preparation. Before the first dose of ATG [equine], patients should undergo intradermal sensitivity testing to look for a local allergic reaction. However, allergic reactions such as anaphylaxis have occurred even in patients whose skin test is negative. ATG [equine] should only be administered by physicians experienced in immunosuppressive therapy in the treatment of renal transplant or aplastic anemia patients. Additionally, ATG [equine] should only be administered to patients in facilities equipped and staffed with adequate laboratory and supportive medical resources. Immunosuppression with ATG [equine], which may be combined with other immunosuppressive therapy (e.g., corticosteroids, antimetabolites), may result in increased susceptibility to infection (e.g., with cytomegalovirus); patients receiving ATG [equine] should be closely observed for signs of leukopenia, thrombocytopenia, and/or concurrent infection. Treatment with ATG [equine] should be discontinued if any of the following occurs: symptoms of anaphylaxis, severe and unremitting thrombocytopenia in renal transplant patients, or severe and unremitting leukopenia in renal transplant patients. Use of ATG [equine] may carry a risk of transmitting infectious agents such as viruses and the Creutzfeldt-Jakob disease agent because the product is made using equine and human blood components.

ATG [equine] is administered by slow IV infusion, and intradermal sensitivity testing is recommended in all individuals prior to administration of the initial dose.

### **Renal Allograft Recipients**

Dosing is based on weight and dosages of ATG [equine] have ranged from 10–30 mg/kg daily in adults and 5–25 mg/kg daily in a limited number of children. For the prevention of renal allograft rejection, it is recommended that ATG [equine] be given in a fixed dosage of 15 mg/kg daily for 14 days, then every other day for 14 days for a total of 21 doses in 28 days. The first dose of ATG [equine] should be administered within 24 hours before or after the transplant. For the treatment of acute renal allograft rejection, the recommended dosage of ATG [equine] is 10–15 mg/kg daily for 14 days; if necessary, additional alternate-day therapy up to a total of 21 doses can be given. Initiation of therapy with ATG [equine] can be delayed until the first rejection episode is diagnosed.

### **Aplastic Anemia**

The recommended dosage of ATG [equine] is 10–20 mg/kg daily for 8–14 days; if necessary, additional alternate-day therapy up to a total of 21 doses can be administered. Because thrombocytopenia can occur in patients receiving ATG [equine] for the treatment of aplastic anemia, prophylactic platelet transfusions may be needed to maintain platelet counts at clinically acceptable levels during therapy with the drug.

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## **Coding/Billing Information**

**Note:** This section is not in use.

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## **References**

1. Drug Facts and Comparisons St. Louis, MO: Wolters Kluwer Health, Inc; 2004.

2. Klasco, RK, ed. DRUGDEX<sup>®</sup> System. Greenwood Village, CO: Thomson Micromedex; 2006.
3. McEvoy GK, ed. AHFS 2008 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2008.
4. Pfizer. Lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution (Atgam<sup>®</sup>) injection package insert. NY, NY: Pfizer, November 2005.

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## Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	7/15/2008	5004	Lymphocyte Immune Globulin, Anti-Thymocyte Globulin [Equine] (Atgam <sup>®</sup> )

Great-West Healthcare

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