

POLICY: Immune Globulin – Cytogam[®] (human cytomegalovirus immune globulin liquid – CSL Behring)

DATE REVIEWED: 12/04/2019

OVERVIEW

Cytogam[®] is an intravenous (IV) formulation consisting of human cytomegalovirus immune globulin.¹ It is an immunoglobulin (IG) G containing a standardized amount of antibody to cytomegalovirus (CMV) indicated for the prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas and heart. In transplants of these organs other than kidney from CMV seropositive donors into seronegative recipients, prophylactic Cytogam should be considered in combination with ganciclovir. The maximum recommended dosage is 150 mg Ig/kg per infusion with a total of 7 infusions. The first infusion should be within 72 hours of transplant followed by infusions done at Week 2, 4, 6, 8, 12, and 16 post-transplant.

Disease Overview

CMV is a herpesvirus, which is spread by direct contact with infectious body fluids, including saliva, tears, and urine.² It is a common infection in the US, with approximately 50% of the population seropositive for CMV. The initial infection may be asymptomatic or follow a self-limiting course; this is followed by life-long latency where the virus resides in cells without causing damage or clinical illness. Intermittent shedding of virus may occur without any signs or symptoms. In patients who are immunocompromised, viral reactivation may lead to symptomatic disease that may cause significant morbidity and mortality. In the case of persons who may be exposed to CMV, Cytogam can raise the relevant antibodies to levels sufficient to attenuate or reduce the incidence of serious CMV disease.¹

Clinical Efficacy

Clinical studies with Cytogam have shown a 50% reduction in primary CMV disease in renal transplant patients and a 56% reduction in serious CMV disease in liver transplant patients.¹ Cytogam prophylaxis was associated with increased survival in liver transplant recipients. Other studies of combined prophylaxis with Cytogam and ganciclovir have shown reductions in the incidence of serious CMV-associated disease in CMV-seronegative recipients of CMV seropositive organs below that expected from one drug alone.

Guidelines

International consensus guidelines (2018) are published recommendations for the management of CMV in solid organ transplantation.³ The multidisciplinary of experts identify CMV management for prevention, treatment, diagnostics, immunology, drug resistance, and pediatric use. A considerable amount of posttransplant patients develop hypogammaglobulinemia with severe cases showing a significant increased risk of CMV disease. Replacement with Cytogam may prevent CMV disease. The guidelines state Cytogam is recommended for use in specific circumstances, especially in thoracic organs, when used in combination with antivirals. Ganciclovir and valganciclovir are antivirals mentioned for use in universal prophylaxis or preemptive therapies for CMV prevention in solid organ transplant patients. Drug-resistant CMV should be considered when there is persistent or recurrent CMV present during prolonged antiviral therapy. Cytogam is considered an alternative therapy to drug-resistant CMV that may improve antiviral host defenses. The guidelines did note, given the lack of controlled trial data there is not a defined best practice for alternative therapy with drug-resistant CMV. Management strategies in pediatric solid organ transplant patients are similar to the adult

recommendations. Cytogam is sometimes used in combination with antiviral prophylactic or preemptive therapy to prevent CMV.

Other Uses With Supportive Evidence

Maternal transmission of CMV to the fetus may occur at any gestation, leading to congenital CMV.⁴ A study of 304 pregnant women with a primary CMV infection were offered CMV IG. In the therapy group, 157 women were treated with an average of 2 doses (range 1 to 6) of CMV IG low dose (100 mg/kg/infusion given once every month) or high dose (200 mg/kg/infusion given once every 2 weeks for up to 3 doses if needed). The trial demonstrated a 1.8 fold (30% vs. 56%) increase in the rate of congenital infection in patients without CMV IG ($P < 0.0001$), along with long-term sequelae ($P < 0.001$).

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Cytogam. 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. 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 Cytogam as well as the monitoring required for adverse events and long-term efficacy, approval requires Cytogam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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- 1. Prophylaxis of Cytomegalovirus Associated with Solid Organ Transplant.** Approve for 4 months if the medication is prescribed by or in consultation with a physician affiliated with a transplant center, hematologist, or an infectious disease physician.

Dosing. Approve the following dosing regimen (A and B):

- A) The dose is ≤ 150 mg/kg; AND
- B) The dose is given no more frequently than every 2 weeks.

Other Uses with Supportive Evidence

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- 2. Cytomegalovirus Associated with Pregnancy.** Approve for 6 months if the medication is prescribed by or in consultation with an infectious disease physician or an obstetrician-gynecologist.

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

- A) The dose meets both of the following criteria (i and ii):
 - i. The dose is ≤ 100 mg/kg; AND
 - ii. The dose is given no more frequently than every month; OR

- B)** The dose meets both of the following criteria (i and ii):
- i.** The dose is ≤ 200 mg/kg; AND
 - ii.** The amount of doses given is ≤ 3 doses total.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cytogam has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

- 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

1. Cytogam [prescribing information]. Kankakee, IL: CSL Bering; May 2018.
2. Centers for Disease Control and Prevention. Cytomegalovirus (CMV) and congenital CMV infection. US Health and Human Services Web site. Updated May 31, 2019. Available at: <https://www.cdc.gov/cmvc/clinical/features.html>. Accessed on October 3, 2019.
3. Kotton C, Kumar D, Caliendo A, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*. 2018;102:900-931.
4. Swanson E, Schleiss M. Congenital cytomegalovirus infection: New prospects for prevention and therapy. *Pediatric Clinics of North America*. 2013;60:335-349.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	12/04/2019