Cytogam® Prior Authorization & Appeal Support Packet

How to Use This Resource

This non-promotional support packet has been developed by Medical Affairs to assist healthcare providers and transplant centers in preparing prior authorization (PA) submissions, medical necessity letters, and appeal documentation for Cytogam® (CMV-IGIV).

It is designed as a reference tool that clinicians may copy, edit, and adapt based on the individual patient's clinical circumstances and the requirements of the health plan.

Purpose of this Packet

This resource is intended to help clinical teams by providing:

- Clinical justification letter templates (Prophylaxis)
- Relevant clinical evidence supporting Cytogam® use
- Package insert excerpts (indication, dosing, administration)
- Coverage support materials, including guideline references and peer-reviewed publications
- Key clinical data on CMV risk, outcomes, and CMVIG utility across organ transplant populations

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How Providers Should Use This Packet

1. Open the template letter in this packet.
2. Copy and paste the text into the institution's letterhead or EMR communication tool.
3. Edit the content to reflect patient-specific information, payer criteria, and transplant center protocols.
4. Attach supporting materials (included in this packet) if the payer requires evidence or references.
5. Submit through the payer's preferred PA or appeal channel.

Note: All templates are intentionally written to be modifiable by the healthcare provider and must not be submitted as-is.

Intended Audience

- Transplant physicians
- Infectious disease specialists
- Transplant pharmacists
- Transplant coordinators / nurse coordinators
- PA specialists, reimbursement teams, and case managers

Important Compliance Note

This packet is non-promotional and is provided only on request to support clinicians in preparing payer documentation.
It is not intended to dictate clinical practice or payer engagement strategies.
Final submitted letters must be authored and signed by the treating provider.

Contents

Clinical Justification Letter Templates for the HCP to tailor and submit

Prophylaxis Justification Letter

Date: XX/XX/XXXX

RE: Prior Authorization Request for Cytogam® (CMV-IGIV)

Patient information: insert as requested

To [health plan/payer],

I am requesting prior authorization for Cytogam® (CMV-IGIV) for my patient who is a [insert organ] transplant recipient at high risk for cytomegalovirus (CMV) disease. This patient meets criteria for adjunctive CMV prophylaxis due to:

- CMV donor/recipient serostatus mismatch (CMV D+/R-)
- Receipt of lymphocyte-depleting therapy
- History of prior viremia
- Increased net state of immunosuppression
- Inability to tolerate full-dose anti-viral prophylaxis (due to myelotoxicity)
- Renal dysfunction
- Immune senescence
- Short telomere syndrome (STS)
- CMV-specific immune defects due to belatacept-based immunosuppression.

Cytogam has demonstrated safety and efficacy in reducing the incidence and severity of CMV disease in high-risk solid organ transplant populations. Its use is supported by the 2024 CMV Consensus Guidelines and peer-reviewed clinical literature.

Medical Necessity:

Without adjunctive CMV immunoglobulin therapy, this patient faces increased risk of CMV reactivation, CMV disease, hospitalization, graft dysfunction, and even graft loss. These outcomes are potentially preventable with Cytogam® administration.

Thank you for your review and consideration.

Sincerely,

Provider Name, credential
Tite/institution
Signature

Package Insert: include a copy of the PI

Cytogam® is an intravenous immunoglobulin containing a standardized amount of antibody to CMV.

Indication and Usage:

Cytogam® is indicated for the prophylaxis of CMV disease associated with transplantation of the kidney, lung, liver, pancreas, and heart. In transplants of these organs other than the kidney from CMV seropositive donors into seronegative recipients, prophylactic CMV-IGIV should be considered in combination with ganciclovir.

Dosing and administration guide:

CYTOGAM dosing is based on body weight, and is administered within 72 hours after transplantation and every 2-4 weeks until 16 weeks after transplantation.

The maximum recommended total dosage per infusion is 150 mg Ig/kg, administered according to the following schedule:

	Type of Transplant				
	Kidney	Liver	Pancreas	Lung	Heart
Within 72 hours of transplant	150 mg/kg				
2 weeks post-transplant	100 mg/kg	150 mg/kg			
4 weeks post-transplant					
6 weeks post-transplant					
8 weeks post-transplant					
12 weeks post-transplant	50 mg/kg	100 mg/kg			
16 weeks post-transplant					

Coverage Support Materials

Recommended literature to provide clinical support for CMVIG, support the economic benefits of a product, and improve patient outcomes.

The goal:

- Demonstrate full value proposition for payers
- Assist with approval of and access to CMVIG via data support
- Provide context for payers to assist decision-making for approval of which patients can benefit from CMVIG.

CMVIG Meta-analysis:

- **Barten MJ, et al. Effectiveness of Prophylactic Human Cytomegalovirus Hyperimmunoglobulin in Preventing Cytomegalovirus Infection following Transplantation: A Systematic Review and Meta-Analysis. Life. 2022; 12 (361): 1-13. https://doi.org/10.3390/life12030361**

Summary: A meta-analysis of studies that analyzed the use of CMV-specific hyperimmunoglobulin (CMVIG) and the prophylactic effects on the infection rate of cytomegalovirus (CMV) in patients who have undergone a solid organ transplant (SOT)

Details:

- Includes data from 32 individual studies where patients received prophylactic or pre-emptive CMVIG regimen
- 26 studies included the use of Cytogam (human cytomegalovirus immunoglobulin [CMVIG]; FDA-approved) or Cytotect® (human cytomegalovirus immunoglobulin [CMVIG]); European Medicines Agency [EMA] approved)
- The meta-analysis did not summarize results specific to Cytogam only, as Cytogam results were pooled with those of Cytotect

Conclusion:

- In the 32 studies reviewed (CMVIG [n=1521] vs controls [n=1196]), prophylactic CMVIG was often associated with a lower risk of CMV infection in SOT recipients. Results suggest that prophylactic CMVIG treatment in patients undergoing solid organ transplantation may be beneficial, particularly in those at high risk of CMV infection or disease.

CMVIG and functional properties: Studies that demonstrate the difference in titers and functional properties of IVIG vs CMVIG

Auerbach T, et al. Comparative functional properties of CMV immune globulin vs. polyvalent IVIG against CMV and other viruses. Poster presented at: ISHLT 2025; Apr. 2025; Boston, MA.

Summary: Poster presentation of the functional properties of Kamada-produced CMVIG (since 2024) and commercially available IGIVs for CMV and other viruses

Conclusions:

- CMVIG demonstrated 4-fold higher CMV antibody titers as well as higher neutralization ability compared to commercial polyclonal IGIVs

Wang X, et al. Binding and neutralizing anti-cytomegalovirus activities in immune globulin products. Biologicals. 2017; 50: 35-41

Summary: This study compared anti-CMV antibody binding activity and avidity for lots of CMV-specific and polyclonal IVIG products available on the US market. Data revealed that anti-CMV activity was higher in CMVIG lots compared with polyclonal IVIG lots.

Conclusion:

- CMV-specific IG products exhibit higher CMV binding(at least >4 fold), and neutralizing activities (at least >2-3 fold) compared with polyclonal IVIG products

Germer M, et al. Functional properties of human cytomegalovirus hyperimmune globulin and standard immunoglobulin preparations. Ann Transplant. 2016; 21: 558-564.

Summary: The functionality of 2 CMVIG preparations (Cytotect® CP and Cytogam®) and 2 IVIg preparations was compared. CMVIG demonstrates a higher CMV antibody titer and viral neutralization titer. This correlation shows a more biologically relevant measure of efficacy vs. IVIG.

Conclusion:

- CMVIg antibody titers are 5-8-fold higher in Cytogam/Cytotect vs. polyclonal IVIG
- There does not appear to be any relevant distinctions between the Cytotect® CP and Cytogam® CMV-HIG products in terms of functional activity
- The CMV neutralization capacity of the polyclonal IVIg products was 4-fold lower than the CMV-specific products (1:64)

Use of CMVIG for CMV prophylaxis: (on label): *Heart and Lung:*

Kotton CN, et al. The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation. Transplantation 2025 Jul 1;109(7):1066-1110. (doi: 10.1097/TP.0000000000005374)

Summary: Given many recent advances in the field of CMV, under the auspices of The Transplantation Society, a panel of experts on CMV and SOT recipients convened in June 2024 in Montreal, Canada, to update the guidelines and published the fourth international consensus guidelines on CMV management

Conclusions:

- Some experts add CMVIG (Cytogam®) to CMV prophylaxis as an alternative approach for CMV prevention in high-risk or intermediate-risk thoracic and intestinal transplant recipients, as well as high-risk vascular composite allograft transplant recipients.
- CMVIG can be considered in combination with antiviral agents in specific circumstances, including thoracic organ transplantation, D+/R– serostatus, patients with prolonged neutropenia who are intolerant of ganciclovir, and severe IgG hypogammaglobulinemia
- The combination demonstrated reduced incidence of CMV disease and bronchiolitis obliterans syndrome (chronic rejection), with improved survival in a cohort of lung transplant recipients.

Banga N, et al. Long-term outcomes among lung transplant recipients with high-risk cytomegalovirus mismatch managed with a multimodality regimen. Clin Transplant. 2025; 39:370219. doi.org/10.1111/ctr.70219

Summary: Overall, this publication provides compelling recent data to support the potential benefit of CMVIG as part of a proactive, multimodal approach to CMV prevention in high-risk lung transplant recipients. The findings demonstrate that the D+/R- high-risk CMV mismatch recipients achieved comparable 1- and 3-year CLAD-free survival and 1,3, and 8-year overall survival to CMV non-high-risk groups, despite experiencing higher rates of viremia, elevated median viral loads, increased incidence of antiviral drug resistance, and a greater likelihood of end-organ involvement. These findings reinforce the potential value of incorporating immune augmentation with CMVIG alongside antiviral prophylaxis in CMV high-risk lung transplant recipients. While the protocol is resource-intensive, it was well tolerated, posed no safety concerns, and had a favorable impact on outcomes, supporting broader implementation in similar at-risk populations.

Lopez Garcia-Gallo C, et al. Cytomegalovirus immunoglobulin for prophylaxis and treatment of cytomegalovirus Infection in the (val)ganciclovir era: a single-center experience. Ann Transplant. 2015; 20: 661-666. (Lung Transplant •use of CMVIG with current AV Val/Ganciclovir)

Summary: retrospective study evaluating the effectiveness of anti-cytomegalovirus immunoglobulin (CMVIg) following lung transplantation in the era of Val/ganciclovir. CMV serologic status of donor and recipient, time to first CMV viral replication, CMV disease, acute and chronic rejection, non-CMV infections, and survival were measured. Patients at risk were classified as high-risk patients (D+/R–) or low-risk patients (D+/R+ or D–/R+)

Conclusions:

- Combined prophylaxis with valganciclovir and CMVIg delayed CMV viremia and tissue-invasive disease in D+/R– lung transplant recipients, and prevented CMV-related mortality and development of ganciclovir resistance.
- CMVIg monotherapy prophylaxis was effective in R+ patients with ganciclovir-related toxicity.

Solidoro P, et al. Combined Prophylaxis Decreases Incidence of CMV-Associated Pneumonia After Lung Transplantation. *Transplantation Proceedings*, 41, 1347–1348 (2009)

Summary: evaluated the effect of combined CMV antiviral prophylaxis and CMV-immunoglobulin prophylaxis on CMV-associated pneumonia diagnosed in 303 follow-up transbronchial biopsy (TBB) specimens from lung transplant recipients.

- CMV-Ig in the first postoperative year in combination with ganciclovir or valganciclovir therapy after lung transplantation, reduced the incidence of CMV pneumonia during the first 2 years.

Use of CMVIG for CMV prophylaxis: (on label): *Kidney and Liver –*

Zhong L, Tang S, Pu Z, Chen K, Di W, Hou Y, and Yang H (2025). Impact of prophylactic cytomegalovirus immunoglobulin on cytomegalovirus viremia and graft function in ABO-incompatible living donor kidney transplantation: a retrospective analysis. Front. Immunol. 16:1562951.doi: 10.3389/fimmu.2025.156295

Summary: Retrospective study in ABO-incompatible kidney transplant recipients where patients received weekly CMVIG in addition to standard preemptive antiviral therapy (valganciclovir or ganciclovir), with evidence that CMVIG significantly reduced clinically relevant CMV viremia (16% vs. 34%, P = 0.04). CMVIG shows promise as an adjunctive treatment to improve outcomes in high-risk kidney transplant patients.

Barten, M.J. et al. Effectiveness of Prophylactic Human Cytomegalovirus Hyperimmunoglobulin in Preventing Cytomegalovirus Infection following Transplantation: A Systematic Review and Meta-Analysis. Life 2022, 12, 361.
https://doi.org/10.3390/life12030361

Summary: A meta-analysis of studies that analyzed the use of CMV-specific hyperimmunoglobulin (CMVIG) and the prophylactic effects on the infection rate of cytomegalovirus (CMV) in patients who have undergone a solid organ transplant (SOT)

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CMV and Mortality Data: support use of CMVIG to decrease the impact of CMV: *Heart/Lung:*

Belga, S et al. Impact of recipient age on mortality among Cytomegalovirus (CMV)-seronegative lung transplant recipients with CMV-seropositive donors. *The Journal of Heart and Lung Transplantation*, Vol 43, No 4, April 2024

Summary: lung outcomes

This national study of over 10,000 lung transplant recipients (LTRs) evaluated outcomes among CMV-seronegative recipients on standard valganciclovir (vGCV) prophylaxis. Among them, 61% were CMV D+/R−, a high-risk serostatus associated with a 6.8% absolute increase in mortality compared to CMV D−/R−. The CMV D+/R− group demonstrated a 27% increased risk of death post-transplant.

Critically, the study revealed a biological interaction between advanced recipient age (≥60 years) and CMV D+ status, suggesting that older CMV-seronegative recipients experience disproportionately poor outcomes.

- These findings support the consideration of adjunctive prophylaxis strategies—beyond standard antiviral therapy—in older, high-risk seronegative recipients to mitigate the elevated risk.

Heim C, et al. Cytomegalovirus donor seropositivity negatively affects survival after heart transplantation. *Transplantation*. 2022; 106: 1243-1252.

Summary: heart outcomes and CAV

The study looked at a large contemporary cohort (15,885) of heart transplant recipients (HTx) and demonstrated a significant association between donor CMV seropositivity and reduced short- and long-term survival after HTx.

- Follow-up of 10 y revealed significantly worse survival for both D+ groups as compared to the CMV low-risk group (D+R+: 56.61% [95% confidence interval, 53.94-59.41] versus D–R–: 63.09% [59.74-66.64] P < 0.01 and D+R–: 57.69% [56.03-59.39] versus D–R–;P < 0.001), whereas recipient seropositivity alone was not associated with reduced survival (D–R+ versus D–R– P = 0.178).

Kawashima M et al., Association between cytomegalovirus viremia and long-term outcomes in lung transplant recipients, American Journal of Transplantation, https://doi.org/10.1016/j.ajt.2024.01.027

Summary: lung outcomes and CLAD

This single-center retrospective study analyzed outcomes in 668 adult lung transplant recipients (first, bilateral/single-lung transplants) between 2010 and 2016. The study evaluated risks for death, retransplantation, CLAD, and RAS/mixed phenotypes. These findings underscore the persistent impact of CMV DNAemia on survival despite contemporary prophylaxis and highlight the importance of CMV prevention strategies to optimize long-term outcomes.

- CMV DNAemia with viral load >10,000 IU/mL was significantly associated with worse overall survival, although it was not linked to CLAD development
- CMV serostatus mismatch (D+/R−) was associated with an increased risk of CLAD and showed a non-significant trend toward RAS/mixed phenotype.
- CMV DNAemia is a significant determinant of survival even in the era of contemporary prophylaxis and treatment, reinforcing the ongoing importance of CMV-preventative strategies to improve long-term outcomes.

Bisono-Garcia, BS et al. Cytomegalovirus infection in heart transplant recipients: Epidemiology, risk factors, and long-term outcomes from a major transplant center in the United States. JHLT Open, Vol 4C, May 2024

Summary: heart

This study is a retrospective cohort study of 553 heart transplant recipients who underwent heart transplantation between January 1, 2011, and March 31, 2019. The study shows that the most important risk factor is CMV serostatus mismatch and a decrease in ALC among CMV seropositive recipients

- csCMVi was linked to higher mortality
- CMV D+/R– serostatus was associated with an increased risk of csCMVi
- Lower absolute lymphocyte counts increase the risk of csCMVi only in CMV seropositive recipients.

CMV and Mortality Data: support use of CMVIG to decrease the impact of CMV: Kidney/liver

Gill J, et al. (2025)Clinical management and burden of cytomegalovirus in D+/R-Kidney transplant recipients in Canada. *Front. Immunol.* 16:1618748. doi: 10.3389/fimmu.2025.1618748

Summary: A retrospective cohort study of 311 CMV D+/R– kidney transplant recipients between 2018 and 2021, evaluating demographic, clinical, therapeutic, and health resource utilization during the first post-transplant year. All patients received antiviral prophylaxis—90% with valganciclovir—for a median of 180 days, consistent with current consensus guidelines. Despite this, CMV infection occurred in 34% (median peak viral load 14,224 IU/mL), CMV disease in 43%, and 45% required hospitalization. These findings underscore the need for more effective and less toxic personalized strategies to reduce CMV-related morbidity and healthcare burden in this high-risk population.

Dobrer S, et al. Viral load kinetics and the clinical consequences of cytomegalovirus in kidney transplantation. *Front Immunol. 2024*; 14: 130627. doi: 10.3389/fimmu.2023

Summary: longitudinal CMV testing in 2,464 kidney transplant recipients transplanted between 2008 and 2018. CMV infection, defined as viremia ≥1,000 copies/mL with or without clinical manifestations, was associated with significantly higher risks of graft loss (p=0.0041) and death (p=0.0056). Severity, duration, and peak viral load predicted clinical risk, with viral load kinetics providing a simple, practical index for identifying patients at greatest risk.

Viral load kinetics are closely related to CMV severity and to graft loss following kidney transplantation and provide a simple index of risk which may be valuable in guiding trials and treatment to prevent transplant failure.

Raiha, J et al. **The burden of cytomegalovirus infection remains high in high-risk kidney transplant recipients despite six-month valganciclovir prophylaxis. Transpl Infect Dis. 2021;23:e13577. https://doi.org/10.1111/tid.13577**

Summary: This study analyzed post-prophylaxis primary CMV infections in D+/R− kidney transplant recipients (2004–2018) after 6-month valganciclovir prophylaxis. Despite prophylaxis, the incidence remained high, with many infections presenting late and symptomatic. These findings highlight the limitations of fixed-duration prophylaxis and the challenges of post-prophylaxis surveillance.

Leeaphorn N, et al. **Cytomegalovirus mismatch still negatively affects patient and graft survival in the era of routine prophylaxis and preemptive therapy: a paired kidney analysis.** *Am J Transplant*. *2019*; 19: 573-584.

Summary: Leeaphorn et al demonstrated that CMV still affects both patient and graft survival in the United States despite the use of prophylactic treatment.

Using United Network for Organ Sharing/Organ Procurement and Transplantation Network data, recipients with first deceased donor kidney transplant (≥18 years, 2010-2015) were stratified into 4 groups in the main cohort: CMV-seronegative donor (D−)/CMV-seronegative recipient (R−), CMV-seropositive donor (D+)/R−, D+/CMV-seropositive recipient (R+), and D−/R+. 2899 pairs of D− kidney transplant with discordance of recipient serostatus (D−/R− vs D−/R+) and 4567 pairs of D+ kidney transplant with discordance of recipient serostatus (D+/R− vs D+/R+).CMV mismatch is still an independent risk factor for graft loss and patient mortality. The negative impact of D+/R− serostatus on mortality persists after fully matching for donor factors.

Hakimi Z, et al. **Burden of cytomegalovirus disease in solid organ transplant recipients: a national matched cohort study in an inpatient setting.** *Transpl Infect Dis*. *2017*;19:e12732.https://doi.org/10.1111/tid.12732

Summary: A retrospective analysis of 20,473 solid organ transplant recipients in France (2007–2011) evaluated the impact of early (E-CMV) and late-onset (L-CMV) CMV disease. CMV disease was significantly associated with increased risks of graft rejection and mortality, while L-CMV was correlated with higher graft failure. Both E-CMV and L-CMV were linked to increased hospitalization costs at 3 and 6 months, underscoring the substantial clinical and economic burden of CMV in SOT.

Desai R, Collett D, Watson CJ, Johnson PJ, Moss P, Neuberger J. Impact of Cytomegalovirus on Long-term Mortality and Cancer Risk After Organ Transplantation. Transplantation. 2015 Sep;99(9):1989-94. doi: 10.1097/TP.0000000000000641. PMID: 25706273.

Summary: In a large cohort of kidney, liver, heart and lung transplant patients (n=22,461), demonstrated CMV serostatus impact on survival , the risk-adjusted hazard of death within 10 years of transplantation for the D+ R- group was higher than that of the D-R-group.

Health Economic Outcomes Research:

Abidi, MZ, et al. **Cognitive Impairment in CMV Seropositive and CMV Seronegative Deceased Donor Kidney Transplant Recipients.** Transplantation Direct 11(9):p e1818, September 2025. | DOI: 10.1097/TXD.0000000000001818

Abidi MZ, Schold JD, Kaplan B, Weinberg A,Erlandson KM, and Malamon JS (2024). **Patient years lost due to cytomegalovirus serostatus mismatching in the scientific registry of transplant recipients.** Front. Immunol. 14:1292648. doi: 10.3389/fimmu.2023.1292648

- CMV D+/R- mismatching poses a more significant risk
- greater health burden than previously reported, thus obviating the need for
- better preventive strategies, including CMV serodirected organ allocation to prolong lifespans and graft survival in high-risk patients

Wendy Y. Cheng, Robin K. Avery, Philippe Thompson-Leduc, Hoi Ching Cheung, Tien Bo, Mei Sheng Duh & Ishan Hirji (2022). **Evaluation of treatment patterns, healthcare resource utilization, and costs among patients receiving treatment for cytomegalovirus following allogeneic hematopoietic cell or solid organ transplantation.** Journal of Medical Economics, 25:1, 367-380, DOI: 10.1080/13696998.2022.2046388

- Conventional treatment options for CMV infection or disease in transplant recipients are limited by toxicities, and the development of refractory CMV (with or without resistance) to treatment may contribute to poorer outcomes.
- Findings indicate the high HCRU and costs associated with the management of CMV in the vulnerable immunosuppressed transplant patient population, highlighting the substantial burden of CMV management

CMV risk in kidney transplant recipients receiving belatacept immunosuppression

Use if needed to support adjunctive prophylaxis

Kleiboeker, H et al. **Belatacept may result in profound and persistent loss of cytomegalovirus-specific cell-mediated immunity: A case report.** *Transpl Infect Dis* 2022. 2022;24:e13795

Summary: case report notable for loss of CMV-specific CMI. Belatacept could result in impaired development of CMI in the setting of primary CMV in high-risk serostatus patients, particularly in combination with lymphocyte-depleting therapy.

Chavarot N, et al. **Increased incidence and unusual presentations of CMV disease in kidney transplant recipients after conversion to belatacept**. *Am J Transplant. 2021*;21:2448–2458.

Summary: Belatacept may increase cytomegalovirus (CMV) disease risk after conversion from CNI-based therapy. Among 181 belatacept treated patients matched to 181 controls, 17.7% experienced CMV disease vs. controls 2.8%.CMV disease risk was particularly high in elderly patients (converted >70 years) and those with eGFR <30 ml/min; CMV diseases under belatacept were atypical, with late-onset disease (60%), high CMV seropositivity (67%), increased severe and tissue-invasive disease rates and life-threatening diseases.