Clinical Policy: Valganciclovir (Valcyte)

Reference Number: CP.PCH.06
Effective Date: 12.01.17
Last Review Date: 02.23
Line of Business: Commercial, HIM* Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Valganciclovir (Valcyte®) is a deoxynucleoside analogue cytomegalovirus (CMV) DNA polymerase inhibitor.

**For Health Insurance Marketplace (HIM),* *valganciclovir oral solution 50 mg/mL is non-formulary and should not be approved using these criteria; refer to the formulary exception policy, HIM.PA.103.*

FDA Approved Indication(s)

Valcyte is indicated for:

- Adult patients
  - Treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS).
  - For the prevention of CMV disease in kidney, heart, or kidney-pancreas transplant patients at high risk (donor CMV seropositive/recipient CMV seronegative [D+/R-]).
- Pediatric patients
  - Prevention of CMV disease in kidney transplant patients (4 months to 16 years of age) and heart transplant patients (1 month to 16 years of age) at high risk.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Valcyte is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. CMV Prophylaxis in Heart, Kidney, or Kidney-Pancreas Transplant (must meet all)**:**

1. Member has a history of heart, kidney, or kidney-pancreas transplant;
2. Organ donor or recipient is CMV seropositive;
3. Member must use generic valganciclovir for the formulation being requested, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 900 mg per day.

Approval duration:
Heart or kidney-pancreas transplant – 6 months
Kidney transplant – 200 days
(For HIM, approve valganciclovir tablets 450 mg only. Refer to HIM.PA.103 for valganciclovir oral solution 50 mg/mL)

B. CMV Retinitis (must meet all)**:**
1. Diagnosis of CMV retinitis;
2. Prescribed by or in consultation with an ophthalmologist;
3. Age > 16 years;
4. Member is human immunodeficiency virus (HIV)-positive;
5. Member must use generic valganciclovir for the formulation being requested, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed the following:
   a. Induction: 1,800 mg per day for 21 days;
   b. Maintenance: 900 mg per day.

Approval duration: 4 months
(For HIM, approve valganciclovir tablets 450 mg only. Refer to HIM.PA.103 for valganciclovir oral solution 50 mg/mL)

C. CMV Prophylaxis in Liver or Lung Transplant (off-label) (must meet all)**:**
1. Member has a history of liver or lung transplant;
2. Organ donor or recipient is CMV seropositive;
3. Member must use generic valganciclovir for the formulation being requested, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 900 mg per day.

Approval duration:
Liver transplant – 6 months
Lung transplant– 12 months
(For HIM, approve valganciclovir tablets 450 mg only. Refer to HIM.PA.103 for valganciclovir oral solution 50 mg/mL)

D. CMV-Associated Gastrointestinal Diseases (off-label) (must meet all)**:**
1. Diagnosis of CMV-associated gastrointestinal disease (e.g., CMV esophagitis, colitis);
2. Prescribed by or in consultation with an infectious disease specialist or gastroenterologist;
3. Age > 16 years;
4. Member is HIV-positive;
5. Member must use generic valganciclovir for the formulation being requested, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 1,800 mg per day.

Approval duration: 42 days
(For HIM, approve valganciclovir tablets 450 mg only. Refer to HIM.PA.103 for valganciclovir oral solution 50 mg/mL)

E. Post-Transplant CMV Infection (off-label) (must meet all)**:**
1. Diagnosis of CMV infection following hematopoietic stem cell transplant or solid organ transplant (e.g., kidney, lung, heart, liver, pancreas, intestine);
2. Member must use generic valganciclovir for the formulation being requested, unless contraindicated or clinically significant adverse effects are experienced;
3. Dose does not exceed 1,800 mg per day.

Approval duration: 14 days
(For HIM, approve valganciclovir tablets 450 mg only. Refer to HIM.PA.103 for valganciclovir oral solution 50 mg/mL)

F. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial and HIM.PA.33 for health insurance marketplace; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial and HIM.PA.103 for health insurance marketplace; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial and HIM.PA.154 for health insurance marketplace.

II. Continued Therapy

A. CMV Prophylaxis in Heart, Kidney, or Kidney-Pancreas Transplant (must meet all)**:**
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Valcyte for a covered indication and has received this medication for at least 30 days;
2. Member meets one of the following (a or b):
   a. Heart or kidney-pancreas transplant: Member has not received ≥ 6 months of therapy;
   b. Kidney transplant: Member has not received ≥ 200 days of therapy;
3. Member must use generic valganciclovir for the formulation being requested, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, new dose does not exceed 900 mg per day.

Approval duration:
Heart or kidney-pancreas transplant – Up to 6 months total
Kidney transplant – Up to 200 days total
(For HIM, approve valganciclovir tablets 450 mg only. Refer to HIM.PA.103 for valganciclovir oral solution 50 mg/mL)

B. CMV Retinitis (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*

2. Adherent to antiretroviral therapy (ART) as evidenced by pharmacy claims history;
3. If member has received ≥ 4 months of therapy, member meets one of the following (a or b):
   a. CD4 count is < 100 cells/mm^3 (within the last 3 months);
   b. Continuation of therapy is recommended by an ophthalmologist;
4. Member must use generic valganciclovir for the formulation being requested, unless contraindicated or clinically significant adverse effects are experienced;
5. If request is for a dose increase, new dose does not exceed 900 mg per day.

Approval duration: 3 months
(For HIM, approve valganciclovir tablets 450 mg only. Refer to HIM.PA.103 for valganciclovir oral solution 50 mg/mL)

C. CMV Prophylaxis in Liver or Lung Transplant (off-label) (must meet all)**:**
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Valcyte for a covered indication and has received this medication for at least 30 days;
2. Member meets one of the following (a or b):
   a. Liver transplant: Member has not received ≥ 6 months of therapy;
   b. Lung transplant: Member has not received ≥ 12 months of therapy;
3. Member must use generic valganciclovir for the formulation being requested, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, new dose does not exceed 900 mg per day.

Approval duration:
Liver transplant: Up to 6 months total
Lung transplant: Up to 12 months total
(For HIM, approve valganciclovir tablets 450 mg only. Refer to HIM.PA.103 for valganciclovir oral solution 50 mg/mL)

D. CMV-Associated Gastrointestinal Diseases (off-label) (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Adherent to ART as evidenced by pharmacy claims history;
3. Member has experienced disease relapse since initial request;
4. Member must use generic valganciclovir for the formulation being requested, unless contraindicated or clinically significant adverse effects are experienced;
5. If request is for a dose increase, new dose does not exceed 900 mg per day.

Approval duration: Duration of request or 3 months (whichever is less)
(For HIM, approve valganciclovir tablets 450 mg only. Refer to HIM.PA.103 for valganciclovir oral solution 50 mg/mL)

E. Post-Transplant CMV Infection (off-label) (must meet all)**:**
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Valcyte for a covered indication and has received this medication for at least 30 days;
2. Member continues to have clinical symptoms and a virologic clearance above a threshold negative value based on laboratory monitoring with CMV quantitative nucleic acid testing (QNAT) or pp65 antigenemia once a week;
3. Member must use generic valganciclovir for the formulation being requested, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, new dose does not exceed 1,800 mg per day.

Approval duration: Duration of request or 3 months (whichever is less)
(For HIM, approve valganciclovir tablets 450 mg only. Refer to HIM.PA.103 for valganciclovir oral solution 50 mg/mL)

F. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial and HIM.PA.33 for health insurance marketplace; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial and HIM.PA.103 for health insurance marketplace; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial and HIM.PA.154 for health insurance marketplace.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial and HIM.PA.154 for health insurance marketplace.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AIDS: acquired immunodeficiency syndrome
ART: antiretroviral therapy
BSA: body surface area
CMV: cytomegalovirus
CrCl: creatinine clearance
FDA: Food and Drug Administration
HIV: human immunodeficiency virus
QNAT: quantitative nucleic acid testing

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): hypersensitivity
- Boxed warning(s): hematologic toxicity, impairment of fertility, fetal toxicity, mutagenesis, and carcinogenesis

Appendix D: General Information

- Based on the 2019 American Society of Transplantation and the 2018 Third International Consensus guidelines for CMV management in solid organ transplantation:
  - 3 to 6 months of prophylaxis therapy is recommended for donor+/recipient- and recipient+ heart transplant, kidney/pancreas transplant, and liver transplant recipients.
  - 6 to 12 months of prophylaxis therapy is recommended for donor+/recipient- and recipient+ lung transplant recipients.
  - CMV disease should be treated with either IV ganciclovir (for severe, life-threatening disease or mild-to-moderate disease) or PO Valcyte (for mild-to-moderate disease). Patients should be treated for a minimum of 2 weeks and until clinical symptoms have resolved and virologic clearance is below a threshold negative value based on weekly laboratory monitoring with CMV QNAT or pp65 antigenemia. After completion of full-dose antiviral treatment, secondary prophylaxis intended to prevent CMV relapse is not recommended as a routine practice.
- Based on the results of the IMPACT study, Valcyte prophylaxis for 200 days in kidney transplant patients resulted in a reduction in CMV disease. At 2 years post-transplant, CMV disease occurred in significantly less patients in the 200- vs. the 100-day group: 21.3% vs. 38.7%, respectively ($p < 0.001$).
- Although Valcyte is not FDA approved for the prevention of CMV disease in liver transplant patients, consensus treatment guidelines support the use of Valcyte in this transplant type. The FDA has cautioned against valganciclovir prophylaxis in liver recipients due to high rate of tissue-invasive disease compared to oral ganciclovir.
- Data supporting the use of Valcyte for lung transplant patients come from Finlen et al, who concluded that 12 months of Valcyte prophylaxis compared with 3 months provided a protective benefit with a CMV incidence of 12% vs 55% respectively (HR 0.13, CI: 0.03-0.61, $p = 0.009$). In another randomized clinical trial by Palmer et al, extending the duration of Valcyte prophylaxis from 3 months to 12 months decreased the incidence of CMV disease from 64% to 10% ($p < 0.001$).
- Per CDC guidelines for the treatment of CMV retinitis, Valcyte may be used in combination with ganciclovir intraocular implant for patients with immediate sight-threatening lesions (adjacent to the optic nerve or fovea).
- Chronic maintenance therapy is not routinely recommended for CMV gastrointestinal disease, unless there is concurrent retinitis or relapses have occurred.
- The safety and efficacy of Valcyte for oral solution and tablets have not been established in children for prevention of CMV disease in pediatric liver transplant patients, in kidney transplant patients less than 4 months of age, in heart transplant patients less than 1 month of age, in pediatric AIDS patients with CMV retinitis, and in infants with congenital CMV infection. In 2010, the FDA added an upper limit to pediatric dosing calculation to prevent Valcyte overdosing in children with low body weight, surface area and below normal serum creatinine.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Adult Dosage		
Prevention of CMV disease in heart or kidney-pancreas transplant patients	900 mg (two 450 mg tablets) PO QD within 10 days of transplantation until 100 days post-transplantation	900 mg/day
Prevention of CMV disease in kidney transplant patients	900 mg (two 450 mg tablets) PO QD within 10 days of transplantation until 200 days post-transplantation	900 mg/day
Treatment of CMV retinitis	Induction: 900 mg (two 450 mg tablets) PO BID for 14-21 days Maintenance: 900 mg (two 450 mg tablets) PO QD	Induction: 1,800 mg/day; Maintenance: 900 mg/day
Prevention of CMV disease in liver transplantation†	900 mg (two 450 mg tablets) PO QD within 10 days of transplantation	900 mg/day
Prevention of CMV disease in lung transplantation†	900 mg (two 450 mg tablets) PO QD within 10 days of transplantation	900 mg/day
Treatment of CMV esophagitis† or colitis†	Induction: 900 mg (two 450 mg tablets) PO BID for 21-42 days Maintenance (may be considered in patients with relapse): 900 mg (two 450 mg tablets) PO QD	Induction: 1,800 mg/day; Maintenance: 900 mg/day
Treatment of post-transplant CMV infection†	900 mg PO BID for at least 14 days	1,800 mg/day
Pediatric Dosage		
Prevention of CMV disease in kidney transplant patients 4 months to 16 years of age	Calculated dose in mg (7 x BSA x CrCl*) PO QD within 10 days of transplantation until 200 days post-transplantation	900 mg/day
Prevention of CMV disease in heart transplant patients 1 month to 16 years of age	Calculated dose in mg (7 x BSA x CrCl*) PO QD within 10 days of transplantation until 100 days post-transplantation	900 mg/day
Treatment of post-transplant CMV infection†	Calculated dose in mg (7 x BSA x CrCl*) PO BID for at least 14 days	1,800 mg/day

***** *Calculated using a modified Schwartz formula*
† *Off-label indication*

VI. Product Availability

- Oral solution: 50 mg/mL
- Tablet: 450 mg

VII. References

1. Valcyte Prescribing Information. South San Francisco, CA: Genentech USA, Inc.; December 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021304.s17_22257s12lbl.pdf. Accessed October 24, 2022.
2. Clinical Pharmacology [database online]. Elsevier, Inc.; 2022. Updated periodically. Available at: https://www.clinicalkey.com/pharmacology/. Accessed October 24, 2022.
3. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: cytomegalovirus disease: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/cytomegalovirus-disease. Last updated July 1, 2021. Last reviewed July 13, 2022. Accessed October 24, 2022.
4. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. June 2018; 102 (6): 900-931.
5. Zamora MR, Davis RD, Leonard C. Management of cytomegalovirus infection in lung transplant recipients: evidence-based recommendations. Transplantation 2005;80: 157–163.
6. Razonable RR, Humar A, and the AST Infectious Disease Community of Practice. Cytomegalovirus in solid organ transplantation. Am J Transplant. 2013 Mar;13 Suppl 4:93-106.
7. Marcelin JR, Beam E, Razonable RR. Cytomegalovirus infection in liver transplant recipients: Updates on clinical management. *World Journal of Gastroenterology : WJG*. 2014;20(31):10658-10667. doi:10.3748/wjg.v20.i31.10658.
8. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clinical Transplantation. 2019; 33: e13512.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2019 annual review: no significant changes, references reviewed and updated.	11.05.18	02.19
1Q 2020 annual review: no significant changes; references reviewed and updated.	09.26.19	02.20
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	10.20.20	02.21
1Q 2022 annual review: added off-label coverage for treatment of post-transplant CMV infection as supported by practice guidelines; references reviewed and updated.	12.02.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.28.22	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2023 annual review: added requirement in both initial and continuation requests that member must use generic valganciclovir for the formulation being requested, unless contraindicated or clinically significant adverse effects are experienced; references reviewed and updated.	10.24.22	02.23
COC applied to transplant-related indications in continued therapy sections (Section II.A., II.C., II.E.).	07.10.23	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.