Clinical Policy: Valganciclovir (Valcyte)

Reference Number: ERX.NPA.33
Effective Date: 06.01.15
Last Review Date: 08.18 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.

FDA Approved Indication(s)
Valcyte is indicated for:

- Adult patients
  - Treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS)
  - Prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-])
- Pediatric patents
  - 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 Envolve Pharmacy Solutions™ 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. Dose does not exceed 900 mg/day.

Approval duration:
Heart or kidney-pancreas transplant: 6 months
Kidney transplant: 200 days

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. Dose does not exceed the following:
   a. Induction: 1800 mg/day for 21 days;
   b. Maintenance: 900 mg/day.

Approval duration: 4 months

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. Dose does not exceed 900 mg/day.

Approval duration:
Liver transplant: 6 months
Lung transplant: 12 months

***The US FDA has cautioned against valganciclovir prophylaxis in liver recipients due to high rate of tissue-invasive disease compared to oral ganciclovir. However, many experts still recommend its use as prophylaxis in liver recipients.*

D. CMV-Associated Gastrointestinal Diseases (off-label) (must meet all)**:**
1. Diagnosis of a 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. Dose does not exceed 1800 mg/day.

Approval duration: 42 days

E. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. CMV Prophylaxis in Heart, Kidney, or Kidney-Pancreas Transplant (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
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. If request is for a dose increase, new dose does not exceed 900 mg/day.

Approval duration:
Heart or kidney-pancreas transplant: up to 6 months total
Kidney: up to 200 days total

B. CMV Retinitis (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
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. If request is for a dose increase, new dose does not exceed 900 mg/day.

Approval duration: 3 months

C. CMV Prophylaxis in Liver or Lung Transplant (off-label) (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
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. If request is for a dose increase, new dose does not exceed 900 mg/day.

Approval duration:
Liver transplant: up to 6 months total
Lung transplant: up to 12 months total

D. CMV-Associated Gastrointestinal Diseases (off-label) (must meet all)**:**
1. Previously received medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Adherent to ART as evidenced by pharmacy claims history;
3. Member has experienced disease relapse since initial request;
   **Chronic maintenance therapy is not routinely recommended for CMV gastrointestinal disease, unless there is concurrent retinitis or relapses have occurred*
4. If request is for a dose increase, new dose does not exceed 900 mg/day.

Approval duration: Duration of request or 3 months (whichever is less)

E. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ART: antiretroviral therapy
CMV: cytomegalovirus
FDA: Food and Drug Administration
HIV: human immunodeficiency virus

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications

Not applicable

Appendix D: General Information

- Based on the 2009 Solid Organ Transplant Guidelines for CMV prophylaxis and the 2010 International guidelines, 3 to 6 months of prophylaxis therapy is recommended for donor+/recipient- heart transplant recipients and kidney/pancreas recipients. Three months of prophylactic therapy is recommended for recipient+ heart transplant recipients.
- 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.
- 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).
- The prescribing information contains a boxed warning regarding potential hematologic toxicity, impairment of fertility, fetal toxicity, mutagenesis, and carcinogenesis. .
- 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).
- 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 overdoing 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) orally once a day 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) orally once a day within 10 days of transplantation until 200 days post-transplantation	900 mg/day
Treatment of CMV retinitis	Induction: 900 mg (two 450 mg tablets) orally twice a day for 21 days Maintenance: 900 mg (two 450 mg tablets) orally once a day	900 mg/day; 1800 mg/day during CMV retinitis induction therapy
Prevention of CMV disease in liver transplantation†	900 mg (two 450 mg tablets) orally once a day within 10 days of transplantation	900 mg/day
Prevention of CMV disease in lung transplantation†	900 mg (two 450 mg tablets) orally once a day within 10 days of transplantation	900 mg/day
Treatment of CMV esophagitis† or colitis†	Doses are the same as for CMV retinitis	900 mg/day; 1800 mg/day during induction therapy
Pediatric Dosage		
Prevention of CMV disease in kidney transplant patients 4 months to 16 years of age	Dose once a day within 10 days of transplantation until 200 days post-transplantation according to dosage algorithm (7 x body surface area [BSA] x creatinine clearance [CrCl]*)	Dosage is based on BSA and CrCl; not to exceed 900 mg/day
Prevention of CMV disease in heart transplant patients 1 month to 16 years of age	Dose once a day within 10 days of transplantation until 100 days post-transplantation according to dosage algorithm (7 x BSA x CrCl*)	Dosage is based on BSA and CrCl; not to exceed 900 mg/day

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

VI. Product Availability

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

VII. References

1. Valcyte Prescribing Information. South San Francisco, CA: Genentech USA, Inc.; June 2017. Available at http://www.valcyte.com/. Accessed April 25, 2018.
2. 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: herpes: 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://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/337/cmv. Accessed April 25, 2018.
3. Kotton CN, Kumar D, Caliendo AM, et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2013 Aug 27;96(4):333-60.
4. Zamora MR, Davis RD, Leonard C. Management of cytomegalovirus infection in lung transplant recipients: evidence-based recommendations. Transplantation 2005;80: 157–163.
5. 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.

6. 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	06.15	06.15
Updated to new template (converted algorithm to bulleted criteria, added background and references). Updated criteria to indicate donor (not recipient) should be seropositive for CMV prophylaxis in organ transplant per FDA labeling. Separated initial and continued approval durations for treatment of CMV and modified from "120 days total" for both to "4 months" for initial then "3 months" for continued per literature review. Added requirement for adherence to ART for continuation of CMV prophylaxis per literature review.	07.16	09.16
Converted to new template. All indications: modified general FDA approved maximum recommended dose statement to reflect actual max dose. CMV prophylaxis in heart, kidney, or kidney-pancreas transplant: per consensus guidelines and/or Razonable et al, modified to include CMV seropositive recipients; increased approval duration for heart transplant from 100 days to 6 months/decreased approval duration for kidney-pancreas transplant from 200 days to 6 month-updated re-auth criteria to align with initial approval duration. CMV retinitis: added prescriber specialty; modified age restriction from ≥ 16 years to > 16 per Clinical Pharmacology; CMV-associated GI diseases: separated from CMV retinitis criteria to indicate off-label indication; added prescriber specialty; modified age restriction from ≥ 16 years to > 16 per Clinical Pharmacology; modified initial approval duration from 4 months to 42 days per opportunistic infections in HIV guideline; for re-auth, added requirement for disease relapse. Added off-label criteria set for CMV prophylaxis in liver or lung transplant per consensus treatment guidelines. Updated references.	07.17	08.17
3Q 2018 annual review: no significant changes; references reviewed and updated.	04.25.18	08.18

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.