Clinical Policy: Letermovir (Prevymis)

Reference Number: CP.PHAR.367
Effective Date: 03.01.18
Last Review Date: 02.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

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

Description

Letermovir (Prevymis®) is a cytomegalovirus (CMV) DNA terminase complex inhibitor.

FDA Approved Indication(s)

Prevymis is indicated for:

- Prophylaxis of CMV infection and disease in adult and pediatric patients 6 months of age and older and weighing at least 6 kg who are CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)
- Prophylaxis of CMV disease in adult and pediatric patients 12 years of age and older and weighing at least 40 kg who are kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-])

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 Prevymis is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Prophylaxis of CMV Infection in CMV-Seropositive Recipients of an Allogeneic HSCT (must meet all)**:**

1. Member has received or is scheduled to receive allogeneic HSCT;
2. Member is CMV-seropositive;
3. Prescribed by or in consultation with an oncology, hematology, infectious disease, or transplant specialist;
4. Age ≥ 6 months;
5. Weight ≥ 6 kg;
6. Prevymis must be initiated within 28 days post-transplant;
7. If request is for IV Prevymis, documentation supports inability to use oral therapy;
8. At the time of request, member is not receiving any of the following contraindicated agents:
   a. Pimozide or ergot alkaloids;
   b. Cyclosporine co-administered with pitavastatin or simvastatin;
9. If request is for prophylaxis beyond 100 days post-transplantation, both of the following (a and b):
   a. Member is at risk for late CMV infection and disease (see *Appendix D*);

b. Prevymis is prescribed up to day 200 post-HSCT;
10. Dose does not exceed any of the following (a or b):
    a. For age ≥ 12 years (i or ii):
        i. Weight ≥ 30 kg (1 or 2):
            1) 480 mg per day;
            2) If co-administered with cyclosporine: 240 mg per day;
        ii. Weight < 30 kg: Dose does not exceed the FDA approved maximum recommended dose based on weight (*see Section V);*
    b. For age 6 months to < 12 years: Dose does not exceed the FDA approved maximum recommended dose based on weight (*see Section V).*

Approval duration: Through Day 100 post-transplantation (or through Day 200 post-transplantation if at risk for late CMV infection and disease)

B. Prophylaxis of CMV in Kidney Recipients at High Risk (must meet all):
1. Member has received or scheduled to receive an allograft kidney transplant from a CMV-seropositive donor;
2. Member is CMV-seronegative;
3. Prescribed by or in consultation with a nephrologist or transplant specialist;
4. Age ≥ 12 years;
5. Weight ≥ 40 kg;
6. Prevymis must be initiated within 7 days post-transplant;
7. If request is for IV Prevymis, documentation supports inability to use oral therapy;
8. At the time of request, member is not receiving any of the following contraindicated agents:
    a. Pimozide or ergot alkaloids;
    b. Cyclosporine co-administered with pitavastatin or simvastatin;
9. Prevymis is prescribed up to day 200 post-transplantation;
10. Dose does not exceed any of the following (a or b):
    a. 480 mg per day;
    b. If co-administered with cyclosporine: 240 mg per day.

Approval duration: Through Day 200 post-transplantation

C. 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, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; 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, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; 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, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Prevymis for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. One of the following (a or b):
   a. For HSCT, one of the following (i or ii):
      i. Member has not received Prevymis therapy beyond 100 days post-transplantation;
      ii. Member is at risk for late CMV infection and disease (see *Appendix D*) and has not received Prevymis therapy beyond 200 days post-transplantation;
   b. Kidney transplant: Member has not received Prevymis therapy beyond 200 days post-transplantation;
4. If request is for a dose increase, request meets one of the following (a or b):
   a. For age ≥ 12 years and weight ≥ 30 kg (for HSCT) or 40 kg (for kidney transplant): New dose does not exceed (i or ii):
      i. 480 mg per day;
      ii. If co-administered with cyclosporine: 240 mg per day;
   b. New dose does not exceed the FDA approved maximum recommended dose based on weight (*see Section V).*

Approval duration: Through Day 100 (for HSCT) or Day 200 (for kidney transplant or HSCT at risk for late CMV infection and disease) post-transplantation

B. 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, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; 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, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; 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, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CMV: cytomegalovirus
FDA: Food and Drug Administration
D+: donor CMV seropositive
HSCT: hematopoietic stem cell transplant
R+: seropositive recipients
R-: recipient CMV seronegative

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): patients receiving any of the following - pimozide, ergot alkaloids, pitavastatin and simvastatin when co-administered with cyclosporine
- Boxed warning(s): none reported

Appendix D: General Information

- Prophylaxis strategy against early CMV replication (i.e., < 100 days after HSCT) for allogeneic recipients involves administering prophylaxis to all allogeneic recipients at risk throughout the period from engraftment to 100 days after HSCT.
  - CMV prophylaxis has been studied using a variety of agents, including ganciclovir, valganciclovir, foscarnet, acyclovir, and valacyclovir.
- Preemptive strategy targets antiviral treatment to those patients who have evidence of CMV replication after HSCT.
- Positive response to therapy may be demonstrated if there is no evidence of CMV viremia.
- The 2021 American Society for Transplantation and Cellular Therapy Guideline for prevention of CMV infection after HCT states that primary prophylaxis in CMV-seropositive adult allogeneic recipients with alternative agents such as valganciclovir, ganciclovir, or foscarnet is generally not recommended.
- Examples of risk factors for late CMV infection and disease include, but are not limited to, the following:
  - HLA-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or –DR;
  - Haploidentical donor;
  - Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1;
  - Use of umbilical cord blood as stem cell source;
  - Use of ex vivo T-cell-depleted grafts;
  - Receipt of anti-thymocyte globulin;
  - Receipt of alemtuzumab;

- Use of systemic prednisone (or equivalent) at a dose of ≥1 mg/kg of body weight per day

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>Prophylaxis of CMV infection in CMV-seropositive recipients [R+] of an allogeneic HSCT</td><td>Age ≥ 12 years and weight ≥ 30 kg:*
480 mg administered once daily PO or as an IV infusion over 1 hour through 100 days post-transplant. In patients at risk for late CMV infection and disease, Prevymis may be continued through 200 days post-transplant.

If co-administered with cyclosporine, the dosage should be decreased to 240 mg once daily.

Age 6 months to < 12 years OR age ≥ 12 years and weight < 30 kg:**
<table>
<tr><th>Body Weight</th><th>Daily PO Dose</th><th>Daily IV Dose</th></tr>
<tr><td>≥ 30 kg</td><td>480 mg</td><td>480 mg</td></tr>
<tr><td>≥ 15 kg to < 30 kg</td><td>240 mg</td><td>120 mg</td></tr>
<tr><td>≥ 7.5 kg to < 15 kg</td><td>120 mg</td><td>60 mg</td></tr>
<tr><td>≥ 6 kg to < 7.5 kg</td><td>80 mg</td><td>40 mg</td></tr>
</table>
If co-administered with cyclosporine, the dosage of Prevymis may require adjustment as shown below:
<table>
<tr><th>Body Weight</th><th>Daily PO Dose</th><th>Daily IV Dose</th></tr>
<tr><td>≥ 30 kg</td><td>240 mg</td><td>240 mg</td></tr>
<tr><td>≥ 15 kg to < 30 kg</td><td>120 mg</td><td>120 mg</td></tr>
<tr><td>≥ 7.5 kg to < 15 kg</td><td>60 mg</td><td>60 mg</td></tr>
<tr><td>≥ 6 kg to < 7.5 kg</td><td>40 mg</td><td>40 mg</td></tr>
</table>
* No dosage adjustment is necessary when switching formulations in adult and pediatric patients 12 years of age and older
** Dosage adjustment may be necessary for pediatric patients less than 12 years of age when switching between oral and intravenous formulations</td><td>Weight ≥ 30 kg: 480 mg (or 240 mg when co-administered with cyclosporine) per day

Weight < 30 kg: See regimen</td></tr>
<tr><td>Prophylaxis of CMV disease in kidney transplant recipients at high risk (D+/R-)</td><td>Age ≥ 12 years and weight ≥ 40 kg:
480 mg administered once daily PO or as an IV infusion over 1 hour through 200 days post-transplant.</td><td>480 mg (or 240 mg when co-administered with cyclosporine) per day</td></tr>
</table>

Indication	Dosing Regimen	Maximum Dose
	If co-administered with cyclosporine, the dosage of should be decreased to 240 mg once daily.	

VI. Product Availability

- Tablets: 240 mg, 480 mg
- Oral pellets in packets: 20 mg, 120 mg
- Single-dose vials: 240 mg/12 mL, 480 mg/24 mL

VII. References

1. Prevymis Prescribing Information. Whitehouse Station, NJ: Merck and Co., Inc.: August 2024. Available at: https://www.merck.com/product/usa/pi_circulars/p/prevymis/prevymis_pi.pdf. Accessed October 31, 2024.
2. Clinical Pharmacology [database online]. Elsevier, Inc. Available at: https://www.clinicalkey.com/pharmacology/. Accessed November 14, 2024.

HSCT

3. Ljungman P, de La Camara R, Milpied N, Volin L, Russell CA, Crisp A, Webster A; Valacyclovir International Bone Marrow Transplant Study Group. Randomized study of valacyclovir as prophylaxis against cytomegalovirus reactivation in recipients of allogeneic bone marrow transplants. Blood. 2002; 99: 3050-6.
4. Winston DJ, Yeager AM, Chandrasekar PH, Snydman DR, Petersen FB, Territo MC; Valacyclovir Cytomegalovirus Study Group. Randomized comparison of oral valacyclovir and intravenous ganciclovir for prevention of cytomegalovirus disease after allogeneic bone marrow transplantation. Clin Infect Dis. 2003; 36:749-58. Epub 2003 Mar 3.
5. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective. Biol Blood Marrow Transplant. 2009; 15: 1143-1238.
6. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood 2009; 113:5711-9.
7. Schmidt-Hieber, M., Schwarck, S., Stroux, A. et al. Immune reconstitution and cytomegalovirus infection after allogeneic stem cell transplantation: the important impact of in vivo T cell depletion. Int J Hematol (2010) 91: 877-885.
8. Hakki M, Aitken SL, Danziger-Isakov L, et al. American Society for Transplantation and Cellular Therapy Series: #3-Prevention of Cytomegalovirus Infection and Disease After Hematopoietic Cell Transplantation. Transplant Cell Ther. 2021 Sep; 27(9):707-719.
9. Extension of Letermovir (LET) From Day 100 to Day 200 Post-transplant for the Prevention of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant (HSCT) Participants (MK-8228-040). ClinicalTrials.gov identifier: NCT03930615. Updated November 1, 2022. Available at: https://clinicaltrials.gov/study/NCT03930615. Accessed November 14, 2024.

Kidney Transplant

10. Kotton CN, Kumar D, Caliendo AM, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation 2018; 102:900.

11. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019; 33:e13512.
12. Limaye AP, Budde K, Humar A, et al. Letermovir vs Valganciclovir for prophylaxis of cytomegalovirus in high-risk kidney transplant recipients: A randomized clinical trial. JAMA 2023.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J8499	Prescription drug, oral, non chemotherapeutic, nos

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: no significant changes; added additional definitions of high risk to Appendix D; added coding implications; references reviewed and updated.	10.20.20	02.21
1Q 2022 annual review: no significant changes; converted HIM-Medical Benefit to HIM; references reviewed and updated.	09.14.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.22.22	
1Q 2023 annual review: removed redirection to valacyclovir or ganciclovir per 2021 American Society for Transplantation and Cellular Therapy Guidelines and bypass that was allowed for CMV-seropositive recipients as this is the only indicated use for Prevymis, added requirement for initial approval that member is CMV-seropositive; for continued therapy added the following requirement to support existing approval duration: Member has not received Prevymis therapy beyond 100 days post-transplantation; added HCPCS code J8499; references reviewed and updated.	10.24.22	02.23
RT4: added new indication for prophylaxis of CMV disease in adult kidney transplant recipients at high risk to policy; added HCPCS code C9399.	06.21.23	
1Q 2024 annual review: per updated prescribing information for allogeneic HSCT, added allowance for use through Day 200 post-transplantation if at risk for late CMV infection and disease; added examples of risk factors for late CMV infection and disease to Appendix D; references reviewed and updated.	10.06.23	02.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
RT4: added pediatric extension to include age ≥ 6 months and weight ≥ 6 kg for prophylaxis of CMV in patients who are CMV-R+ of an allogenic HSCT and age ≥ 12 years and weight ≥ 40 kg for prophylaxis of CMV in kidney transplant recipients at high risk per updated PI; added newly approved dosage form (oral pellets).	09.05.24	
1Q 2025 annual review: no significant changes; references reviewed and updated.	10.31.24	02.25
For prophylaxis of CMV in kidney transplant recipients, added criterion limiting usage of Prevymis up to day 200 post-transplantation.	05.16.25	
Added criterion Prevymis must be initiated within 7 days post kidney transplant and 28 days post HSCT per PI.	09.25.25	

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.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.