Original Effective Date: 02/2019
Current Effective Date: 12/29/2024
Last P&T Approval/Version: 10/30/2024
Next Review Due By: 01/2025
Policy Number: C15922-A

Prevymis (letermovir)

PRODUCTS AFFECTED

Prevymis (letermovir)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Prophylaxis of cytomegalovirus (CMV) infection

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PROPHYLAXIS OF CYTOMEGALOVIRUS (CMV) INFECTION - HSCT:
1. Documentation that member has received, or is scheduled to receive, an allogeneic hematopoietic stem cell transplant (HSCT)
   AND

2. Documentation that member is a confirmed cytomegalovirus (CMV) seropositive recipient (R+) [DOCUMENTATION REQUIRED]
   AND
3. Prescriber attests Prevymis (letermovir) will be initiated between Day 0 and Day 28 post-transplant
   AND
4. Prescriber attests the members medication profile has been reviewed and member is not concurrently receiving medications that are contraindicated with Prevymis (letermovir) (i.e., pimozide, ergot alkaloids [ergotamine and dihydroergotamine, pitavastatin and simvastatin when co-administered with cyclosporine)
   AND
5. FOR IV THERAPY REQUESTS: Medical justification (with supporting documentation) must be provided explaining why the member is unable to use oral therapy AND Anticipated duration of IV therapy has been documented AND Member will be switched to oral Prevymis therapy as soon as able to take oral medications (if applicable)
   AND
6. Documentation of ONE of the following:
   (a) Inadequate treatment response, serious side effects, contraindication, or non- susceptibility to treatment with ganciclovir (IV) AND valganciclovir
   OR
   (b) Request is for a continuation of therapy that was started at an in-patient setting (within the last 14 days) and member is at time of request transitioning to an outpatient site of care [DISCHARGE DOCUMENTATION REQUIRED WHICH INCLUDES SPECIALIST PRESCRIBER NOTES (SEE PRESCRIBER REQUIREMENTS), DURATION OF THERAPY, START AND END DATE]
   AND
7. Documentation member weighs at least 6kg

B. PROPHYLAXIS OF CYTOMEGALOVIRUS (CMV) DISEASE – KIDNEY TRANSPLANT:
1. Documentation that member has received, or is scheduled to receive, a kidney transplant
   AND
2. Documentation that member is confirmed cytomegalovirus (CMV) seronegative receiving from donor who is CMV seropositive (D+/R-) [DOCUMENTATION REQUIRED]
   AND
3. Prescriber attests Prevymis (letermovir) will be initiated between Day 0 and Day 7 post-transplant
   AND
4. Prescriber attests the members medication profile has been reviewed and member is not concurrently receiving medications that are contraindicated with Prevymis (letermovir) (i.e., pimozide, ergot alkaloids [ergotamine and dihydroergotamine, pitavastatin and simvastatin when co-administered with cyclosporine)
   AND
5. FOR IV THERAPY REQUESTS: Medical justification (with supporting documentation) must be provided explaining why the member is unable to use oral therapy AND Anticipated duration of IV therapy has been documented AND Member will be switched to oral Prevymis therapy as soon as able to take oral medications (if applicable)
   AND
6. Documentation of ONE of the following:
   a) Inadequate treatment response, serious side effects, contraindication, or non- susceptibility to treatment with ganciclovir (IV) AND valganciclovir
      OR
   b) Request is for a continuation of therapy that was started at an in-patient setting (within the last 14 days) and member is at time of request transitioning to an outpatient site of care [DISCHARGE DOCUMENTATION REQUIRED WHICH INCLUDES SPECIALIST PRESCRIBER NOTES (SEE PRESCRIBER REQUIREMENTS), DURATION OF THERAPY, START AND END DATE]

AND

7. Documentation member weighs at least 40kg

CONTINUATION OF THERAPY:
N/A

DURATION OF APPROVAL:
Initial authorization: Per FDA label to be continued through day 100 post HSCT transplantation OR OR through day 200 post HSCT transplantation if at risk for late CMV infection and disease OR day 200 post kidney transplant, Continuation of therapy: N/A

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with an infectious disease specialist, hematologist or transplant specialist. [If prescribed in consultation, consultation notes must be submitted with initial request]

AGE RESTRICTIONS:
PROPHYLAXIS OF CMV INFECTION – HSCT: 6 months of age and older
PROPHYLAXIS OF CMV DISEASE – KIDNEY TRANSPLANT: 12 years of age and older

QUANTITY:
HSCT Recipients:
Adults and pediatrics 12 years and older weighing at least 30kg: 480mg once daily orally or intravenously
Pediatrics 6 months to less than 12 years weighing less than 30kg: Weight based dosing once daily orally or intravenously
30kg and greater: 480mg
15kg to less than 30kg: 240mg
7.5kg to less than 15kg: 120mg (tablets not recommended)
6kg to less than 7.5kg: 80mg (tablets not recommended)

Kidney Transplant Recipients:
12 years or age and older weighing at least 40kg: 480mg once daily orally or intravenously

Maximum Quantity Limits – 28 days per fill
Tablets: 4-28 count cartons per 100 days (112 tabs)
Pellet Packets: Max 4 packets per day
Infusion: 1 vial per day
*If Prevymis is co-administered with cyclosporine, the dose of Prevymis (letermovir) should be decreased to 240 mg once daily

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral and Intravenous

DRUG CLASS:
CMV Agents

FDA-APPROVED USES:
PREVYMIS is indicated for:

- Prophylaxis of cytomegalovirus (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-])

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Prevymis (letermovir) inhibits the CMV DNA terminase complex (pUL51, pUL56, and pUL89) which is required for viral DNA processing and packaging. Biochemical characterization and electron microscopy demonstrated that letermovir affects the production of proper unit length genomes and interferes with virion maturation. Genotypic characterization of virus resistant to letermovir confirmed that letermovir targets the terminase complex.

Current therapy for CMV in allogeneic stem cell transplant patients is either prophylactic or preemptive therapy. Prophylactic therapy involves administering a drug to prevent infection in patients at increased risk, while preemptive therapy involves starting therapy based upon screening with a sensitive assay to detect early infection. The goal of preemptive therapy is to avoid disease progression. If the antimicrobial therapy is very toxic, preemptive therapy may be a more cautious approach. Medications used for CMV prophylaxis: Cytovene (ganciclovir), Foscarvir (foscarnet) (not an approved FDA indication), Acyclovir (zovirax) (not an approved FDA indication, alternative therapy), Valtrex (valacyclovir) (not an approved FDA indication). Cytovene has been shown to be the most active product but the bone marrow toxicity side effect limits its use. High-dose Zovirax and Valtrex are less toxic than Cytovene but also have lower in vitro activity against CMV. Thus far, there are no comparative studies comparing Prevymis to any of the other antiviral medications.
Prophylaxis Therapy: Intravenous Cytovene, which has substantially greater anti-CMV activity than Zovirax or Valtrex, has been shown to be associated with a substantial reduction in both infection and disease (almost complete absence of disease) and is the most commonly used anti-CMV agent (1, 2, 3). IV Cytovene did not improve survival in these trials because it was associated with neutropenia and secondary bacterial and fungal infections. There was no difference in the risk of CMV disease at day 180 or survival between Cytovene prophylaxis and Cytovene given as preemptive therapy, although there was less CMV disease before day 100. Although survival improvement in individual Cytovene trials was not seen, the trials were underpowered to detect survival differences. However, in an observational study, patients who received prophylactic Cytovene had a survival benefit compared with patients who did not receive either antiviral prophylaxis or preemptive therapy (4). Preemptive Therapy: The efficacy of preemptive therapy has been demonstrated in several trials (3, 4, 5, 6, 7, 8). As an example, in a trial in which allogeneic HCT recipients who were CMV-seropositive or who had received a CMV-seropositive allograft were screened for CMV excretion by cultures from multiple sites, 72 patients who were virus excreters were randomly assigned to receive Cytovene (5 mg/kg IV twice daily for one week, then once daily for the first 100 days) or placebo (8). The primary adverse effect was neutropenia, which occurred in30% of patients. Cytovene markedly reduced the incidence of CMV disease (3% versus 43%) and significantly increased overall survival. Another randomized trial showed that Foscarvir (90 mg/kg IV twice daily) was as effective as

Cytovene (5 mg/kg IV twice daily) for preemptive therapy of CMV infection in allogeneic HCT recipients (9). As far as combination therapy is concerned, Cytovene with Foscarvir, both at one-half of the usual dose, was not more effective than full-dose Cytovene (10). The combination regimen was also associated with more toxicity.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Prevymis (letermovir) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Prevymis (letermovir) include: use with pimozide, ergot alkaloids (ergotamine and dihydroergotamine), pitavastatin and simvastatin when co-administered with cyclosporine.

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J3490	Unclassified drugs

AVAILABLE DOSAGE FORMS:
Prevymis SOLN 240MG/12ML single dose vial
Prevymis SOLN 480MG/24ML single dose vial
Prevymis TABS 240MG
Prevymis TABS 480MG

REFERENCES

1. Prevymis (letermovir) tablets and injection [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; August 2024.
2. Kropeit D, McCormick D, Erb-Zohar K, et al. Pharmacokinetics and safety of the anti- human cytomegalovirus drug letermovir in subjects with hepatic impairment. Br J Clin Pharmacol. 2017a;83(12):2678-2686. doi: 10.1111/bcp.13376
3. Centers for Disease Control and Prevention. Cytomegalovirus (CMV) and congenital CMV infection. 2017 December. URL: https://www.cdc.gov/cmv/clinical/features.html.
4. Ljungman P, Hakki M, and Boeckh M. Cytomegalovirus in hematopoietic stem cell transplant recipients. Hematol Oncol Clin North Am. 2011; 25(1):151–69.
5. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med. 2017; 377(25):2433-44.
6. 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.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Duration of Approval Age Restrictions Quantity FDA-Approved Uses	Q4 2024
REVISION- Notable revisions: Required Medical Information Duration of Approval Quantity FDA-Approved Uses References	Q1 2024
REVISION- Notable revisions: Required Medical Information Duration of Approval Prescriber Requirements Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q1 2023
Q2 2022 Established tracking in new format	Historical changes on file