CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
1Q18 January – February

BRAND NAME
Prevymis™

GENERIC NAME
Letermovir

MANUFACTURER
Merck & Co., Inc.

DATE OF APPROVAL
November 9, 2017

PRODUCT LAUNCH DATE
TBD

REVIEW TYPE
☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Review for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
For prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

OFF LABEL USES
None

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CLINICAL EFFICACY

Background

Hematopietic cell transplant (HCT) recipients at risk for post-transplant CMV disease (i.e. all CMV-seropositive HCT recipients, and all CMV-seronegative recipients with a CMV seropositive donor) should be placed on a CMV disease prevention program from the time of engraftment until at least 100 days after HCT (i.e. phase II) (AI). Ganciclovir, high-dose acyclovir, and valacyclovir have all shown efficacy in randomized studies in reducing the risk for CMV infection after HCT[1].

	Prevymis Prescribing Information[2]
Study Design	Multicenter, double-blind, placebo-controlled Phase 3 trial in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)
N	565 (325 received Prevymis, 170 received placebo, 70 subjects with CMV viremia prior to study drug initiation were excluded)
Drug Regimen	Subjects were randomized (2:1) to receive placebo or Prevymis 480 mg once daily orally or intravenously, adjusted to 240 mg when coadministered with cyclosporine.
Primary Outcome(s)	The primary efficacy endpoint was the incidence of clinically significant CMV infection through Week 24 post-transplant (prophylaxis failure). Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV pre-emptive therapy (PET) based on documented CMV viremia and the clinical condition of the subject.
Secondary Outcome(s)	Not reported
Results	The proportion of patients who failed prophylaxis was 38% in the Prevymis group compared to 61% in the placebo group (difference of -23.5% (95% CI -32.5 to -14.6; p <0.001). The Kaplan-Meier event rate for all-cause mortality in the Prevymis vs. placebo groups was 12% vs. 17% at Week 24 post-transplant, and 24% vs. 28% at Week 48 post-transplant.
# Withdrew due to Lack of Efficacy	The proportion of patients who experienced clinically significant CMV infection by Week 24 was 18% in the Prevymis group compared to 42% in the placebo group.
# Withdrew due to Adverse Effects	The proportion of patients who withdrew from the study before Week 24 was 17% in the Prevymis group compared to 16% in the placebo group.

CONTRAINDICATIONS

Prevymis is contraindicated in patients receiving pimozide or ergot alkaloids:

- Concomitant administration of Prevymis in patients receiving pimozide may result in increased concentrations of pimozide due to inhibition of cytochrome P450 3A (CYP3A) by letermovir, which may lead to QT prolongation and torsades de pointes.
- Concomitant administration of Prevymis in patients receiving ergot alkaloids may result in increased concentrations of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by letermovir, which may lead to ergotism.

Prevymis is contraindicated with pitavastatin and simvastatin when co-administered with cyclosporine.

- Concomitant administration of Prevymis in combination with cyclosporine may result in significantly increased pitavastatin or simvastatin concentrations, which may lead to myopathy or rhabdomyolysis.

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS
Potential for Other Drugs to Affect Prevymis
Letermovir is a substrate of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) transporters. Coadministration of Prevymis with drugs that are inhibitors of OATP1B1/3 transporters may result in increases in letermovir plasma concentrations.

Potential for Prevymis to Affect Other Drugs
Co-administration of Prevymis with midazolam results in increased midazolam plasma concentrations, indicating that letermovir is a moderate inhibitor of CYP3A. Coadministration of Prevymis with drugs that are CYP3A substrates may result in clinically relevant increases in the plasma concentrations of co-administered CYP3A substrates.

Letermovir is an inhibitor of OATP1B1/3 transporters. Co-administration of Prevymis with drugs that are substrates of OATP1B1/3 transporters may result in a clinically relevant increase in plasma concentrations of co-administered OATP1B1/3 substrates.

The magnitude of CYP3A- and OATP1B1/3-mediated drug interactions on co-administered drugs may be different when Prevymis is co-administered with cyclosporine. See the prescribing information for cyclosporine for information on drug interactions with cyclosporine.

Established and Other Potentially Significant Drug Interactions
If dose adjustments of concomitant medications are made due to treatment with Prevymis, doses should be readjusted after treatment with Prevymis is completed.
Refer to Table 3 in the prescribing information. It provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with Prevymis or are predicted drug interactions that may occur with Prevymis

Concomitant Drug Class and/or Clearance	Effect on Concentration†	Clinical Comments
Anti-arrhythmic agents		
amiodarone	↑ amiodarone	Close clinical monitoring for adverse events related to amiodarone is recommended during co-administration. Frequently monitor amiodarone concentrations when amiodarone is co-administered with letermovir.
Anticoagulants		
warfarin	↓ warfarin	When letermovir is co-administered with warfarin, frequently monitor International Normalized Ratio (INR)§.
Anticonvulsants		
phenytoin	↓ phenytoin	When letermovir is co-administered with phenytoin, frequently monitor phenytoin concentrations§.
Antidiabetic agents		
Examples: glyburide, repaglinide, rosiglitazone	↑ glyburide ↑ repaglinide ↑ rosiglitazone	When letermovir is co-administered with glyburide, repaglinide, or rosiglitazone, frequently monitor glucose concentrations§. When letermovir is co-administered with cyclosporine, use of repaglinide is not recommended.
Antifungals		
voriconazole‡	↓ voriconazole	If concomitant administration of voriconazole is necessary, closely monitor for reduced effectiveness of voriconazole§.
Antimycobacterial		
rifampin	↓ letermovir	Co-administration of letermovir and rifampin is not recommended.
Antipsychotics		
pimozide	↑ pimozide	Co-administration is contraindicated due to risk of QT prolongation and torsades de pointes
Ergot alkaloids		
ergotamine, dihydroergotamine	↑ ergotamine, dihydroergotamine	Co-administration is contraindicated due to risk of ergotism

Concomitant Drug Class and/or Clearance	Effect on Concentration†	Clinical Comments
HMG-CoA Reductase Inhibitors		
atorvastatin‡	↑ atorvastatin	When letermovir is co-administered with atorvastatin, do not exceed an atorvastatin dosage of 20 mg daily§. Closely monitor patients for myopathy and rhabdomyolysis. When letermovir is co-administered with cyclosporine, use of atorvastatin is not recommended.
pitavastatin, simvastatin	↑ HMG-CoA reductase inhibitors	Co-administration of letermovir and pitavastatin or simvastatin is not recommended. When letermovir is co-administered with cyclosporine, use of either pitavastatin or simvastatin is contraindicated due to significantly increased pitavastatin or simvastatin concentrations and risk of myopathy or rhabdomyolysis
fluvastatin, lovastatin, pravastatin, rosuvastatin	↑ HMG-CoA reductase inhibitors	When letermovir is co-administered with these statins, a statin dosage reduction may be necessary§. Closely monitor patients for myopathy and rhabdomyolysis. When letermovir is co-administered with cyclosporine, use of lovastatin is not recommended. When letermovir is co-administered with cyclosporine, refer to the statin prescribing information for specific statin dosing recommendations.
Immunosuppressants		
cyclosporine‡	↑ cyclosporine ↑ letermovir	Decrease the dosage of letermovir to 240 mg once daily. Frequently monitor cyclosporine whole blood concentrations during treatment and after discontinuation of letermovir and adjust the dose of cyclosporine accordingly§ .

Concomitant Drug Class and/or Clearance	Effect on Concentration†	Clinical Comments
sirolimus‡	↑ sirolimus	When letermovir is co-administered with sirolimus, frequently monitor sirolimus whole blood concentrations during treatment and after discontinuation of letermovir and adjust the dose of sirolimus accordingly§ . When letermovir is co-administered with cyclosporine and sirolimus, refer to the sirolimus prescribing information for specific sirolimus dosing recommendations§ .
tacrolimus‡	↑ tacrolimus	Frequently monitor tacrolimus whole blood concentrations during treatment and after discontinuation of letermovir and adjust the dose of tacrolimus accordingly§ .
Proton pump inhibitors		
omeprazole	↓omeprazole	Clinical monitoring and dose adjustment may be needed.
pantoprazole	↓ pantoprazole	Clinical monitoring and dose adjustment may be needed.
CYP3A Substrates		
Examples: alfentanil, fentanyl, midazolam, and quinidine	↑ CYP3A substrate	When letermovir is co-administered with a CYP3A substrate, refer to the prescribing information for dosing of the CYP3A substrate with a moderate CYP3A inhibitor§ . When letermovir is co-administered with cyclosporine, the combined effect on CYP3A substrates may be similar to a strong CYP3A inhibitor. Refer to the prescribing information for dosing of the CYP3A substrate with a strong CYP3A inhibitor§ . CYP3A substrates pimozide and ergot alkaloids are contraindicated.

** This table is not all inclusive. † ↓ =decrease, ↑=increase ‡ These interactions have been studied[2]. § Refer to the respective prescribing information.*

ADVERSE REACTIONS

The most common adverse events occurring in at least 10% of subjects in the Prevymis group and at a frequency at least 2% greater than placebo are nausea, diarrhea, vomiting, peripheral edema, cough, headache, fatigue, and abdominal pain.

DOSAGE AND ADMINISTRATION
The recommended dosage of Prevymis is 480 mg administered orally or intravenously once daily. Initiate Prevymis between Day 0 and Day 28 post-transplantation (before or after engraftment), and continue through Day 100 post-transplantation. If oral or intravenous Prevymis is co-administered with cyclosporine, the dosage of Prevymis should be decreased to 240 mg once daily.

Prevymis injection, which contains hydroxypropyl betadex, should be used only in patients unable to take oral therapy. Patients should be switched to oral Prevymis as soon as they are able to take oral medications. Prevymis tablet and injection may be used interchangeably at the discretion of the physician, and no dosage adjustment is necessary when switching formulations.

PRODUCT AVAILABILITY
Tablets: 240 mg, 480 mg
Vials: 240 mg/12 mL, 480 mg/24 mL

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
ganciclovir (Cytovene®)	<u>Treatment of CMV retinitis</u> Induction: 5 mg/kg (given IV at a constant rate over 1 hour) Q12 hrs for 14 to 21 days. Maintenance: 5 mg/kg (given IV at a constant-rate over 1 hour) QD for 7 days per week, or 6 mg/kg QD for 5 days per week. <u>Prevention of CMV disease in transplant recipients</u> Induction: 5 mg/kg (given IV at a constant rate over 1 hour) Q12 hrs for 7 to 14 days. Maintenance: 5 mg/kg (given IV at a constant-rate over 1 hour) QD, 7 days	

	per week, or 6 mg/kg once daily, 5 days per week until 100 to 120 days posttransplantation.	
valacyclovir (Valtrex®)	Prevention of CMV disease in transplant recipients 2 grams PO QID	Off-label regimen[3, 4]

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Utilization Management Recommendation

- There is significant potential for inappropriate use and utilization management should be considered for the following reason(s):
  - ☒ To ensure appropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes.
    - i) Prevymis is indicated for prophylaxis of cytomegalovirus for patients who received allogeneic hematopoietic stem cell transplant.
    - ii) This is to be used for 100 days post-transplant.
    - iii) The injection form should only be used in patients who are unable to take oral therapy.
    - iv) Recommended utilization management tool(s): (check all that apply)
      - (1) ☒ Prior authorization
      - (2) ☐ Quantity limits
      - (3) ☐ Provider newsletter
      - (4) ☐ Hard block (plan exclusion)
      - (5) ☐ Messaging
      - (6) ☐ Electronic step therapy
      - (7) ☐ Clinical program

Product Comparison

- CPAC score: 52 vs. Cytovene - Equal therapeutic outcomes anticipated
- CPAC score: 48 vs. Valtrex - Equal therapeutic outcomes anticipated
  - Equal therapeutic outcomes are anticipated for Prevymis and Cytovene; therefore, it would be clinically appropriate to provide equal access to both or to require a trial of one before the other.
  - Equal therapeutic outcomes are anticipated for Prevymis and Valtrex; therefore, it would be clinically appropriate to provide equal access to both or to require a trial of one before the other.

REFERENCES

[1] Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 15:1143-1238.

[2] Prevymis Prescribing Information. Whitehouse Station, NJ: Merck and Co., Inc.; November, 2017. Available at: https://www.merck.com/product/usa/pi_circulars/p/prevymis/prevymis_pi.pdf. Accessed November 17, 2017.

[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.