PDL DRUG REVIEW

Proprietary Name: Prevymis® Tablets
Common Name: letermovir
PDL Category: Cyto-Megalovirus Agents

Comparable Products	Preferred Drug List Status
Cytovene	Non-Preferred

Summary

Pharmacology/Usage: Letermovir, the active ingredient of Prevymis®, is an antiviral agent. It is an inhibitor of the cytomegalovirus DNA terminase complex which is required for viral DNA processing and packaging.

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

There is no pregnancy category for this product; however, the risk summary indicates that there are no adequate human data available to establish if use poses a risk to pregnancy outcomes. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Tablets: 240mg, 480mg; Injection, solution in a single-dose vial: 240mg/12ml, 480mg/24ml

Recommended Dosage: Take 480mg given PO or IV infusion QD. Start between day 0 and day 28 post-transplantation (before or after engraftment), and continue through day 100 post-transplantation. Adjust the dose of Prevymis® if used concomitantly with cyclosporine. After completed prophylaxis, monitor for CMV reactivation.

Prevymis® injection contains hydroxypropyl betadex and should be used only in patients not able to take oral therapy. Patients should be switched to Prevymis® PO tablets as soon as they are able to take oral medications. Furthermore, Prevymis® tablet and injection may be used interchangeably at the discretion of the physician, with no dosage adjustment needed when switching formulations.

Dose adjustments are not required in renal impairment with creatinine clearance (CrCl) >10ml/min; however, there are insufficient data on use in patients with CrCl ≤10ml/min or in patients on dialysis to make dosing recommendations. Closely monitor serum creatinine levels in patients with CrCl <50ml/min receiving Prevymis® injection. Dose adjustments are not required with mild to moderate hepatic impairment; however, use is not recommended with severe hepatic impairment.

Drug Interactions: If PO or IV Prevymis® is co-administered with cyclosporine, decrease the dose of Prevymis® to 240mg QD. If cyclosporine is started after starting Prevymis®, the next dose of Prevymis® should be decreased to 240mg QD. If cyclosporine is discontinued after starting Prevymis®, the next dose of Prevymis® should be

increased to 480mg QD. If cyclosporine dosing is interrupted due to high cyclosporine levels, no dose adjustment of Prevymis® is needed.

Letermovir is a substrate of OATP1B1/3 transporters. Concomitant use with drugs that are inhibitors of these transporters may result in increases in letermovir plasma levels. Letermovir is a moderate inhibitor of CYP3A and concomitant use with midazolam resulted in increased midazolam levels. Letermovir is also an inhibitor of OATP1B1/3 transporters.

The following are potentially significantly drug interactions if used concomitantly with Prevymis®: amiodarone (close monitoring for adverse reactions and monitor amiodarone levels), warfarin (frequently monitor INR), phenytoin (frequently monitor phenytoin levels), antidiabetic drugs such as glyburide, repaglinide, rosiglitazone (frequently monitor glucose levels; when Prevymis® is co-administered with cyclosporine, use of repaglinide is not recommended); voriconazole (closely monitor for reduced efficacy of voriconazole), rifampin (concomitant use not recommended), pimozide (concomitant use contraindicated), ergot alkaloids (concomitant use contraindicated), atorvastatin (do not exceed atorvastatin 20mg QD and closely monitor for myopathy; when Prevymis® is co-administered with cyclosporine, use of atorvastatin is not recommended), pitavastatin and simvastatin (co-administration with either is not recommended; when Prevymis® is co-administered with cyclosporine, use of either pitavastatin or simvastatin is contraindicated), fluvastatin/lovastatin/pravastatin/rosuvastatin (a statin dose reduction may be needed, closely monitor for myopathy; when Prevymis® is co-administered with cyclosporine, use of lovastatin is not recommended), cyclosporine (adjust Prevymis® dose and monitor cyclosporine levels), sirolimus (monitor blood levels and adjust sirolimus dose prn), tacrolimus (monitor blood levels and adjust tacrolimus dose prn), omeprazole/pantoprazole (monitor and adjust dose prn), and CYP3A substrates (refer to the PI for dosing of the CYP3A substrate with a moderate inhibitor).

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Prevymis®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its comparator.* The most frequently reported adverse events included nausea (4%), diarrhea (2%), vomiting (5%), peripheral edema (5%), cough (4%), headache (5%), fatigue (2%), and abdominal pain (3%). Laboratory abnormalities included absolute neutrophil count (ANC) <500 (0%), hemoglobin <6.5 (1%), platelets <25000 (6%), and serum creatinine >2.5 (0%).

The cardiac adverse event rate was higher with Prevymis® as compared to placebo (13% vs 6%). The most common cardiac adverse events were tachycardia (4% vs 2%) and atrial fibrillation (3% vs 1%).

Contraindications: In patients receiving pimozide or ergot alkaloids; With pitavastatin and simvastatin when co-administered with cyclosporine

Manufacturer: Merck Sharp & Dohme Corp

Analysis: The safety and efficacy of Prevymis® were assessed in a multicenter, randomized, double-blind, phase 3 study that included adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). Subjects were randomized to receive either Prevymis® or placebo, with the study drug administered as either PO or IV. All received CMV DNA monitoring weekly until post-transplant week 14 and then bi-weekly until post-transplant week 24, with initiation of standard-of-care CMV pre-emptive therapy if CMV viremia was considered clinically significant.

Of the 565 treated adults, 70 were found to have CMV viremia prior to study drug initiation and thus were excluded from the studies. The efficacy population consisted of 325 patients who received Prevymis® and 170 who received placebo. The median time to starting study drug was 8 days after transplantation. At baseline, 30% of all subjects had ≥1 of specific factors associated with increased risk for CMV reactivation (high risk stratum). The remaining 70% did not meet any of the high-risk stratum criteria and thus were included in the low risk stratum.

The primary 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. Results can be seed in the table below, which was adapted from the prescribing information.

	letermovir (N=325)	placebo (N=170)
Proportion of subjects who failed prophylaxis	38%	61%
Reasons for failure		
Clinically significant CMV infection by week 24	18%	42%
Initiation of PET based on documented CMV viremia	16%	40%
CMV end-organ disease	2%	2%
Discontinued from study before week 24	17%	16%
Missing outcome in week 24 visit window	3%	3%
Stratum-adjusted treatment difference (letermovir-placebo)		
Difference	-23.5; p<0.0001	

Efficacy results were consistent across high and low risk strata for CMV reactivation. The cumulative rate of clinically significant CMV infection was 6.8% with letermovir vs 41.3% with placebo at week 14 post-transplant and 18.9% letermovir vs 44.3% placebo at week 24 post-transplant.

The Kaplan-Meier event rate for all-cause mortality in the letermovir vs placebo groups was 12% vs 17% at week 24 post-transplant, and 24% vs 28% at 48 weeks post-transplant.

Place in Therapy: Prevymis®, available as an injection and as an oral tablet, is indicated for the prophylaxis of CMV infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). In a phase 3 clinical trial, significantly fewer in the Prevymis® group developed clinically significant CMV infection through week 24 post-transplant (prophylaxis failure) as compared with placebo.

There is no evidence at this time to support that Prevymis® is safer or more effective than the currently available medications. It is therefore recommended that Prevymis® remain non-preferred to ensure it is used in clinically appropriate situations.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Prevymis [package insert]. Whitehouse Station, NJ: Merck & Co; 2017.