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Merck Receives FDA Approval of PREVYMIS™ (letermovir) for Prevention of Cytomegalovirus (CMV) Infection and Disease in Adult Allogeneic Stem Cell Transplant Patients

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KENILWORTH, N.J.

CMV Prophylaxis with PREVYMIS Associated with Lower All-Cause Mortality Through Week 24 and Week 48 Post-Transplant

KENILWORTH, N.J.--([BUSINESS WIRE](#))--Merck & Co., Inc. (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved PREVYMIS™ (letermovir) once-daily tablets for oral use and injection for intravenous infusion. PREVYMIS is indicated for prophylaxis (prevention) of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

CMV is a common and potentially serious viral infection in allogeneic HSCT recipients. CMV-seropositive patients who undergo an HSCT are at high risk for CMV reactivation. Any level of CMV infection is associated with increased mortality in HSCT patients.

In the pivotal Phase 3 clinical trial supporting approval, significantly fewer patients in the PREVYMIS group (38%, n=122/325) compared to the placebo group (61%, n=103/170) developed clinically significant CMV infection, discontinued treatment or had missing data through Week 24 post-HSCT [treatment difference: -23.5 (95% confidence interval -32.5 to -14.6), (p<0.0001)], the primary efficacy endpoint. All-cause mortality in patients receiving PREVYMIS was lower compared to placebo, 12% vs. 17%, respectively, at week 24 post-transplant. In this study, the incidence of bone marrow suppression in the PREVYMIS group was comparable to the placebo group. The median time to engraftment was 19 days in the PREVYMIS group and 18 days in the placebo group.

PREVYMIS is contraindicated in patients receiving pimozone or ergot alkaloids. Increased pimozone concentrations may lead to QT prolongation and torsades de pointes. Increased ergot alkaloids concentrations may lead to ergotism. PREVYMIS is contraindicated with pitavastatin and simvastatin when co-administered with cyclosporine. Significantly increased pitavastatin or simvastatin concentrations may lead to myopathy or rhabdomyolysis.

The concomitant use of PREVYMIS (letermovir) and certain drugs may result in potentially significant drug interactions, some of which may lead to adverse reactions (PREVYMIS or concomitant drugs) or reduced therapeutic effect of PREVYMIS or the concomitant drug. Consider the potential for drug interactions prior to and during PREVYMIS therapy; review concomitant medications during PREVYMIS therapy; and monitor for adverse reactions associated with PREVYMIS and concomitant medications.

“Our findings demonstrate that letermovir is a significant and welcomed advance in the prevention of clinically significant CMV infection and lowers mortality in this highly vulnerable patient population,” said Dr. Francisco M. Marty, associate professor of medicine at Harvard Medical School and attending physician in transplant and oncology infectious diseases at Dana-Farber Cancer Institute and Brigham and Women’s Hospital in Boston.

The recommended dosage of PREVYMIS is 480 mg administered once daily, initiated as early as Day 0 and up to Day 28 post-transplantation (before or after engraftment), and continued through Day 100 post-transplantation. If PREVYMIS is co-administered with cyclosporine, the dosage of oral or intravenous PREVYMIS should be decreased to 240 mg once daily. PREVYMIS is available as 240 mg and 480 mg tablets, which may be administered with or without food. PREVYMIS is also available as 240 mg and 480 mg injection for intravenous infusion via a peripheral catheter or central venous line at a constant rate over one hour.

“PREVYMIS is the first new medicine for CMV infection approved in the U.S. in 15 years,” said Dr. Roy Baynes, senior vice president, head of clinical development, and chief medical officer, Merck Research Laboratories. “PREVYMIS continues Merck’s longstanding tradition of bringing forward important new therapies to address serious infectious diseases. We are proud to add this breakthrough medicine to our existing offerings for physicians and patients.”

PREVYMIS is expected to be available in December. The list price (wholesaler acquisition cost) per day for PREVYMIS tablets is \$195.00 and for PREVYMIS injection is \$270.00. Wholesaler acquisition costs do not include discounts that may be paid on the product.

The cardiac adverse event rate (regardless of investigator-assessed causality) was higher in patients receiving PREVYMIS than placebo (13% vs. 6%). The most common cardiac adverse events were tachycardia (reported in 4% PREVYMIS patients and 2% placebo patients) and atrial fibrillation (reported in 3% PREVYMIS patients and 1% placebo patients). These adverse events were reported as mild or moderate in severity. The rate of adverse events occurring in at least 10% of PREVYMIS-treated HSCT recipients and at a frequency at least 2% greater than placebo were nausea (27% vs. 23%), diarrhea (26% vs. 24%), vomiting (19% vs. 14%), peripheral edema (14% vs. 9%), cough (14% vs. 10%), headache (14% vs. 9%), fatigue (13% vs. 11%), and abdominal pain (12% vs. 9%). The most frequently reported adverse event that led to study drug discontinuation was nausea (occurring in 2% of PREVYMIS patients and 1% of placebo patients). Hypersensitivity reaction, with associated moderate dyspnea, occurred in one patient following the first infusion of IV PREVYMIS after switching from oral PREVYMIS, leading to treatment discontinuation.

Clinical data supporting PREVYMIS (letermovir)

To evaluate prophylaxis with PREVYMIS as a preventive strategy for CMV infection or disease in transplant recipients at high risk for CMV reactivation, the efficacy of PREVYMIS was assessed in a multicenter, double-blind, placebo-controlled Phase 3 trial in adult CMV-positive recipients [R+] of an allogeneic HSCT. Patients were randomized (2:1) to receive either PREVYMIS at a dose of 480 mg once daily adjusted to 240 mg when co-administered with cyclosporine, or placebo. Study drug was initiated after HSCT (at any time from Day 0-28 post-transplant) and continued through Week 14 post-transplant. Patients were monitored through Week 24 post-transplant for the primary efficacy endpoint, with continued follow-up through Week 48 post-transplant. The primary efficacy endpoint was the incidence of clinically significant CMV infection through Week 24 post-transplant, defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV pre-emptive therapy based on documented CMV viremia and the clinical condition of the patient. The Non-Completer equals Failure approach was used, where patients who discontinued from the trial prior to Week 24 post-transplant or had a missing outcome at Week 24 post-transplant were counted as failures.

Among the 565 treated patients, 34% were engrafted at baseline and 30% had one or more factors associated with additional risk for CMV reactivation. The most common primary reasons for transplant were acute myeloid leukemia (38%), myelodysplastic syndrome (16%), and lymphoma (12%).

Fewer patients in the PREVYMIS group had clinically significant CMV infection by Week 24 post-HSCT compared to the placebo group, 18% vs. 42%, respectively. Through the Week 14 post-HSCT treatment period, 8% of patients in the PREVYMIS group and 39% of patients in the placebo group experienced clinically significant CMV infection. Clinically significant CMV infection was defined as CMV end-organ disease or initiation of pre-emptive therapy based on documented CMV viremia and the clinical condition of the patient.

Efficacy results were consistent across high- and low-risk strata for CMV reactivation.

PREVYMIS demonstrated significant benefit compared to placebo in time to clinically significant CMV infection through Week 24 post-HSCT (18.9% vs. 44.3% cumulative rate; stratified log-rank test, two-sided p-value <0.0001). Post-hoc analysis demonstrated that among PREVYMIS-treated patients, inclusion in the high-risk stratum for CMV reactivation at baseline, occurrence of graft-versus-host disease (GVHD), and steroid use at any time after randomization may be associated with the development of clinically significant CMV infection between Week 14 and Week 24 post-transplant.

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.

Additional Selected Safety Information about PREVYMIS (letermovir)

Co-administration of PREVYMIS with drugs that are inhibitors of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) transporters may result in increases in letermovir plasma concentrations.

Co-administration of PREVYMIS with midazolam results in increased midazolam plasma concentration. Co-administration of PREVYMIS with drugs that are CYP3A substrates may result in clinically relevant increases in the plasma concentrations of co-administered CYP3A substrates.

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.

If dose adjustments of concomitant medications are made due to treatment with PREVYMIS, doses should be readjusted after PREVYMIS treatment is completed.

Established or potentially clinically significant drug interactions may occur with co-administration of PREVYMIS and drug/drug classes (without cyclosporine, unless otherwise indicated), including, but not limited to, the following:

- Anti-arrhythmic agents
 - Amiodarone: increases amiodarone concentration
- Anticoagulants
 - Warfarin: decreases warfarin concentration
- Anticonvulsants
 - Phenytoin: decreases phenytoin concentration
- Antidiabetic agents
 - Glyburide: increases glyburide concentration
 - Repaglinide: increases repaglinide concentration

- Rosiglitazone: increases rosiglitazone concentration
- Antifungals
 - Voriconazole: decreases voriconazole concentration
- Antimycobacterial
 - Rifampin: decreases letemovir concentration
- Antipsychotics
 - Pimozide: increases pimozide concentration; co-administration is contraindicated
- Ergot alkaloids
 - Ergotamine: increases ergotamine concentration; co-administration is contraindicated
 - Dihydroergotamine: increases dihydroergotamine concentration; co-administration is contraindicated
- HMG-CoA reductase inhibitors
 - Pitavastatin, Simvastatin: increases HMG-CoA reductase inhibitors concentration; co-administration is contraindicated when PREVYMIS is co-administered with cyclosporine
 - Atorvastatin: increases atorvastatin concentration
 - Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin: increases HMG-CoA reductase inhibitors concentration
- Immunosuppressants
 - Cyclosporine: increases both cyclosporine and letemovir concentrations
 - Sirolimus: increases sirolimus concentration
 - Tacrolimus: increases tacrolimus concentration
- Proton pump inhibitors
 - Omeprazole: decreases omeprazole concentration
 - Pantoprazole: decreases pantoprazole concentration
- CYP3A substrate examples
 - Alfentanil, fentanyl, midazolam and quinidine: may increase CYP3A substrate concentration
 - Pimozide and ergot alkaloids are contraindicated

The safety and efficacy of PREVYMIS (letemovir) in patients below 18 years of age have not been established.

For patients with CLCr greater than 10 mL/min (by Cockcroft-Gault equation), no dosage adjustment of PREVYMIS is required based on renal impairment. The safety of PREVYMIS in patients with end-stage renal disease (CLCr less than 10 mL/min), including patients on dialysis, is unknown.

No dosage adjustment of PREVYMIS is required based on mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment.

About PREVYMIS (letemovir)

PREVYMIS is a member of a new class of non-nucleoside CMV inhibitors (3,4 dihydro-quinazolines) and inhibits viral replication by specifically targeting the viral terminase complex. Cross resistance is not likely with drugs outside of this class. PREVYMIS is fully active against viral populations with substitutions conferring resistance to CMV DNA polymerase inhibitors. These DNA polymerase inhibitors are fully active against viral populations with substitutions conferring resistance to PREVYMIS. PREVYMIS has no activity against other viruses. Letemovir has been granted orphan designation for the prevention of CMV disease in at-risk populations in the U.S., EU and Japan, and is under accelerated review in the EU and Japan.

Under an agreement signed in 2012, Merck (through a subsidiary) purchased worldwide rights to develop and commercialize letemovir from AiCuris GmbH & Co KG (www.aicuris.com).

About CMV and Treatment

CMV is a common virus that infects people of all ages. Many adults in the United States are CMV seropositive, meaning they have CMV antibodies in their blood, indicating a previous exposure to or primary infection with CMV. People with normal immune systems rarely develop CMV symptoms after initial infection, with the virus typically remaining inactive or latent in the body for life. A weakened immune system may give the virus a chance to reactivate, potentially leading to symptomatic disease or a secondary infection due to other pathogens. CMV disease can lead to end-organ damage, including gastrointestinal tract disease, pneumonia or retinitis. Transplant recipients who develop CMV infection post-transplant are at increased risk for transplant failure and death. CMV prophylaxis with certain existing antivirals has been associated with drug-specific effects, including myelosuppression and renal toxicity, in HSCT recipients.

About Merck

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola. For more information, visit www.merck.com and connect with us on [Twitter](#), [Facebook](#), [Instagram](#), [YouTube](#) and [LinkedIn](#).

Forward-Looking Statement

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2016 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

Please see Prescribing Information for PREVYMIS (Ietermovir) at http://www.merck.com/product/usa/pi_circulars/p/prevymis/prevymis_pi.pdf and Patient Information for PREVYMIS at http://www.merck.com/product/usa/pi_circulars/p/prevymis/prevymis_ppi.pdf.

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