



NEWS RELEASE

U.S. FDA Approves New Indication for Merck's PREVYMIS® (letermovir) for Prevention of Cytomegalovirus (CMV) Disease in High-Risk Adult Kidney Transplant Recipients

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PREVYMIS now approved for CMV prophylaxis after kidney transplant in Donor CMV-seropositive/Recipient CMV-seronegative patients

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced the U.S. Food and Drug Administration (FDA) has approved a new indication for PREVYMIS® (letermovir) for prophylaxis of cytomegalovirus (CMV) disease in adult kidney transplant recipients at high risk (Donor CMV-seropositive/Recipient CMV-seronegative [D+/R-]) following a priority review.

PREVYMIS is an antiviral agent that was initially approved by the FDA in 2017 for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). PREVYMIS is administered once-daily as an oral tablet or as an injection for intravenous infusion.

PREVYMIS is contraindicated in patients receiving pimozide or ergot alkaloids. Increased pimozide concentrations due to concomitant administration of PREVYMIS may lead to QT prolongation and torsades de pointes. Increased ergot alkaloids concentrations due to concomitant administration of PREVYMIS 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 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. See additional Selected Safety Information below.

“PREVYMIS has been an important addition to the care of high-risk adult CMV-seropositive patients who have received allogeneic stem cell transplants to help prevent CMV infection and disease. We are delighted that PREVYMIS is now approved to help prevent CMV disease in adult kidney transplant patients at high risk,” said Dr. Elizabeth Rhee, vice president, global clinical development, Merck Research Laboratories. “At Merck, we are proud to continue to bring innovative medicines to people to address serious infectious diseases.”

Phase 3 study for PREVYMIS in high-risk adult kidney transplant recipients [CMV D+/R-]

The FDA approval of PREVYMIS for CMV disease prophylaxis in adult kidney transplant recipients was supported by a Phase 3, randomized, multicenter, double-blind, active comparator-controlled non-inferiority trial (P002, NCT03443869) in 589 adult kidney transplant recipients at high risk (CMV D+/R-). Participants were randomized (1:1) to receive either PREVYMIS concomitantly with acyclovir (n=292), or valganciclovir concomitantly with a placebo to acyclovir (n=297). Study drug was initiated between Day 0 and Day 7 post-kidney transplant and continued through Week 28 (~200 days) post-transplant. Study drug was administered either orally or IV; the dose of PREVYMIS was the same regardless of the route of administration. Three participants received IV PREVYMIS for a mean duration of 1.7 days. Participants were monitored through Week 52 post-transplant. The median age was 51 years (range: 18 to 82 years); 72% were male; 84% were White; 9% were Black; 3% were multiple; 2% were Asian; 1% Alaskan native or American Indian; 17% were Hispanic or Latino; and 60% received a kidney from a deceased donor. The most common primary reasons for transplant were congenital cystic kidney disease (17%), hypertension (16%), and diabetes/diabetic nephropathy (14%).

The study demonstrated that PREVYMIS was non-inferior to valganciclovir, the current standard of care, for the primary endpoint of incidence of CMV disease (CMV end-organ disease or CMV syndrome, confirmed by an independent adjudication committee) through Week 52 post-kidney transplant. The proportion of study participants with CMV disease through Week 52 post-kidney transplant was 10% with PREVYMIS and 12% with valganciclovir (stratum-adjusted treatment difference = -1.4, [95% confidence interval, -6.5, 3.8], meeting the pre-specified non-inferiority margin of 10%). The incidence of CMV syndrome (defined as evidence of CMV in blood by viral isolation, rapid culture, antigenemia, or nucleic acid testing, and two or more of the following: 1) fever $\geq 38^{\circ}\text{C}$ for at least 2 days, 2) new or increased malaise/fatigue, 3) leukopenia or neutropenia on two separate measurements at least 24 hours apart, 4) $\geq 5\%$ atypical lymphocytes, 5) thrombocytopenia, 6) elevation of ALT or AST to 2x the upper limit of normal) was 8% vs 11%, respectively. The incidence of CMV end organ disease was 2%

vs less than 1%, respectively. For purposes of these analyses, participants who discontinued prematurely from the study for any reason or were missing data at the timepoint were not counted as failures. The number of participants who discontinued from the study before Week 52 was 32 (11%) in the PREVMIS arm and 28 (9%) in the valganciclovir arm. The number of participants with a missing outcome in the Week 52 visit window was 24 (8%) in the PREVMIS arm and 25 (8%) in the valganciclovir arm.

Efficacy was comparable across all subgroups. This included the subgroups that used or did not use highly cytolytic, anti-lymphocyte immunotherapy during induction, which was a stratification factor at randomization.

In an exploratory analysis of the incidence of CMV disease through Week 28 post-transplant, the difference (PREVMIS – valganciclovir) was -1.7% with a 95% CI of (-3.4, 0.1). No subjects in the PREVMIS group experienced CMV disease through Week 28 post-transplant (end of treatment period) compared with five subjects in the valganciclovir group.

The safety of PREVMIS was also evaluated in the Phase 3 (P002) study. Adverse events (AEs) were those reported while participants were on study medication or within two weeks of study medication completion/discontinuation. Diarrhea was reported in at least 10% of participants in the PREVMIS group and at a frequency greater than valganciclovir (PREVMIS, 32%; valganciclovir, 29%). Study drug was discontinued due to an AE in 4% of PREVMIS participants and 14% of valganciclovir participants. The most frequently reported AEs that led to study drug discontinuation were neutropenia (PREVMIS, 1%; valganciclovir, 2%) and leukopenia (PREVMIS, 1%; valganciclovir, 5%).

The Phase 3 study also collected information on laboratory abnormalities reported through week 28 post-transplant. Selected laboratory abnormalities were as follows:

	PREVMIS N=292	Valganciclovir N=297
Absolute neutrophil count (cells/ μ L)		
< 500	2%	7%
500 – < 750	1%	4%
750 – < 1000	1%	8%
Total < 1000	5%	18%
Hemoglobin (g/dL)		
< 6.5	2%	0%
6.5 – < 8.0	4%	5%
8.0 – < 9.5	29%	32%
Total < 9.5	34%	37%
Platelets (cells/ μ L)		
< 50000	0%	0%
50000 – < 100000	1%	3%
Total < 100000	1%	3%
Leukocytes (cells/ μ L)		
< 1000	1%	2%
1000 – < 2000	5%	19%

2000 – < 2500	4%	14%
Total < 2500	10%	35%
Serum creatinine (mg/dL)		
> 2.5	24%	22%
> 1.5 – 2.5	49%	52%
Total > 1.5	73%	73%

Dosing of PREVYMIS in high-risk adult kidney transplant recipients

The recommended dosage of PREVYMIS is 480 mg administered once daily orally or as an intravenous infusion, initiated as early as Day 0 and up to Day 7 post-kidney transplant and continued through Day 200 post-transplant. If PREVYMIS is co-administered with cyclosporine, the dosage of oral or intravenous PREVYMIS should be decreased to 240 mg once daily. PREVYMIS 240 mg and 480 mg tablets may be administered with or without food. Following the completion of PREVYMIS prophylaxis, monitoring for CMV reactivation is recommended.

For patients with creatinine clearance (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. In patients with CLcr less than 50 mL/min receiving PREVYMIS injection, accumulation of the intravenous vehicle, hydroxypropyl betadex, could occur. Serum creatinine levels should be closely monitored in these patients.

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.

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

About PREVYMIS (letermovir)

PREVYMIS inhibits viral replication by targeting the CMV DNA terminase complex. PREVYMIS is now approved for prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV-seropositive/Recipient CMV-seronegative [D+/R-]). Since 2017, PREVYMIS has been the only drug approved in the United States for prophylaxis of CMV infection and disease in adults who are CMV-seropositive [R+] and have received an allogeneic HSCT, and has also been approved for this indication in more than 60 countries including EU member states, Canada, Japan and China. Under an agreement signed in 2012, Merck (through a subsidiary) purchased worldwide rights to develop and commercialize letermovir from AiCuris GmbH & Co KG (www.aicuris.com).

Selected Safety Information about PREVYMIS

PREVYMIS is contraindicated in patients receiving pimozide or ergot alkaloids. Increased pimozide 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 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.

The rates of adverse events in the first 100 days following HSCT occurring in at least 10% of transplant recipients treated with PREVYMIS 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%).

Hypersensitivity reaction, with associated moderate dyspnea, occurred in one HSCT subject following the first infusion of IV PREVYMIS after switching from oral PREVYMIS, leading to treatment discontinuation.

The most common adverse event occurring in at least 10% of kidney transplant recipients treated with PREVYMIS and at a frequency greater than valganciclovir was diarrhea (32% vs 29%).

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

Co-administration of PREVYMIS may alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PREVYMIS. Consult the full Prescribing Information prior to and during treatment for potential drug interactions.

Closely monitor serum creatinine levels in patients with CLCr less than 50 mL/min using PREVYMIS injection.

PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment.

The safety and efficacy of PREVYMIS 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.

About CMV

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 healthy immune systems rarely develop CMV symptoms after initial infection, with the virus typically remaining inactive or latent in the body for life. CMV-seronegative recipients who receive an organ from a CMV-seropositive donor [D+/R-] are at high risk of CMV disease after transplantation.

About Merck

At Merck, known as MSD outside of the United States and Canada, we are unified around our purpose: We use the power of leading-edge science to save and improve lives around the world. For more than 130 years, we have brought hope to humanity through the development of important medicines and vaccines. We aspire to be the premier research-intensive biopharmaceutical company in the world – and today, we are at the forefront of research to deliver innovative health solutions that advance the prevention and treatment of diseases in people and animals. We foster a diverse and inclusive global workforce and operate responsibly every day to enable a safe, sustainable and healthy future for all people and communities. For more information, visit www.merck.com and connect with us on **Twitter**, **Facebook**, **Instagram**, **YouTube** and **LinkedIn**.

Forward-Looking Statement of Merck & Co., Inc., Rahway, N.J., USA

This news release of Merck & Co., Inc., Rahway, 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 candidates that the candidates 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 the global outbreak of novel coronavirus disease (COVID-19); 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 Annual Report on Form 10-K for the year ended December 31, 2022 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 at https://www.merck.com/product/usa/pi_circulars/p/prevymis/prevymis_pi.pdf and Patient Information/Medication Guide for PREVYMIS at https://www.merck.com/product/usa/pi_circulars/p/prevymis/prevymis_ppi.pdf.

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