Gilead Submits Supplemental New Drug Application to U.S. Food and Drug Administration for Once-Daily Descovy® for HIV Pre-Exposure Prophylaxis

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- Filing Supported by Data Demonstrating Non-inferiority Compared to Truvada® Coupled with Bone and Renal Safety Advantages in People at Risk of Sexually Acquired HIV Infection -

FOSTER CITY, Calif.--(BUSINESS WIRE)--Apr. 5, 2019-- Gilead Sciences, Inc. (NASDAQ: GILD) announced today that the company has submitted a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) for Descovy® (emtricitabine 200 mg and tenofovir alafenamide 25 mg tablets) for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection among individuals who are HIV-negative and at risk for HIV. A Priority Review voucher was submitted with the filing, leading to an anticipated review time of six months.

The filing is based on the results of the Phase 3 DISCOVER trial which evaluated the safety and efficacy of Descovy compared to Truvada in men and transgender women who have sex with men at high-risk for sexually acquired HIV infection. Truvada® (emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg tablets) for PrEP is currently the only FDA approved product indicated to reduce the risk of sexually acquired HIV-1 in individuals (≥35 kg) who are HIV-negative and at risk for HIV.

Results from the DISCOVER trial, presented at the 2019 Conference on Retroviruses and Opportunistic Infections, demonstrated that Descovy achieved non-inferiority to Truvada in study participants who were at substantial and sustained risk of HIV acquisition. Additionally, statistically significant improvements in renal and bone laboratory parameters were observed for participants receiving Descovy versus those receiving Truvada.

“Data have shown that when used in combination with other agents for HIV treatment, Descovy offers high efficacy and additional benefits with respect to renal and bone safety compared with Truvada. Now, the results from the DISCOVER trial suggest that Descovy may offer those same benefits for HIV prevention, which are important considerations for the potential long-term use of PrEP,” said John McHutchison, AO, MD, Chief Scientific Officer and Head of Research and Development, Gilead Sciences. “We look forward to working with the FDA to help evaluate bringing this option to people at risk of acquiring HIV infection.”

In the United States, Descovy is approved in combination with other antiretroviral agents for the treatment of HIV infection in patients weighing ≥25 kg and is not indicated for PrEP. Truvada is indicated in combination with safer sex practices for HIV PrEP to reduce the risk of sexually acquired HIV in at-risk individuals who are HIV-negative and weigh ≥35 kg. Descovy and Truvada each have a Boxed Warning in their respective product labels regarding the risk of post-treatment acute exacerbation of hepatitis B; the Truvada label also carries a Boxed Warning for the risk of drug resistance with PrEP in undiagnosed early HIV infection. See below for Important Safety Information and complete Indications.

“Studies, including DISCOVER, have shown that adherence to a once-daily PrEP regimen can decrease the risk of HIV acquisition,” said Edwin DeJesus, MD, FACP, FIDSA, Medical Director, Orlando Immunology Center. “If approved, Descovy may help equip health care providers with an additional preventive option thereby potentially expanding the impact of PrEP.”

Among DISCOVER trial participants, Descovy and Truvada were well tolerated and had low discontinuation rates due to adverse events of 1.3 percent and 1.8 percent, respectively. The most common (≥5 percent in the Descovy group) drug-related adverse event was diarrhea.

The use of Descovy for the prevention of HIV is investigational and has not been determined to be safe or efficacious and is not approved anywhere globally.

Important U.S. Safety Information and Indication for Descovy for HIV Treatment

BOXED WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- **Descovy is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of Descovy have not been established in patients coinfected with HIV-1 and HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of Descovy. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue Descovy. If appropriate, initiation of anti-hepatitis B therapy may be warranted.**

Warnings and precautions

- Immune reconstitution syndrome, including the occurrence of autoimmune disorders with variable time to onset, has been reported.
- New onset or worsening renal impairment: Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. In clinical trials of FTC and tenofovir alafenamide with elvitegravir and cobicistat, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Do not initiate Descovy in patients with estimated creatinine clearance (CrCl) <30 mL/min. Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue Descovy in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.
  Renal monitoring: In all patients, monitor CrCl, urine glucose, and urine protein prior to initiating and during therapy. In

patients with chronic kidney disease, additionally monitor serum phosphorus.
- Lactic acidosis and severe hepatomegaly with steatosis: Fatal cases have been reported with the use of nucleoside analogs, including FTC and TDF. Discontinue Descovy if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity develop, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

Adverse reactions

- Most common adverse reaction (incidence ≥10%; all grades) in clinical studies was nausea (10%).

Drug interactions

- Prescribing information: Consult the full prescribing information for Descovy for more information on potentially significant drug interactions, including clinical comments.
- Metabolism: Drugs that inhibit P-gp can increase the concentrations of components of Descovy. Drugs that induce P-gp can decrease the concentrations of components of Descovy, which may lead to loss of efficacy and development of resistance.
- Drugs affecting renal function: Coadministration of Descovy with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine and tenofovir and the risk of adverse reactions.

Dosage and administration

- Dosage: Patients who weigh ≥25 kg: 1 tablet taken orally once daily with or without food.
- Renal impairment: Not recommended in patients with CrCl <30 mL/min.
- Testing prior to initiation: Test patients for HBV infection and assess CrCl, urine glucose and urine protein.
- Pediatrics: The safety and effectiveness of Descovy coadminstered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

Pregnancy and lactation

- Pregnancy: There is insufficient human data on the use of Descovy during pregnancy. An Antiretroviral Pregnancy Registry (APR) has been established; available data from the APR for FTC shows no difference in the rates of birth defects compared with a U.S. reference population.
- Lactation: Women infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV-1 transmission.

INDICATION

Descovy is indicated in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in patients weighing at least 35 kg.

Descovy is also indicated, in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor, for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg.

Limitations of Use:

Descovy is not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of acquiring HIV-1 infection.

Important U.S. Safety Information and Indication for Truvada for PrEP

BOXED WARNING: RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR PrEP IN UNDIAGNOSED EARLY HIV-1 INFECTION and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- **Truvada for PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiation and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of Truvada for PrEP following undetected acute HIV-1 infection. Do not initiate if signs or symptoms of acute HIV-1 infection are present unless HIV-negative status is confirmed**
- **Severe acute exacerbations of hepatitis B have been reported in HBV-infected patients who discontinued Truvada. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients with HBV after discontinuing Truvada. If appropriate, initiation of anti-hepatitis B therapy may be warranted**

Contraindications

- Do not use Truvada for PrEP in individuals with unknown or positive HIV status

Warnings and precautions: Comprehensive risk reduction strategies

- **Reduce HIV-1 risk:** Truvada for PrEP is not always effective in preventing HIV-1. Use only as part of a comprehensive

prevention strategy that includes safer sex practices, regular testing for HIV-1 and other STIs, and counseling on reducing sexual risk behaviors
- **Reduce potential for drug resistance:** Truvada for PrEP should only be used in individuals confirmed to be HIV-negative immediately prior to initiation, at least every 3 months while taking Truvada, and upon an STI diagnosis. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only Truvada. Truvada alone is not a complete regimen for treating HIV-1
- HIV antibody tests may not detect acute HIV infection. If recent exposures are suspected or symptoms of acute HIV infection are present (e.g., fever, fatigue, myalgia, skin rash), delay initiating (≥1 month) or discontinue use and confirm HIV-negative status with a test approved by U.S. Food and Drug Administration (FDA) for the diagnosis of acute HIV infection
- If a screening test indicates possible HIV-1 infection, convert the HIV-1 PrEP regimen to an HIV treatment regimen until HIV-negative status is confirmed.
- **Counsel on adherence:** Counsel individuals to strictly adhere to their dosing schedule, as efficacy is strongly correlated with adherence. Some individuals, such as adolescents, may benefit from more frequent visits and counseling.

Warnings and precautions

- **New onset or worsening renal impairment:** Cases of acute renal impairment and Fanconi syndrome have been reported with the use of tenofovir disoproxil fumarate (TDF). Truvada is not recommended in individuals with estimated creatinine clearance (CrCl) <60 mL/min. Avoid concurrent or recent use with a nephrotoxic agent. Acute renal failure has been reported after initiation of high dose or multiple NSAIDs in patients at risk for renal dysfunction; consider alternatives to NSAIDs in these patients. Monitor renal function in all patients – See Dosage and Administration
- **Bone effects:** Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia associated with proximal renal tubulopathy, have been reported with the use of TDF Consider monitoring BMD in patients with a history of pathologic fracture or risk factors for bone loss
- **Lactic acidosis and severe hepatomegaly with steatosis:** Fatal cases have been reported with the use of nucleoside analogs, including Truvada. Discontinue use if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity develop, including hepatomegaly and steatosis in the absence of marked transaminase elevations
- **Drug interactions:** See Drug Interactions section. Consider the potential for drug interactions prior to and during use of Truvada and monitor for adverse reactions

Adverse reactions

- **Common adverse reactions** (>2% and more frequently than placebo) of Truvada for PrEP in clinical trials were headache, abdominal pain, and weight loss

Drug interactions

- **Prescribing information:** Consult the full Prescribing Information for Truvada for more information, warnings, and potentially significant drug interactions, including clinical comments
- **Hepatitis C antivirals:** Coadministration with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, or sofosbuvir/velpatasvir /voxilaprevir increases TDF exposure; monitor for adverse reactions
- **Drugs affecting renal function:** Coadministration of Truvada with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine and/or tenofovir

Pregnancy and lactation

- **Pregnancy:** An Antiretroviral Pregnancy Registry (APR) has been established. Available data from observational studies and the APR show no increase in the rate of major birth defects for Truvada compared with a US reference population. Consider HIV prevention methods, including Truvada for PrEP in at-risk women due to the potential increased risk of HIV-1 infection during pregnancy and mother to child transmission during acute HIV-1 infection
- **Lactation:** Emtricitabine and tenofovir have been detected in human milk. Evaluate the benefits and risks of Truvada for PrEP in breastfeeding women, including the risk of HIV-1 acquisition due to nonadherence, and subsequent mother to child transmission. Health benefits of breastfeeding should be considered along with potential adverse effects of Truvada on the child, which are unknown

Dosage and administration

- **Dosage:** One tablet once daily with or without food
- **HIV screening:** Test for HIV-1 infection prior to initiating and at least every 3 months during treatment
- **HBV screening:** Test for HBV infection prior to or when initiating treatment
- **Renal impairment and monitoring:** Not recommended in individuals with CrCl <60 mL/min. In all patients, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein on a clinically appropriate schedule. In patients

with chronic kidney disease, also assess serum phosphorus

INDICATION

Truvada for PrEP (pre-exposure prophylaxis) is indicated to reduce the risk of sexually acquired HIV-1 in adults and adolescents (≥35 kg) who are at risk for HIV, when used in combination with safer sex practices. HIV-negative status must be confirmed immediately prior to initiation

- If clinical symptoms of acute HIV-1 infection are present and recent exposures (<1 month) are suspected, delay initiation for at least 1 month until HIV-negative status is reconfirmed. Alternatively, confirm HIV-negative status with a test cleared by FDA to aid in the diagnosis of acute HIV-1 infection

Individuals at risk for sexually acquired HIV-1 may include those:

- With HIV-1 infected partner(s), or
- Who engage in sexual activity in a high prevalence area or social network and have additional risk factors, such as: inconsistent or no condom use, diagnosis of sexually transmitted infections (STIs), exchange of sex for commodities, use of illicit drugs or alcohol dependence, incarceration, or sexual partners of unknown HIV status with any of these risk factors

About Gilead Sciences

Gilead Sciences, Inc. is a research-based biopharmaceutical company that discovers, develops and commercializes innovative medicines in areas of unmet medical need. The company strives to transform and simplify care for people with life-threatening illnesses around the world. Gilead has operations in more than 35 countries worldwide, with headquarters in Foster City, California.

For nearly 30 years, Gilead has been a leading innovator in the field of HIV, driving advances in treatment, prevention, testing and linkage to care, and cure research. Today, it's estimated that more than 11.5 million people living with HIV globally receive antiretroviral therapy provided by Gilead or one of the company's manufacturing partners.

For more information on Gilead Sciences, please visit the company's website at www.gilead.com.

Forward-Looking Statement

This press release includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 that are subject to risks, uncertainties and other factors, including the risk that FDA and other regulatory agencies may not approve Descovy for PrEP in the currently anticipated timelines or at all, and any marketing approvals, if granted, may have significant limitations on its use. As a result, Descovy for PrEP may never be successfully commercialized. There is also the possibility of unfavorable results from additional studies involving Descovy and Truvada for PrEP. These risks, uncertainties and other factors could cause actual results to differ materially from those referred to in the forward-looking statements. The reader is cautioned not to rely on these forward-looking statements. These and other risks are described in detail in Gilead's Annual Report on Form 10-K for the year ended December 31, 2018, as filed with the U.S. Securities and Exchange Commission. All forward-looking statements are based on information currently available to Gilead, and Gilead assumes no obligation to update any such forward-looking statements.

*U.S. full Prescribing Information for Descovy and Truvada, including **BOXED WARNINGS**, is available at www.gilead.com*

Descovy, Descovy for PrEP, Truvada, Truvada for PrEP and Gilead are trademarks of Gilead Sciences, Inc. or its related companies.

For more information on Gilead Sciences, please visit the company's website at www.gilead.com, follow Gilead on Twitter (@GileadSciences) or call Gilead Public Affairs at 1-800-GILEAD-5 or 1-650-574-3000.

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