Merck’s PIFELTRO™ (doravirine) and DELSTRIGO™ (doravirine/lamivudine/tenofovir disoproxil fumarate) Receive US FDA Approval for Use in Appropriate Adults Living with HIV-1 Who Are Virologically Suppressed

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Approvals Based on Findings from the Phase 3 DRIVE-SHIFT Trial Evaluating a Switch to DELSTRIGO

KENILWORTH, N.J. -- (BUSINESS WIRE) -- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) approved supplemental New Drug Applications (sNDAs) for PIFELTRO™ (in combination with other antiretroviral agents) and DELSTRIGO™ (as a complete regimen) that expand their indications to include adult patients with HIV-1 infection who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to PIFELTRO or the individual components of DELSTRIGO.

PIFELTRO (doravirine, 100 mg) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) to be administered in combination with other antiretroviral agents. DELSTRIGO is a once-daily fixed-dose combination tablet of doravirine (100 mg), lamivudine (3TC, 300 mg) and tenofovir disoproxil fumarate (TDF, 300 mg). DELSTRIGO contains a boxed warning regarding post-treatment acute exacerbation of hepatitis B virus (HBV) infection. DELSTRIGO and PIFELTRO do not cure HIV-1 infection or AIDS. PIFELTRO and DELSTRIGO were approved in the United States on August 30, 2018 for the treatment of HIV-1 infection in adults with no prior antiretroviral treatment history.

PIFELTRO and DELSTRIGO are contraindicated when co-administered with drugs that are strong cytochrome P450
(CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of PIFELTRO and DELSTRIGO (doravirine/lamivudine (3TC)/tenofovir disoproxil fumarate (TDF)). DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to 3TC. For more information, please see “Selected Safety Information” below.

“Thanks to developments in HIV science, more treatment options are becoming available to address the medical needs of people living with HIV,” said Dr. Princy Kumar, Chief, Division of Infectious Diseases and Tropical Medicine at MedStar Georgetown University Hospital and Professor of Medicine and Microbiology, Georgetown University School of Medicine, Washington, D.C. “The expanded indications offer certain people with HIV-1 infection, and their doctors, the choice to switch their current antiretroviral therapy to DELSTRIGO or PIFELTRO in combination with other antiretroviral agents.”

Immune reconstitution syndrome can occur in patients treated with combination antiretroviral therapy, including the occurrence of autoimmune disorders with variable time to onset, which may necessitate further evaluation and treatment. Renal impairment, including cases of acute renal failure and Fanconi syndrome, have been reported with the use of TDF. DELSTRIGO should be avoided with concurrent or recent use of a nephrotoxic agent, as cases of acute renal failure after initiation of high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients with risk factors for renal dysfunction who appeared stable on TDF.

Data Supporting the sNDA Approvals of PIFELTRO (doravirine) and DELSTRIGO

The FDA’s approval of the sNDAs of PIFELTRO and DELSTRIGO was based on findings from DRIVE-SHIFT, the Phase 3 randomized, international, multicenter, open-label trial evaluating a switch to DELSTRIGO in virologically suppressed participants (HIV-1 RNA <50 copies/mL) on a baseline regimen for at least six months prior to trial entry with no history of virologic failure. The baseline regimen consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a protease inhibitor plus either ritonavir or cobicistat, or elvitegravir plus cobicistat, or an NNRTI.

In DRIVE-SHIFT, 670 participants were randomized to begin treatment with DELSTRIGO immediately on Day 1 (immediate switch group, ISG; N=447) or after 24 weeks (delayed switch group, DSG; N=223). In the trial, the primary efficacy comparison was between the DELSTRIGO ISG at Week 48 and the baseline regimen DSG at Week 24. Two percent in the DELSTRIGO ISG had HIV-1 RNA ≥50 copies/mL at Week 48 compared to 1% in the baseline regimen DSG at Week 24 (treatment difference: 0.7%, 95% confidence interval: -1.3, 2.6). In addition, 91% of participants who switched to DELSTRIGO on Day 1 (ISG) had HIV-1 RNA <50 copies/mL at Week 48. Ninety-five percent of participants who continued on their baseline regimen (DSG) had HIV-1 RNA <50 copies/mL at Week 24.

At Week 24, participants who switched to DELSTRIGO (doravirine/lamivudine (3TC)/tenofovir disoproxil fumarate
(TDF) on Day 1 showed statistically significant differences in changes from baseline in fasting LDL-cholesterol (LDL-C) and non-HDL-cholesterol (non-HDL-C) compared to those who continued on a boosted protease inhibitor regimen (LDL-C: -16.3 mg/dL vs. -2.6 mg/dL, treatment difference: -14.5, 95% confidence interval: -18.9, -10.1, p<0.0001; non-HDL-C: -24.8 mg/dL vs. -2.1 mg/dL, treatment difference: -22.8, 95% confidence interval: -27.9, -17.7, p<0.0001). The clinical benefit of these findings has not been demonstrated.

Overall, the safety profile in virologically suppressed adult participants was similar to that in participants with no antiretroviral treatment history. The safety of DELSTRIGO and PIFELTRO in participants infected with HIV-1 with no antiretroviral treatment history were evaluated in the Phase 3 DRIVE-AHEAD and DRIVE-FORWARD clinical trials, respectively. In DRIVE-AHEAD, the rate of discontinuation of treatment due to adverse events was lower in the DELSTRIGO treatment group than in the efavirenz (EFV)/emtricitabine (FTC)/TDF treatment group (3% and 6%, respectively). Clinical adverse reactions of all grades occurring in ≥5 percent of participants in the DELSTRIGO treatment group included dizziness (7%), nausea (5%) and abnormal dreams (5%). No adverse reactions of Grade 2 or higher (moderate or severe) occurred in ≥2 percent of participants treated with DELSTRIGO. In DRIVE-FORWARD, the rate of discontinuation of therapy due to adverse events in either treatment group was low (2% in the PIFELTRO group and 3% in the DRV+r group). Clinical adverse reactions of all grades occurring in ≥5 percent of participants in the PIFELTRO treatment group included nausea (7%), headache (6%), fatigue (6%), diarrhea (5%) and abdominal pain (5%). No adverse reactions of Grade 2 or higher (moderate or severe) occurred in ≥2 percent of participants treated with PIFELTRO. In the DRIVE-SHIFT trial, 22% and 16% of participants in the immediate switch group experienced ALT and AST elevations of greater than 1.25 X ULN, respectively, through 48 weeks on DELSTRIGO. For these ALT and AST elevations, no apparent time patterns with regard to time to onset relative to switch were observed. One percent of participants had ALT or AST elevations greater than 5 X ULN through 48 weeks on DELSTRIGO. The ALT and AST elevations were generally asymptomatic, and not associated with bilirubin elevations. In comparison, 4% and 4% of participants in the delayed switch group experienced ALT and AST elevations of greater than 1.25 X ULN through 24 weeks on their baseline regimen.

“Today’s approvals provide doravirine treatment options for people living with HIV-1 who are virally suppressed, reflecting Merck’s continued commitment to research and development of HIV treatments,” said Dr. George Hanna, vice president and therapeutic area head of infectious diseases, Global Clinical Development, Merck Research Laboratories. “We are thankful to the researchers and HIV community for their collaboration that made this possible.”

PIFELTRO (doravirine) and DELSTRIGO (doravirine/lamivudine (3TC)/tenofovir disoproxil fumarate (TDF)) can be co-administered with a wide range of non-antiretroviral agents, and PIFELTRO can be co-administered with a wide range of antiretroviral agents. PIFELTRO and DELSTRIGO cannot be co-administered with enzalutamide, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, mitotane or St. John’s wort.
DELSTRIGO is co-administered with rifabutin, patients should take one tablet of DELSTRIGO once daily, followed by one tablet of PIFELTRO approximately 12 hours after the dose of DELSTRIGO. If PIFELTRO is co-administered with rifabutin, patients need to increase the PIFELTRO dosage to one tablet twice daily approximately 12 hours apart. Use of PIFELTRO with efavirenz, etravirine, or nevirapine is not recommended.

No clinically significant drug interactions have been observed following the co-administration of doravirine and the following drugs: dolutegravir, ritonavir, TDF, 3TC, elbasvir and grazoprevir, ledipasvir and sofosbuvir, ketoconazole, aluminum hydroxide/magnesium hydroxide/simethicone containing antacid, pantoprazole, atorvastatin, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, and midazolam.

For DELSTRIGO, no clinically significant drug interactions have been observed in studies conducted in healthy participants between TDF and the following medications: entecavir, methadone, oral contraceptives, sofosbuvir or tacrolimus. If DELSTRIGO (doravirine/lamivudine (3TC)/tenofovir disoproxil fumarate (TDF)) is co-administered with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir, monitor for adverse reactions associated with TDF. Co-administration of single doses of 3TC and sorbitol resulted in a sorbitol dose-dependent reduction in 3TC exposures. When possible, avoid use of sorbitol-containing medicines with 3TC-containing medicines, such as DELSTRIGO.

Overall Viral Resistance Profile

In the DRIVE-SHIFT clinical trial, there were six participants in the immediate switch group (n=447) and two participants in the delayed switch group (n=209) who met the protocol-defined virologic failure criteria (HIV-1 RNA ≥50 copies/mL). Two of the six virologic failures in the immediate switch group had available resistance data and neither developed detectable genotypic or phenotypic resistance to doravirine, lamivudine, or TDF during treatment with DELSTRIGO (doravirine/lamivudine (3TC)/tenofovir disoproxil fumarate (TDF)). One of the two virologic failures in the delayed switch group had available resistance data and developed the RT M184M/I substitution and phenotypic resistance to emtricitabine and lamivudine during treatment with their baseline regimen.

In the DELSTRIGO and PIFELTRO (doravirine) treatment arms of the two Phase 3 trials DRIVE-AHEAD and DRIVE-FORWARD (n=747), a total of 11 participants showed the emergence of doravirine-associated resistance substitutions, among the 28 participants in the resistance analysis subset (participants with HIV-1 RNA >400 copies per mL at virologic failure or early study discontinuation and having resistance data). Of these 11 participants, seven showed both genotypic and phenotypic resistance to doravirine, with at least a 100-fold reduction in susceptibility to doravirine. The other four participants had substitutions that were associated with less than twofold reduction in susceptibility to doravirine.
In the EFV/FTC/TDF treatment arm of the DRIVE-AHEAD trial (n=364), 12 participants showed the emergence of efavirenz-associated resistance substitutions among 20 participants in the resistance analysis subset. In the darunavir + ritonavir (DRV+r) treatment arm of the DRIVE-FORWARD trial (n=383), no participants showed the emergence of DRV+r associated resistance substitutions among the nine participants with resistance data.

Cross-resistance has been observed among NNRTIs, including doravirine. Treatment-emergent doravirine resistance-associated substitutions can confer cross-resistance to efavirenz, rilpivirine, nevirapine and etravirine.

Selected Safety Information about PIFELTRO and DELSTRIGO

Warning: Posttreatment Acute Exacerbation of Hepatitis B (HBV)

All patients with HIV-1 should be tested for the presence of HBV before initiating ARV therapy. Severe acute exacerbations of HBV have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing lamivudine or tenofovir disoproxil fumarate (TDF), which are components of DELSTRIGO. Patients coinfected with HIV-1 and HBV who discontinue DELSTRIGO should be monitored with both clinical and laboratory follow-up for at least several months after stopping DELSTRIGO. If appropriate, initiation of anti-HBV therapy may be warranted.

PIFELTRO and DELSTRIGO are contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers (including the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; the androgen receptor inhibitor enzalutamide; the antimycobacterials rifampin and rifapentine; the cytotoxic agent mitotane; and the herbal product St. John’s wort (Hypericum perforatum)), as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of DELSTRIGO (doravirine/lamivudine (3TC)/tenofovir disoproxil fumarate (TDF)) and PIFELTRO (doravirine).

DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to lamivudine.

Renal impairment, including cases of acute renal failure and Fanconi syndrome, have been reported with the use of TDF. DELSTRIGO should be avoided with concurrent or recent use of a nephrotoxic agent (eg, high-dose or multiple NSAIDs). Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in patients with risk factors for renal dysfunction who appeared stable on TDF.

Prior to or when initiating DELSTRIGO, and during treatment, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue DELSTRIGO in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Discontinue DELSTRIGO if estimated creatinine clearance declines below 50.
mL/min.

In clinical trials in HIV-1 infected adults, TDF was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher. Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.

Immune reconstitution syndrome can occur, including the occurrence of autoimmune disorders with variable time to onset, which may necessitate further evaluation and treatment.

Because DELSTRIGO (doravirine/lamivudine (3TC)/tenofovir disoproxil fumarate (TDF)) is a complete regimen, co-administration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended.

Co-administration of PIFELTRO (doravirine) with efavirenz, etravirine, or nevirapine is not recommended.

If DELSTRIGO is co-administered with rifabutin, take one tablet of DELSTRIGO once daily, followed by one tablet of doravirine (PIFELTRO) approximately 12 hours after the dose of DELSTRIGO.

If PIFELTRO is co-administered with rifabutin, increase PIFELTRO dosage to one tablet twice daily (approximately 12 hours apart).

Consult the full Prescribing Information prior to and during treatment for more information on potential drug-drug interactions.

Because DELSTRIGO (doravirine/lamivudine (3TC)/tenofovir disoproxil fumarate (TDF)) is a fixed-dose combination tablet and the dosage of lamivudine and TDF cannot be adjusted, DELSTRIGO is not recommended in patients with estimated creatinine clearance less than 50 mL/min.

The most common adverse reactions with DELSTRIGO (incidence ≥5%, all intensities) were dizziness (7%), nausea (5%), and abnormal dreams (5%). The most common adverse reactions with PIFELTRO (incidence ≥5%, all intensities) were nausea (7%), dizziness (7%), headache (6%), fatigue (6%), diarrhea (5%), abdominal pain (5%), and abnormal dreams (5%).

The safety of DELSTRIGO in virologically-suppressed adults was based on Week 48 data from subjects in the DRIVE-SHIFT trial. Overall, the safety profile in virologically-suppressed adult subjects was similar to that in subjects with no ARV treatment history.

Serum ALT and AST Elevations: In the DRIVE-SHIFT trial, 22% and 16% of subjects in the immediate switch group
experienced ALT and AST elevations greater than 1.25 X ULN, respectively, through 48 weeks on DELSTRIGO. For these ALT and AST elevations, no apparent patterns with regard to time to onset relative to switch were observed. One percent of subjects had ALT or AST elevations greater than 5 X ULN through 48 weeks on DELSTRIGO. The ALT and AST elevations were generally asymptomatic, and not associated with bilirubin elevations. In comparison, 4% and 4% of subjects in the delayed switch group experienced ALT and AST elevations of greater than 1.25 X ULN through 24 weeks on their baseline regimen.

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to PIFELTRO (doravirine) or DELSTRIGO during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

 Mothers infected with HIV-1 should be instructed not to breastfeed if they are receiving PIFELTRO or DELSTRIGO due to the potential for HIV-1 transmission.

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 of Merck & Co., Inc., Kenilworth, N.J., USA

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 2018 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 DELSTRIGO (doravirine/3TC/TDF) at: https://www.merck.com/product/usa/pi_circulars/d/delstrigo/delstrigo_pi.pdf and Patient Information for DELSTRIGO (doravirine/3TC/TDF) at: https://www.merck.com/product/usa/pi_circulars/d/delstrigo/delstrigo_ppi.pdf

Please see Prescribing Information for PIFELTRO (doravirine) at: https://www.merck.com/product/usa/pi_circulars/p/pifeltro/pifeltro_pi.pdf and Patient Information for PIFELTRO (doravirine) at: https://www.merck.com/product/usa/pi_circulars/p/pifeltro/pifeltro_ppi.pdf

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