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FDA Approves Merck's DELSTRIGO™ (doravirine / lamivudine / tenofovir disoproxil fumarate), a Once-Daily Fixed-Dose Combination Tablet as a Complete Regimen and PIFELTRO™ (doravirine), an NNRTI, Both for the Treatment of HIV-1 in Appropriate Patients

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Approvals Based on Findings from the Pivotal Phase 3 DRIVE-AHEAD and DRIVE-FORWARD Trials Evaluating the Efficacy and Safety of DELSTRIGO and PIFELTRO

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) has approved two new HIV-1 medicines: DELSTRIGO™, a once-daily fixed-dose combination tablet of doravirine (100 mg), lamivudine (3TC, 300 mg) and tenofovir disoproxil fumarate (TDF, 300 mg); and PIFELTRO™ (doravirine, 100 mg), a new non-nucleoside reverse transcriptase inhibitor (NNRTI) to be administered in combination with other antiretroviral medicines. Both DELSTRIGO and PIFELTRO are indicated for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment experience, and are administered orally once daily with or without food. DELSTRIGO contains a boxed warning regarding post-treatment acute exacerbation of hepatitis B (HBV) infection. DELSTRIGO and PIFELTRO do not cure HIV-1 infection or AIDS.

DELSTRIGO and PIFELTRO 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 DELSTRIGO and PIFELTRO. DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to 3TC. For more information, see "Selected Safety Information" below.

"As part of Merck's 30-year commitment to the care of people with HIV, we are pleased to now bring forward these two new antiretroviral treatment options, DELSTRIGO and PIFELTRO, which we believe offer a compelling clinical profile for clinicians and people living with HIV," 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 as well as those living with HIV and their communities for the collaboration that made today's approval possible."

Immune reconstitution syndrome can occur, 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 Approvals of DELSTRIGO (doravirine 100 mg/3TC 300 mg/TDF 300 mg) and PIFELTRO (doravirine)

The FDA approvals of DELSTRIGO, the once-daily fixed-dose combination tablet as a complete regimen, and PIFELTRO, a new NNRTI, are based on findings from the pivotal, randomized, multicenter, double-blind, active controlled Phase 3 trials, DRIVE-AHEAD and DRIVE-FORWARD, evaluating the efficacy and safety of DELSTRIGO and PIFELTRO, respectively, in participants infected with HIV-1 with no antiretroviral treatment history.

The DRIVE-AHEAD Clinical Trial

In DRIVE-AHEAD, 728 participants with no antiretroviral treatment history were randomized and received at least one dose of either DELSTRIGO or efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV 600 mg/FTC 200 mg/TDF 300 mg) once daily. DELSTRIGO demonstrated sustained viral suppression through 48 weeks, meeting its primary endpoint of non-inferior efficacy compared to EFV/FTC/TDF (84% in the DELSTRIGO group achieved viral suppression of HIV-1 RNA <50 copies/mL vs. 81% in the EFV/FTC/TDF group; treatment difference: 3.5%, [95% CI:] -2.0%, 9.0%). Of the 21 percent of study participants with a high viral load at baseline (HIV-1 RNA >100,000 copies/mL), 77 percent in the DELSTRIGO group and 72 percent in the EFV/FTC/TDF group achieved HIV-1 RNA <50 copies/mL at Week 48.

At Week 48, DELSTRIGO-treated participants showed statistically significant superior lipid profiles as measured by changes from baseline in LDL-cholesterol and non-HDL-cholesterol (LDL-C: -2.1 mg/dL in the DELSTRIGO group vs. 8.3 mg/dL in the EFV/FTC/TDF group; treatment difference: -10.2 mg/dL, [95% CI:] -13.8, -6.7, p<0.0001; non-HDL-C: -4.1 mg/dL in the DELSTRIGO group vs. 12.7 mg/dL in EFV/FTC/TDF; treatment difference: -16.9 mg/dL, [95% CI:] -20.8, -13.0, p<0.0001). However, the clinical benefit of these findings has not been demonstrated. In addition, a statistically significant lower proportion of DELSTRIGO-treated participants compared to EFV/FTC/TDF-treated participants reported neuropsychiatric adverse events in the three pre-specified categories of dizziness (9% vs. 37%; treatment difference: -28.3%, [95% CI:] -34.0, -22.5, p <0.001), sleep disorders and disturbances (12% vs. 26%; treatment difference: -13.5%, [95% CI:] -19.1, -7.9, p <0.001), and altered sensorium (4% vs. 8%; treatment difference: -3.8%, [95% CI:] -7.6, -0.3, p=0.033).

The rate of discontinuation of treatment due to adverse events was lower in the DELSTRIGO treatment group than in the EFV/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.

The DRIVE-FORWARD Clinical Trial

In DRIVE-FORWARD, 766 participants with no antiretroviral treatment history were randomized and received at least one dose of either PIFELTRO once daily or darunavir 800 mg + ritonavir 100 mg (DRV+r) once daily, each in combination with emtricitabine (FTC)/TDF or abacavir (ABC)/3TC selected by the investigator. PIFELTRO demonstrated sustained viral suppression through 48 weeks, meeting its primary endpoint of non-inferior efficacy compared to DRV+r, each in combination with FTC/TDF or ABC/3TC (84% in the PIFELTRO group achieved viral suppression of HIV-1 RNA <50 copies/mL vs. 80% in the DRV+r group; treatment difference: 3.9%, [95% CI:] -1.6%, 9.4%). Of the 20 percent of study participants with a high viral load at baseline (HIV-1 RNA >100,000 copies/mL), 77 percent in the PIFELTRO group and 74 percent in the DRV+r group achieved HIV-1 RNA <50 copies/mL at Week 48.

At Week 48, PIFELTRO-treated participants showed statistically significant superior lipid profiles as measured by changes from baseline in LDL-cholesterol and non-HDL-cholesterol (LDL-C: -4.6 mg/dL in the PIFELTRO group vs. 9.5 mg/dL in the DRV+r group; treatment difference: -14.4 mg/dL, [95% CI:] -18.0, -10.8, p<0.0001; non-HDL-C: -5.4 mg/DL in the PIFELTRO group vs. 13.7 mg/dL in the DRV+r group, treatment difference: -19.4 mg/dL, [95% CI:] -23.4, -15.4, p<0.0001). However, the clinical benefit of these findings has not been demonstrated.

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.

“As a result of the remarkable strides made in the fight against HIV, clinicians and their patients have the opportunity to work together to identify treatment regimens that may be best for each individual, taking into account other aspects of that person’s health, including other medicines they may be taking,” said Dr. David Wohl, professor, Division of Infectious Diseases, University of North Carolina (UNC) Chapel Hill School of Medicine and site leader, UNC AIDS Clinical Trials Unit. “Today’s approvals of DELSTRIGO and PIFELTRO provide two new options for the treatment of HIV-1 in appropriate treatment-naïve adult patients.”

DELSTRIGO and PIFELTRO 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. DELSTRIGO and PIFELTRO cannot be co-administered with enzalutamide, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, mitotane or St. John’s wort. If DELSTRIGO is co-administered with rifabutin, patients should 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, 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 changes in concentration 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 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 DELSTRIGO and PIFELTRO treatment arms of the DRIVE-AHEAD and DRIVE-FORWARD trials (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 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. No significant cross-resistance has been demonstrated between doravirine-resistant HIV-1 variants and 3TC, FTC or tenofovir or between 3TC or tenofovir-resistant variants and doravirine.

“Today, with the right access and care, people living with HIV are better able to manage this chronic condition,” said Kathie Hiers, chief executive officer, AIDS Alabama. “We are thankful for Merck’s unwavering commitment to help address unmet needs through the development of new treatment options, and the provision of community support and educational resources for people living with HIV.”

DELSTRIGO (doravirine/3TC/TDF) and PIFELTRO (doravirine) Availability and Access
The approvals of DELSTRIGO and PIFELTRO come ahead of the original FDA target action date of Oct. 23, 2018. Merck anticipates that PIFELTRO and DELSTRIGO will be stocked through wholesalers within one month. Merck is working to obtain access for patients in government-sponsored programs, including Medicare Part D, Medicaid and AIDS Drug Assistance Programs. Upon approval, DELSTRIGO and PIFELTRO will be covered products under the Merck Patient Assistance Program and will be available to eligible patients when the medicines are available. Doravirine is also under regulatory review by the European Medicines Agency (EMA).

Selected Safety Information about DELSTRIGO (doravirine/3TC/TDF)
Warning: Post treatment Acute Exacerbation of Hepatitis B (HBV)
All patients with HIV-1 should be tested for the presence of HBV before initiating antiretroviral 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 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.

DELSTRIGO is 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. 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, as 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 is a complete regimen, co-administration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended.

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

If 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. The most common adverse reactions with DELSTRIGO (incidence ≥5%, all intensities) were dizziness (7%), nausea (5%) and abnormal dreams (5%).

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to DELSTRIGO during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1-800-258-4263. Mothers infected with HIV-1 should be instructed not to breastfeed if they are receiving DELSTRIGO due to the potential for HIV-1 transmission. Because DELSTRIGO is a fixed-dose combination tablet and the components cannot be altered, it is not recommended in patients with estimated creatinine clearance less than 50 mL/min.

Selected Safety Information about PIFELTRO (doravirine)
PIFELTRO is 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 PIFELTRO plasma concentrations may occur, which may decrease the effectiveness of PIFELTRO. Immune reconstitution syndrome can occur, including the occurrence of autoimmune disorders with variable time to onset, which may necessitate further evaluation and treatment. Co-administration of PIFELTRO with efavirenz, etravirine or nevirapine is not recommended. If 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 important potential drug-drug interactions. The safety of PIFELTRO is based on two studies, DRIVE-FORWARD and DRIVE-AHEAD. In DRIVE-FORWARD, the most common adverse reactions (incidence ≥5%, all intensities) were nausea (7%), headache (6%), fatigue (6%), diarrhea (5%) and abdominal pain (5%). In DRIVE-AHEAD, the most common adverse reactions (incidence ≥5%, all intensities) were dizziness (7%), abnormal dreams (5%) and nausea (5%).

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to PIFELTRO during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1-800-258-4263. Mothers infected with HIV-1 should be instructed not to breastfeed if they are receiving PIFELTRO due to the potential for HIV 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 2017 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
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
Patient Information for PIFELTRO (doravirine) at:
https://www.merck.com/product/usa/pi_circulars/p/pifeltro/pifeltro_ppi.pdf

Language:
English

Contact:

Merck
Media:
Pam Eisele, 267-305-3558
or
Sarra S. Herzog, 908-740-1871