FDA recently approved PIFELTRO (doravirine) tablets, a non-nucleoside reverse transcriptase inhibitor (NNRTI), indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history and DELSTRIGO, a fixed dose combination tablet containing doravirine, lamivudine, and tenofovir disoproxil fumarate indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history. A summary of the dosing, contraindications, adverse reactions and clinical studies for the respective products is provided below.

DOSAGE AND ADMINISTRATION

PIFELTRO

- One tablet taken orally once daily with or without food in adult patients.
- Dosage adjustment with rifabutin: One tablet taken twice daily (approximately 12 hours apart)

DELSTRIGO

- Testing: Prior to or when initiating DELSTRIGO, test for HBV infection. Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.
- One tablet taken orally once daily with or without food in adult patients.
- Renal impairment: Not recommended in patients with estimated creatinine clearance below 50 mL per minute.
- Dosage adjustment with rifabutin: Take one tablet of DELSTRIGO once daily, followed by one tablet of doravirine 100 mg (PIFELTRO) approximately 12 hours after the dose of DELSTRIGO

CONTRAINDICATIONS

- 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. These drugs include, but are not limited to, the following:
  - the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
  - the androgen receptor inhibitor enzalutamide
  - the antimycobacterials rifampin, rifapentine
  - the cytotoxic agent mitotane
  - St. John’s wort (Hypericum perforatum)
DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to lamivudine

WARNINGS AND PRECAUTIONS

PIFELTRO

- Monitor for Immune Reconstitution Syndrome.

DELSTRIGO

- New onset or worsening renal impairment: Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. Avoid administering DELSTRIGO with concurrent or recent use of nephrotoxic drugs.
- Bone loss and mineralization defects: Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss.
- Monitor for Immune Reconstitution Syndrome

ADVERSE REACTIONS

The safety assessment is based on Week 48 data from two Phase 3, randomized, international, multicenter, double-blind, active-controlled trials (DRIVE-FORWARD (Protocol 018) and DRIVE-AHEAD (Protocol 021)).

In DRIVE-FORWARD, 766 adult subjects received either PIFELTRO 100 mg (n=383) or darunavir 800 mg + ritonavir 100 mg (DRV+r) (n=383) once daily, each in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or abacavir/lamivudine (ABC/3TC). By Week 48, 2% in the PIFELTRO group and 3% in the DRV+r group had adverse events leading to discontinuation of study medication.

In DRIVE-AHEAD, 728 adult subjects received either DELSTRIGO [doravirine (DOR)/3TC/TDF] (n=364) or efavirenz (EFV)/FTC/TDF once daily (n=364). By Week 48, 3% in the DELSTRIGO group and 6% in the EFV/FTC/TDF group had adverse events leading to discontinuation of study medication.

Most common adverse reactions (incidence greater than or equal to 5%, all grades) are nausea, dizziness, headache, fatigue, diarrhea, abdominal pain, and abnormal dreams.

Neuropsychiatric Adverse Events

For DRIVE-AHEAD, the analysis of subjects with neuropsychiatric adverse events by Week 48 is presented in Table 2. The proportion of subjects who reported one or more neuropsychiatric adverse events was 24% and 57% in the DELSTRIGO and EFV/FTC/TDF groups, respectively.

A statistically significantly lower proportion of DELSTRIGO-treated subjects compared to EFV/FTC/TDF-treated subjects reported neuropsychiatric adverse events by Week 48 in the three pre-specified categories of dizziness, sleep disorders and disturbances, and altered sensorium.

- The proportion of subjects with sleep disorders and disturbances was 12% for DELSTRIGO and 26% for EFV/FTC/TDF [treatment difference and (95%CI), -13.5 (-19.1, -7.9)]
- The proportion of subjects with dizziness was 9% for DELSTRIGO and 37% for EFV/FTC/TDF [treatment difference and (95%CI), -28.3 (-34.0, -22.5)]
- The proportion of subjects with altered sensorium was 4% for DELSTRIGO and 8% for EFV/FTC/TDF [treatment difference and (95%CI), -3.8 (-7.6, -0.3)]
Neuropsychiatric adverse events in the pre-defined category of depression and suicide/self-injury were reported in 4% and 7% of subjects, in the DELSTRIGO and EFV/FTC/TDF groups, respectively.

In DRIVE-AHEAD through 48 weeks of treatment, the majority of subjects who reported neuropsychiatric adverse events reported events that were mild to moderate in severity (97% [83/86] and 96% [198/207], in the DELSTRIGO and EFV/FTC/TDF groups, respectively) and the majority of subjects reported these events in the first 4 weeks of treatment (72% [62/86] in the DELSTRIGO group and 86% [177/207] in the EFV/FTC/TDF group).

Neuropsychiatric adverse events led to treatment discontinuation in 1% (2/364) and 1% (5/364) of subjects in the DELSTRIGO and EFV/FTC/TDF groups, respectively. The proportion of subjects who reported neuropsychiatric adverse events through Week 4 was 17% (62/364) in the DELSTRIGO group and 49% (177/364) in the EFV/FTC/TDF group. At Week 48, the prevalence of neuropsychiatric adverse events was 12% (44/364) in the DELSTRIGO group and 22% (81/364) in the EFV/FTC/TDF group.

Laboratory Abnormalities

For DRIVE-FORWARD and DRIVE-AHEAD, the difference in proportion of subjects with a laboratory abnormality was similar between PIFELTRO/DELSTRIGO and the comparator groups (within 3%). The only difference was a numerical higher proportion of subjects taking PIFELTRO or DESTRIGO had increases in total bilirubin versus the comparator groups.

Change in Lipids from Baseline

For DRIVE-FORWARD and DRIVE-AHEAD, the LDL and non-HDL comparisons were pre-specified. The differences were statistically significant, showing superiority for doravirine for both parameters. The clinical benefit of these findings has not been demonstrated.

DRUG INTERACTIONS

PIFELTRO and DESTRIGO

- At least a 4-week cessation period is recommended prior to initiation of PIFELTRO and enzalutamide, anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), rifampin, rifapentine, rifabutin, mitotane and St. John’s wort.
- Use with efavirenz, etravirine and nevirapine is not recommended due to decreased doravirine exposures.

Additional DELSTRIGO Drug interaction information

- Monitor for adverse reactions with tenofovir when used with ledipasvir/sofosbuvir and sofosbuvir/velpatasvir
- Coadministration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid use of sorbitol-containing medicines with lamivudine-containing medicine.

CLINICAL STUDIES

The efficacy is based on the analyses of 48-week data from two randomized, multicenter, double-blind, active controlled Phase 3 trials (DRIVE-FORWARD, NCT02275780 and DRIVE-AHEAD, NCT02403674) in HIV-1 infected subjects with no antiretroviral treatment history (n=1494).
In DRIVE-FORWARD, 766 subjects were randomized and received at least 1 dose of either PIFELTRO once daily or darunavir 800 mg + ritonavir 100 mg (DRV+r) once daily each in combination with emtricitabine/tenofovir DF (FTC/TDF) or abacavir/lamivudine (ABC/3TC) selected by the investigator. At baseline, the median age of subjects was 33 years, 16% were female, 27% were non-white, 4% had hepatitis B and/or C virus co-infection, 10% had a history of AIDS, 20% had HIV-1 RNA greater than 100,000 copies/mL, 86% had CD4+ T-cell count greater than 200 cells/mm$^3$, 13% received ABC/3TC, and 87% received FTC/TDF; these characteristics were similar between treatment groups.

In DRIVE-AHEAD, 728 subjects were randomized and received at least 1 dose of either DELSTRIGO (DOR/3TC/TDF) or EFV 600 mg/FTC 200 mg/TDF 300 mg once daily. At baseline, the median age of subjects was 31 years, 15% were female, 52% were non-white, 3% had hepatitis B or C co-infection, 14% had a history of AIDS, 21% had HIV-1 RNA greater than 100,000 copies/mL, and 88% had CD4+ T-cell count greater than 200 cells/mm$^3$; these characteristics were similar between treatment groups.

Week 48 outcomes for DRIVE-FORWARD and DRIVE-AHEAD are provided below.

**DRIVE-FORWARD**

Proportion of subjects with HIV-1RNA < 50 copies/mL was 84% for PIFELTRO vs 80% for DRV+r+2 NRTIs [treatment difference (95% CI), 3.9% (-1.6, 9.4%)]

**DRIVE-AHEAD**

Proportion of subjects with HIV-1RNA < 50 copies/mL was 84% for DELSTRIGO vs 81% for EFV/FTC/TDF [treatment difference (95% CI), 3.5% (-2.0, 9.0%)]

In DRIVE-FORWARD, the mean CD4+ T-cell counts in the PIFELTRO and DRV+r groups increased from baseline by 193 and 186 cells/mm$^3$, respectively.

In DRIVE-AHEAD, the mean CD4+ T-cell counts in the DELSTRIGO and EFV/FTC/TDF groups increased from baseline by 198 and 188 cells/mm$^3$, respectively.

The updated label will soon be available at [drugs@fda](https://www.fda.gov) or [DailyMed](https://www.dailymed.nlm.nih.gov).

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