Doravirine (DOR, Pifeltro)

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Formulations

Tablet: 100 mg

Fixed-Dose Combination (FDC) Tablet

- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg

When using FDC tablets, refer to other sections of the Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Child and **Adolescent (Weighing ≥**35 kg) and Adult Dose

- DOR 100 mg once daily in antiretroviral (ARV)–naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to DOR

[Delstrigo] DOR/Lamivudine (3TC)/Tenofovir Disoproxil Fumarate (TDF)

Child and Adolescent (Weighing ≥35 kg) and Adult Dose

- One tablet once daily in ARV-naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to the individual components of Delstrigo

Selected Adverse Events

- Nausea
- Abdominal pain
- Diarrhea
- Abnormal dreams
- Insomnia, somnolence

Special Instructions

- DOR can be taken with or without food.
- Screen patients for hepatitis B virus (HBV) infection before using Delstrigo, which contains 3TC and TDF. Severe acute exacerbation of HBV can occur when 3TC or TDF are discontinued; therefore, hepatic function and HBV viral load should be monitored for several months after halting therapy with 3TC or TDF.

Metabolism/Elimination

- DOR is metabolized by the enzyme cytochrome P450 3A.
- DOR has multiple interactions with several drugs (see Drug Interactions section below).
- When DOR is coadministered with rifabutin, the dose should be increased from DOR 100 mg once daily to DOR 100 mg twice daily. When DOR/3TC/TDF (Delstrigo) is coadministered with rifabutin, an additional 100-mg dose of freestanding DOR needs to be administered approximately 12 hours later. (See Drug Interactions below.)

	DOR Dosing in Patients with Hepatic Impairment • Dose adjustment is not required in patients with mild or moderate hepatic impairment. DOR has not been studied in patients with severe hepatic impairment. DOR Dosing in Patients with Renal Impairment • Dose adjustment is not required when using DOR in patients with mild, moderate, or severe renal impairment. DOR use has not been studied in patients with end-stage renal disease or in patients on dialysis. • DOR administered with 3TC and TDF as components of Delstrigo **is not recommended** in patients with estimated creatinine clearance <50 mL/min.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- Doravirine (DOR) is a cytochrome P450 (CYP) 3A substrate that is associated with several important drug interactions with drugs that are strong CYP3A enzyme inducers. Coadministration with these drugs may cause significant decreases in DOR plasma concentrations and potential decreases in efficacy, which can lead to the development of resistance. Before DOR is administered, a patient's medication profile should be reviewed carefully for potential drug interactions with DOR.[1,2]
- In a Phase 1 trial (described below under Efficacy in Clinical Trials), DOR plasma exposure transiently decreased by 62% when DOR was started immediately after stopping EFV. A *post hoc* analysis of the Phase 3 DRIVE-SHIFT study (described below under Efficacy in Clinical Trials), however, showed that at Week 4, DOR plasma levels in patients who had switched from an EFV-based regimen to a DOR-based regimen were similar to DOR plasma levels in patients who switched from a protease inhibitor (PI)–based regimen to a DOR-based regimen (all of the regimens in the study used a backbone of lamivudine [3TC] plus tenofovir disoproxil fumarate [TDF]).[3] A similar effect of prior EFV-based ART on the pharmacokinetics (PK) of DOR was demonstrated in IMPAACT 2014 (described below under Efficacy in Clinical Trials) among adolescents weighing ≥45 kg who switched from EFV-based ART to DOR-based ART with 3TC/TDF.[4]
- DOR **should not be coadministered** with the following drugs: the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; the androgen receptor inhibitor enzalutamide; the antimycobacterials rifampin and rifapentine; the cytotoxic agent mitotane; or St. John's wort.[5,6]
- Drug interactions between DOR and rifabutin induce the metabolism of DOR and require an additional dose of DOR 100 mg to be administered 12 hours after a fixed-dose combination of DOR/3TC/TDF or an increase of the DOR dose to 100 mg twice daily.[2,5,6]

Major Toxicities

- *More common:* Nausea, headache, fatigue, diarrhea, abdominal pain, abnormal dreams.

- *Less common (more severe)*: Neuropsychiatric adverse events (AEs), including insomnia, somnolence, dizziness, and altered sensorium. Immune reconstitution inflammatory syndrome may occur.

Resistance

The International Antiviral Society–USA maintains a list of updated drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

DOR is expected to have activity against HIV with isolated non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance that is associated with mutations at positions 103, 181, or 190. Some single mutations and combinations of viral mutations, however, have been shown to significantly decrease susceptibility to DOR. Specifically, clinical HIV isolates containing the Y188L mutation alone or in combinations with K103N or V106I, combinations of V106A with G190A and F227L, or combinations of E138K with Y181C and M230L have shown ≥100-fold reduction in susceptibility to DOR.[5,6] In patients with multiple NNRTI mutations, consult an HIV expert and a resistance database to evaluate the potential efficacy of DOR.

Pediatric Use

Approval

DOR is approved by the U.S. Food and Drug Administration (FDA) for use in children and adolescents weighing ≥35 kg.[5,6] IMPAACT 2014, a Phase 1/2 study (described below under Efficacy in Clinical Trials) evaluated the PK, safety, and tolerability of DOR and DOR/3TC/TDF in children and adolescents with HIV.[4]

Efficacy in Clinical Trials

The efficacy of DOR was evaluated using data from four randomized adult clinical trials. The first study was a Phase 2b dose-selection, double-blind trial that enrolled treatment-naive adults with HIV.[7] The efficacy trials included two randomized, multicenter, double-blind, active-controlled Phase 3 trials (DRIVE-FORWARD and DRIVE-AHEAD) in treatment-naive adults[8-11] and one open-label, active-controlled, randomized noninferiority trial that enrolled virologically suppressed adults on antiretroviral therapy (DRIVE-SHIFT).[12]

The dose-selection trial enrolled treatment-naive adults stratified by HIV RNA level at screening (≤100,000 copies/mL or >100,000 copies/mL) and randomized participants to receive one of four different doses (25 mg, 50 mg, 100 mg, or 200 mg) of once-daily DOR or EFV 600 mg with open-label emtricitabine (FTC) 200 mg/TDF 300 mg. After dose selection at Week 24, all participants were switched to DOR 100 mg and, with additional enrollment, 216 participants were randomized to receive once-daily DOR 100 mg (n = 108) or EFV 600 mg (n = 108) for 96 weeks with FTC/TDF. At Week 24, 72.9% of participants on DOR 100 mg and 73.1% of participants on EFV 600 mg had HIV RNA <40 copies/mL.[7]

In the DRIVE-FORWARD trial, adult subjects received either DOR 100 mg (n = 383) or darunavir 800 mg/ritonavir 100 mg (DRV/r) (n = 383) once daily, each in combination with FTC/TDF or abacavir/3TC.[8] In the DRIVE-AHEAD trial, adult subjects received either coformulated DOR/3TC/TDF (n = 364) or EFV/FTC/TDF (n = 364) once daily.[9] An integrated efficacy analysis

from both trials (DRIVE-FORWARD and DRIVE-AHEAD) at Week 48 demonstrated that 84.1% of patients who were treated with the DOR-based regimen achieved HIV RNA <50 copies/mL, compared with 79.9% of patients who were treated with the DRV/r-based regimen and 80.8% of patients who were treated with EFV/FTC/TDF. Results were similar across different baseline viral loads, genders, races, and HIV-1 subtypes.[9] In a longer-term analysis, at Week 96 in the DRIVE-AHEAD trial, among 728 randomized participants, 77.5% of those treated with DOR/3TC/TDF achieved HIV RNA <50 copies/mL, compared with 73.6% in participants treated with EFV/FTC/TDF. No additional resistance to DOR was observed between Weeks 48 and 96.[11] At Week 96 in the DRIVE-FORWARD trial, 277 (95%) of 292 participants who remained on DOR maintained viral suppression (i.e., 73% of the overall 383 participants), whereas 248 (91%) of 273 participants who remained on DRV/r maintained viral suppression (i.e., 66% of the overall 383 participants).[10]

In the DRIVE-SHIFT study, adult subjects with HIV who were virologically suppressed for ≥6 months on two nucleoside reverse transcriptase inhibitors plus a boosted PI, boosted elvitegravir, or an NNRTI were randomized to switch to a once-daily, single-tablet regimen of DOR 100 mg/3TC 300 mg/TDF 300 mg or continue their current therapy (baseline regimen). At Week 24, 93.7% on DOR/3TC/TDF versus 94.6% on baseline regimen had HIV-1 RNA <50 copies/mL (difference −0.9 [−4.7 to 3.0]). At Week 48, 90.8% on DOR/3TC/TDF had HIV-1 RNA <50 copies/mL, demonstrating noninferiority versus baseline regimen at Week 24 (difference −3.8 [−7.9 to 0.3]).[12] Participants were switched on Day 1 (immediate-switch group [ISG]; n = 447) or at Week 24 (delayed-switch group [DSG]; n = 209). Long-term efficacy in the extension arm at Week 144 showed virologic suppression (HIV RNA<50 copies/mL) in 80.1% of ISG (351 of 438) and 83.7% of DSG (175 of 209) in FDA snapshot (intent-to-treat) analysis.[13]

IMPAACT 2014 study data in antiretroviral (ARV)-naive or ARV-experienced virologically suppressed adolescents suggest favorable antiviral effect comparable to adult data.[4] A total of 45 participants, 43 virologically suppressed (50% on EFV-based ART) and 2 ARV-naive adolescents with mean age 15 years (12–17 years), were treated with DOR/3TC/TDF. At Week 24, 42 of 45 (93.3%; 95% confidence interval [CI], 81.7–98.6) achieved or maintained HIV-1 RNA <40 copies/mL in FDA snapshot (intent-to-treat) analysis, while 42 of 43 (97.7%; 95% CI, 87.7–99.9) achieved or maintained HIV-1 RNA <40 copies/mL in observed failure (on-treatment) analysis.[4]

Pharmacokinetics

The PK of DOR have been evaluated in treatment-naive adults aged ≥18 years and both treatment-naive and treatment-experienced adolescents. A Phase 2 trial evaluated DOR across a dose range of 0.25 times to 2 times the recommended dose in treatment-naive participants with HIV who also received FTC/TDF. No exposure-response relationship for efficacy was reported for DOR.[9]

Toxicity

In trials that compared DOR-based regimens and EFV-based regimens, central nervous system (CNS) AEs (dizziness, sleep disorder and disturbances, and altered sensorium) occurred less frequently among the patients who received DOR than among those who received EFV. In the dose-finding trial, CNS AEs were reported in 26.9% of patients on DOR-based regimens, compared with 47.2% of patients on EFV-based regimens at Week 24.[7] In the integrated safety analysis from the DRIVE-FORWARD and DRIVE-AHEAD trials, 25.5% of patients on DOR-based regimens

experienced CNS AEs at Week 48, compared with 55.9% of patients on EFV-based regimes.[9,14] Neither DRIVE-FORWARD nor DRIVE-AHEAD included an integrase strand transfer inhibitor–based regimen as an active control. Fewer participants who received DOR-based regimens experienced diarrhea than those treated with DRV/r-based regimens (12.4% vs. 22.5%, respectively). In the DRIVE-SHIFT study, among adults who were receiving a ritonavir-boosted PI at study entry, mean reductions in fasting low-density lipoprotein cholesterol (LDL-C) and non–high density lipoprotein cholesterol (HDL-C) at Week 24 were significantly greater in people who received DOR/3TC/TDF compared with the baseline PI-based regimen with 3TC/TDF ($P < 0.0001$).[12] The reduction in fasting lipids was maintained through Week 144 in the extension arm of the DRIVE-SHIFT study.[13] Similarly, the 96 weeks of data from the DRIVE-FORWARD trial supported greater mean reductions in LDL-C (−14.6 mg/dL [95% CI, −18.2 to −11.0]) and non–HDL-C (18.4 mg/dL [95% CI, −22.5 to −14.3]) among participants in the DOR arm than among those in the DRV/r arm.[10] At Week 96 in the DRIVE-AHEAD trial, fasting HDL-C levels increased among participants in the EFV/FTC/TDF arm (mean increases of 10.8 and 15.0 mg/dL) but not among participants treated with DOR/3TC/TDF (−0.6 and −2.1 mg/dL), respectively, while the mean changes from baseline in total cholesterol/HDL-C ratio were similar between both arms[11] (−0.12 for DOR/3TC/TDF and −0.10 for EFV/FTC/TDF; treatment difference, −0.04; 95% CI, −0.23–0.15).

In the IMPAACT 2014 study of 43 treatment-experienced and 2 ARV-naive adolescents aged 12 to <18 years on DOR/3TC/TDF at Week 24, there were no Grade 3 or 4 AEs, serious AEs, or premature study drug discontinuation due to AEs.[4]

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