

Doravirine (DOR, Pifeltro)

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Formulations	
<p>Tablet: 100 mg</p> <p>Fixed-Dose Combination (FDC) Tablet</p> <ul style="list-style-type: none"> [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg <p>When using FDC tablets, refer to other sections of 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.</p> <p>For additional information, see Drugs@FDA or DailyMed.</p>	
Dosing Recommendations	Selected Adverse Events
<p>Child and Adolescent (Weighing ≥ 35 kg) and Adult Dose</p> <ul style="list-style-type: none"> Doravirine (DOR) 100 mg once daily in antiretroviral (ARV)-naïve and ARV-experienced people 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 <p>[Delstrigo] DOR/Lamivudine (3TC)/Tenofovir Disoproxil Fumarate (TDF)</p> <p><i>Child and Adolescent (Weighing ≥ 35 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> One tablet once daily in ARV-naïve and ARV-experienced people 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 	<ul style="list-style-type: none"> Nausea Abdominal pain Diarrhea Abnormal dreams Insomnia, somnolence
	Special Instructions
	<ul style="list-style-type: none"> DOR can be taken with or without food. Screen children 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
	<ul style="list-style-type: none"> DOR is metabolized by the enzyme cytochrome P450 3A. DOR has multiple interactions with several drugs (see the Drug Interactions section below). <p>DOR Dosing in Children With Hepatic Impairment</p> <ul style="list-style-type: none"> Dose adjustment is not required in children with mild or moderate hepatic impairment. DOR has not been studied in people with severe hepatic impairment.

	<p>DOR Dosing in Children With Renal Impairment</p> <ul style="list-style-type: none"> • Dose adjustment is not required when using DOR in children with mild, moderate, or severe renal impairment. DOR use has not been studied in people with end-stage renal disease or in people on dialysis. • DOR administered with 3TC and TDF as components of Delstrigo is not recommended in children with estimated creatinine clearance <50 mL/min.
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Drug Interactions

Additional information about drug interactions is available in the [Liverpool 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 child'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 efavirenz (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 participants who had switched from an EFV-based regimen to a DOR-based regimen were similar to DOR plasma levels in participants 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 antiretroviral therapy (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, depression, suicidality, altered consciousness, and altered sensorium. Autoimmune disorder and immune reconstitution inflammatory syndrome may occur. Serious reactions can also include severe skin and hypersensitivity reactions.

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 children 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.^{4,7}

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 adults with HIV who were treatment-naïve.⁸ The efficacy trials included two randomized, multicenter, double-blind, active-controlled Phase 3 trials ([DRIVE-FORWARD](#) and [DRIVE-AHEAD](#)) in treatment-naïve adults⁹⁻¹³ and one open-label, active-controlled, randomized noninferiority trial that enrolled virologically suppressed adults on ART ([DRIVE-SHIFT](#)).¹⁴

In the DRIVE-FORWARD trial, adults with HIV were randomized to receive either DOR 100 mg (n = 383) or darunavir 800 mg/ritonavir 100 mg (DRV/r) (n = 383) once daily, each in combination with emtricitabine (FTC)/TDF or abacavir/3TC.^{9,11} In the DRIVE-AHEAD trial, adults received either coformulated DOR/3TC/TDF (n = 364) or EFV/FTC/TDF (n = 364) once daily.^{10,12} An integrated efficacy analysis from both trials (DRIVE-FORWARD and DRIVE-AHEAD) at Week 48 demonstrated that 84.1% of participants who were treated with the DOR-based regimen achieved HIV RNA < 50 copies/mL, compared with 79.9% of participants who were treated with the DRV/r-based regimen and 80.8% of participants who were treated with EFV/FTC/TDF. Results were similar across different baseline viral loads, genders, races, and HIV-1 subtypes.¹⁰ In a long-term extension arm for both trials (DRIVE-FORWARD and DRIVE-AHEAD) at Week 192, of 1,494 participants treated in the double-blind phase, 550 continued DOR-based regimens and 502 switched to DOR-based regimens.¹³ In the FDA snapshot analysis, HIV RNA < 50 copies/mL was maintained in 457 (83%) of 550 participants who continued DOR-based ART and 404 (80%) of 502 participants who switched to DOR-based regimens. Protocol-defined virological failure and development of resistance were low, occurring mainly before Week 96.¹³

In the DRIVE-SHIFT study, adults 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 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]).¹⁴ Long-term efficacy in the extension arm at Week 144 showed HIV RNA <50 copies/mL in 80.1% of those who switched to DOR/3TC/TDF immediately and 83.7% of those who switched to DOR/3TC/TDF during the open-label extension in FDA snapshot analysis.¹⁵

IMPAACT 2014 study data in treatment-naïve or treatment-experienced virologically suppressed adolescents aged 12 years to ≤18 years demonstrated efficacy comparable to adult data.^{4,7} A total of 45 participants (median age 15 years; 58% females; two ART-naïve) were treated with DOR/3TC/TDF. At Week 24, 42 of 45 (93.3%) participants achieved or maintained HIV-1 RNA <40 copies/mL in FDA snapshot analysis, while 42 of 43 (97.7%) achieved or maintained HIV-1 RNA <40 copies/mL in observed failure (on-treatment) analysis.⁴ At Week 48, 41 of 42 (97.6%) participants had achieved or maintained HIV-1 RNA <40 copies/mL, and at Week 96, 37 of 40 (92.5%) had achieved or maintained HIV-1 RNA <40 copies/mL.⁷

Toxicity in Clinical Trials

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 participants who received DOR than among those who received EFV.⁸ In the integrated safety analysis from the DRIVE-FORWARD and DRIVE-AHEAD trials, 25.5% of participants on DOR-based regimens experienced CNS AEs at Week 48, compared with 55.9% of participants on EFV-based regimens.^{10,16} In a long-term follow-up including extension stages for both trials (DRIVE-FORWARD and DRIVE-AHEAD), at Week 192, <1% of 550 participants who continued DOR-based ART reported serious drug-related AEs, and 1% who continued DOR-based regimens and <1% of those who switched to DOR-based ART discontinued ART due to drug-related AEs. Participants continuing or switching to DOR showed generally favorable lipid profiles, little weight gain, and small decreases in estimated glomerular filtration rates, with no discontinuations due to increased creatinine or renal AEs.¹³ In the DRIVE-SHIFT study, among adults who were receiving a ritonavir-boosted PI at study entry, the reduction in fasting lipids was achieved at Week 24 and maintained through Week 144 in the extension arm of the DRIVE-SHIFT study.¹⁵

In the IMPAACT 2014 study of 43 treatment-experienced (50% who switched from EFV-based ART) and 2 ARV-naïve adolescents aged 12 years to <18 years on DOR/3TC/TDF, at Week 24, there were no Grade 3 or 4 AEs, serious AEs, or premature study drug discontinuations due to AEs.⁴ At Week 96, there were no treatment-related discontinuations due to AEs and no deaths or drug-related AEs ≥Grade 3.⁷ While the study did not measure fasting lipids in all adolescents, favorable lipid profile changes from baseline to Week 96 were observed.

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