Doravirine (Pifeltro, DOR)

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Summary

- Pharmacokinetic data are insufficient to make dosing recommendations for doravirine (DOR) during pregnancy.
- Clinical data are insufficient to characterize the risk for congenital anomalies associated with *in utero* exposure to DOR. No reproductive toxicity or teratogenicity concerns were identified in animal studies.

Human Studies in Pregnancy

Pharmacokinetics

No clinical pharmacokinetic studies of DOR in pregnant women have been reported. Bukkems et al. used full-body, physiologically based pharmacokinetic (PBPK) modeling to predict maternal DOR exposures during pregnancy. Their model predicted lower maternal serum exposures (compared to nonpregnant adults) as pregnancy progresses, with decreases of trough plasma concentration of 65%, 75%, and 84% at 26, 32, and 40 weeks of gestation, respectively. [1]

Placental and Breast Milk Passage

Placental transfer of DOR was noted in two *ex vivo* dually perfused human cotyledon models.[1,2] The study by Le et al. integrated human placenta perfusion experiments with PBPK modeling, which predicted substantial fetal exposure to DOR. No data are available on breast milk passage of DOR in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry[3] has prospectively monitored eight patients treated with DOR during the first trimester and two patients treated with DOR during the second and third trimesters; one infant with first trimester exposure was noted to have a birth defect. These[3] data are insufficient to make conclusions regarding the safety of DOR during pregnancy.

Animal Studies

Carcinogenicity

DOR was not carcinogenic in long-term oral carcinogenicity studies in mice and rats at exposures up to six times and seven times, respectively, the exposure seen in humans who received the recommended dose. A statistically significant incidence of thyroid parafollicular cell adenoma and carcinoma was observed among female rats that received the high dose (which produced the sevenfold increase in exposure) of DOR; however, the incidence was similar to the incidence observed among historical controls that did not receive DOR. DOR was not genotoxic in a battery of *in vitro* and *in vivo* mutagenicity assays.[4]

Reproduction/Fertility

In rats, DOR did not affect fertility, reproductive performance, or early embryonic development at exposures (based on area under the curve [AUC]) that were approximately seven times the exposure seen in humans who received the recommended dose.[4]

Teratogenicity/Adverse Pregnancy Outcomes

No adverse embryo-fetal effects were observed in rats and rabbits at DOR exposures (based on AUC) that were approximately nine times (in rats) and eight times (in rabbits) the exposures seen in humans who received the recommended dose. Similarly, no adverse developmental findings were reported in a prenatal/postnatal study in rats at DOR exposures that were approximately nine times the exposure seen in humans who received the recommended dose.[4]

Placental and Breast Milk Passage

Embryo-fetal studies in rats and rabbits demonstrate placental passage of DOR. Fetal plasma concentrations observed on gestation Day 20 were up to 40% (in rabbits) and 52% (in rats) of maternal concentrations. DOR was excreted into the milk of lactating rats at concentrations that were approximately 1.5 times the maternal concentrations measured 2 hours postdose on lactation Day 14.[4]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Doravirine (DOR) *Pifeltro* (DOR/3TC/TDF) *Delstrigo*	DOR (Pifeltro) • 100-mg tablet DOR/3TC/TDF (Delstrigo) • DOR 100-mg/3TC 300-mg/ TDF 300-mg tablet	Pregnancy *PKs in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy* • Insufficient data to make dosing recommendations For guidance about the use of combination ARV drug products in pregnancy, please see the specific sections on other drug components (i.e., 3TC, TDF). Standard Adult Doses *DOR (Pifeltro)* • DOR 100 mg once daily with or without food *DOR/3TC/TDF (Delstrigo)* • One tablet once daily with or without food	No human *in vivo* data are available on the placental transfer of DOR, but passage is noted in *ex vivo* models. Insufficient data are available to assess for teratogenicity in humans. No evidence exists of teratogenicity in rats or rabbits.

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 11).

Key: 3TC = lamivudine; ARV = antiretroviral; DOR = doravirine; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

References

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2. Le M, Pencole L, Peytavin G, Bouchet-Crivat F, Mandelbrot L. Placental transfer of doravirine, a recent HIV-1 NNRTI in the ex vivo human cotyledon perfusion model,,. *J Antimicrob Chemother*. 2021;76(9):2364-2367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34151361.

3. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2022. Wilmington, NC: Registry Coordinating Center; 2022.Available at: http://www.apregistry.com/forms/interim_report.pdf. Accessed.

4. Doravirine (Pifeltro) [package insert]. Food and Drug Administration. 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/210806s007lbl.pdf.