Darunavir (Prezista, DRV)

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Animal Studies

Carcinogenicity

Darunavir (DRV) was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in both male and female mice and rats, as was an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of DRV to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination; this predisposes rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to DRV (based on area under the curve [AUC]) were between 0.4-fold and 0.7-fold higher (in mice) and 0.7-fold and onefold higher (in rats) than the exposures observed in humans who received the recommended therapeutic doses of darunavir/ritonavir (DRV/r) 600 mg/100 mg twice daily or DRV/r 800 mg/100 mg once daily.[1]

Reproduction/Fertility

No effects on fertility or early embryonic development were seen in rats that received DRV.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No embryotoxicity or teratogenicity was seen in rats that experienced DRV exposures (based on AUC) that were threefold higher than those seen in humans who received recommended DRV/r doses; likewise, no embryotoxicity or teratogenicity was seen in mice and rabbits that experienced DRV exposures that were less than onefold those seen in humans who received the recommended DRV/r doses. Administering DRV alone or with ritonavir to female rats during lactation resulted in a reduction in pup weight gain during a rat prenatal and postnatal development study. DRV/r **is not recommended** for pediatric patients aged <3 years due to the toxicity and mortality observed in juvenile rats dosed with DRV up to 23 to 26 days of age.[1]

Placental and Breast Milk Passage

No animal studies of placental passage of DRV have been reported. Passage of DRV into breast milk has been noted in rats.[1]

Human Studies in Pregnancy

Pharmacokinetics

Several studies of the pharmacokinetics (PKs) of DRV/r during pregnancy have been completed.[2–5] DRV plasma AUC during the third trimester, compared with postpartum, was reduced by 17% to 26% with DRV/r 600 mg/100 mg twice-daily dosing and by 33% to 39% with DRV/r 800 mg/100 mg once-daily dosing.[2–6] DRV trough concentration during the third trimester, compared with postpartum, was reduced by 8% to 12% with DRV/r 600 mg/100 mg twice-daily dosing and by 42% to 58% with DRV/r 800 mg/100 mg once-daily dosing.[3–5]

Three studies measured DRV protein binding during pregnancy. One study found no change in DRV protein binding during the third trimester. The other two studies reported decreased unbound DRV concentrations during pregnancy that were not considered clinically significant.[2,4,5] Because of the low DRV trough levels that occur with once-daily dosing, twice-daily dosing of DRV is recommended during pregnancy, especially for antiretroviral-experienced patients.[3,7] The Food and Drug Administration recommends the use of once-daily DRV/r 800 mg/100 mg dosing only for pregnant women who are virally suppressed on a stable, once-daily DRV/r regimen prior to pregnancy and whose adherence or ability to tolerate a regimen may be compromised by a switch to twice-daily DRV/r.[1] After reviewing the available evidence, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission does not recommend once-daily dosing of

DRV/r in pregnancy. An 800-mg DRV dose administered twice daily did not increase DRV exposure in pregnant women; use of this increased, twice-daily DRV dose during pregnancy **is not recommended.**[6]

Data are available from two studies describing the PK and safety of cobicistat (COBI) boosting of DRV during pregnancy. In both studies, darunavir/cobicistat (DRV/c) 800 mg/150 mg was administered during pregnancy.[8,9] In a study of seven pregnant women with HIV who were treated with DRV/c, no drug-related adverse events were observed. When PK parameters during the second and third trimesters were compared to postpartum PK parameters, total DRV AUC was reduced by 56% and 50%, and trough concentration was reduced by 92% and 89%, respectively. Unbound DRV concentrations decreased during the second and third trimesters of pregnancy compared to postpartum, with AUC 45% and 40% lower and trough concentration 92% and 88% lower, respectively. COBI exposures were lower during pregnancy, with reductions during the second and third trimesters of 63% and 49% for AUC and 83% and 83% for trough concentration, compared to postpartum. Six of seven participants remained virally suppressed during pregnancy. One woman who was not suppressed was found to be nonadherent to treatment, based on pill count. No infants born to study mothers contracted HIV.[9] On the basis of these data, the package insert for the fixed-dose combination of DRV/c was edited to include a statement saying that this product **is not recommended** for use in pregnant women because of substantially lower exposures of DRV and COBI during pregnancy.[10] These findings are consistent with a larger study of 29 pregnant women who received the DRV/c combination. When PK parameters during the second and third trimesters were compared with postpartum PK parameters in these women, total DRV AUC was reduced by 33% and 48%, respectively, and DRV trough concentrations were reduced by 71% and 75%, respectively.[8]

Placental and Breast Milk Passage

In an *ex vivo* human cotyledon perfusion model, the mean fetal transfer rate of DRV was 15%.[11] In 5 studies that reported data from between 6 and 14 subjects each, the median ratio of DRV concentration in cord blood to DRV concentration in maternal delivery plasma ranged from 13% to 24%.[2–4,9,12] No data are available that describe the breast milk passage of DRV in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to DRV to allow detection of at least a twofold increase in the risk of overall birth defects. No such increase in the risk of birth defects has been observed with DRV. Among cases of first-trimester DRV exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.6% (22 of 604 live births; 95% confidence interval, 2.3% to 5.5%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[13]

Excerpt from Table 10

Note: When using FDC tablets, refer to other sections in Appendix B and Table 10 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
Darunavir (DRV) *Prezista* **Note:** Must be combined with low-dose RTV or COBI boosting. (DRV/c) *Prezcobix* (DRV/c/FTC/TAF) *Symtuza*	**DRV (Prezista)** *Tablet:* • 75 mg • 150 mg • 600 mg • 800 mg *Oral Suspension:* • 100 mg/mL **DRV/c (Prezcobix):** • DRV/c 800 mg/ 150 mg tablet **DRV/c/FTC/TAF (Symtuza):** • DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg tablet	**Standard Adult Doses** *ARV-Naive Patients:* • DRV/r 800 mg/ 100 mg once daily with food • DRV/c 800 mg/ 150 mg once daily with food *ARV-Experienced Patients* If Patient Has No DRV Resistance Mutations: • DRV/r 800 mg/ 100 mg once daily with food • DRV/c 800 mg/ 150 mg once daily with food If Any DRV Resistance Mutations Are Present: • DRV/r 600 mg/ 100 mg twice daily with food DRV/c *(Prezcobix)*: • One tablet once daily with food DRV/c/FTC/TAF *(Symtuza)*: • One tablet once daily with food **Pregnancy** *PKs in Pregnancy:* • Decreased exposure in pregnancy with use of DRV/r.	Low placental transfer to fetus.[b] No evidence of teratogenicity in mice, rats, or rabbits. No evidence of human teratogenicity. Must be boosted with low-dose RTV. The Panel **does not recommend** once-daily dosing with DRV/r during pregnancy or the use of DRV/c during pregnancy. If a DRV/c regimen is continued during pregnancy, viral load should be monitored frequently.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing • Recommendations[a]	Use in Pregnancy
		Dosing in Pregnancy: • The Panel **does not recommend** once-daily dosing with DRV/r during pregnancy or the use of DRV/c during pregnancy. • Twice-daily DRV/r dosing (DRV/r 600 mg/100 mg with food) is recommended for all pregnant women. • Increased, twice-daily DRV dose (DRV/r 800 mg/100 mg with food) during pregnancy does not result in an increase in DRV exposure and **is not recommended.** For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF).	

[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 10).
[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:
High: >0.6
Moderate: 0.3–0.6
Low: <0.3

Key: ARV = antiretroviral; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

References

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