

Darunavir (Prezista, DRV)

(Last reviewed October 26, 2016; last updated October 26, 2016)

Darunavir is classified as Food and Drug Administration Pregnancy Category C.

Animal Studies

Carcinogenicity

Darunavir 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 well as 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 darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on area under the curve) were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats) those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg/day).¹

Reproduction/Fertility

No effects on fertility and early embryonic development were seen with darunavir in rats.¹

Teratogenicity/Developmental Toxicity

No embryotoxicity or teratogenicity was seen in mice, rats, or rabbits. Because of limited bioavailability of darunavir in animals and dosing limitation, the plasma exposures were approximately 50% (mice and rats) and 5% (rabbits) of those obtained in humans. In the rat prenatal and postnatal development study, a reduction in pup weight gain was observed with darunavir alone or with ritonavir exposure via breast milk during lactation. In juvenile rats, single doses of darunavir (20 mg/kg–160 mg/kg at age 5–11 days) or multiple doses of darunavir (40 mg/kg–1,000 mg/kg at age 12 days) caused mortality. The deaths were associated with convulsions in some of the animals. Within this age range, exposures in plasma, liver, and brain were dose- and age-dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the cytochrome P450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. Sexual development, fertility, or mating performance of offspring was not affected by maternal treatment.¹

Placental and Breast Milk Passage

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

Human Studies in Pregnancy

Pharmacokinetics

Three intensive pharmacokinetic (PK) studies of darunavir/ritonavir administered as 600 mg/100 mg twice a day or 800 mg/100 mg once a day during pregnancy have been completed.²⁻⁴ These studies demonstrate 17% to 33% reductions in darunavir plasma concentrations during the third trimester compared with postpartum.²⁻⁴ Two of these studies measured darunavir protein binding during pregnancy with conflicting results. One study found no change in darunavir protein binding during the third trimester while the other found a decrease.^{2,4} Because of low trough levels with once-daily dosing, twice-daily dosing of darunavir is recommended during pregnancy, especially for antiretroviral-experienced patients. A study of use of an increased twice-daily darunavir dose (800 mg) during pregnancy reported no increase in darunavir exposure in pregnant women receiving the increased dose; use of this increased twice-daily darunavir dose during pregnancy is not recommended.⁵ The PK and safety of darunavir/cobicistat during pregnancy have not been studied.

Placental and Breast Milk Passage

In an *ex vivo* human cotyledon perfusion model, the mean fetal transfer rate was 15%.⁶ In 4 studies reporting data from between 8 and 14 subjects each, the median ratio of darunavir concentration in cord blood to

that in maternal delivery plasma ranged from 13% to 24%.^{2-4,7} No data are available describing breast milk passage of darunavir in humans.

Teratogenicity Data

Among cases of first-trimester darunavir exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 2.7% (9 of 333 births; 95% CI, 0.9% to 5.0%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁸

Other Safety Issues

No safety issues have been observed in case reports and small PK studies of darunavir in pregnancy.^{2-4,7,9-13}

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Darunavir (DRV) <i>Prezista</i> Note: Must be combined with low-dose ritonavir (RTV) or cobicistat (COBI) boosting Darunavir/ Cobicistat (DRV/COBI) <i>Prezcobix</i>	<u>DRV (Prezista):</u> • 75 mg • 150 mg • 600 mg • 800 mg <u>Oral Suspension:</u> • 100 mg/mL <u>Prezcobiz (Co- Formulated):</u> • DRV 800 mg plus COBI 150 mg	<u>Standard Adult Dose</u> <u>ARV-Naive Patients:</u> • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food <u>ARV-Experienced Patients:</u> <u>If No DRV Resistance Mutations:</u> • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food <u>If Any DRV Resistance Mutations:</u> • DRV 600 mg plus RTV 100 mg twice daily with food <u>PK in Pregnancy:</u> • Decreased exposure in pregnancy with use of DRV/RTV. <u>Dosing in Pregnancy:</u> • Once-daily dosing with DRV/RTV is not recommended during pregnancy. Twice-daily DRV/RTV dosing (DRV 600 mg plus RTV 100 mg with food) recommended for all pregnant women. Increased twice-daily DRV dose (DRV 800 mg plus RTV 100 mg with food) during pregnancy does not result in an increase in darunavir exposure and is not recommended. • No pregnancy PK/safety data for DRV/COBI co-formulation, so not recommended for use in pregnancy.	Low placental transfer to fetus. ^b No evidence of teratogenicity in mice, rats, or rabbits. No evidence of human teratogenicity. Must be given as low-dose, RTV-boosted regimen.

^a Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult and Adolescent Guidelines, Appendix B, Table 7](#)).

^b Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key to Acronyms: ARV = antiretroviral; COBI = cobicistat; DRV = darunavir; PK = pharmacokinetic; RTV = ritonavir

References

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