

Saquinavir (Invirase, SQV)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Saquinavir is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Saquinavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies found no indication of carcinogenic activity in rats and mice administered saquinavir for approximately 2 years at plasma exposures approximately 29% (rat) and 65% (mouse) of those obtained in humans at the recommended clinical dose boosted with ritonavir.¹

Reproduction/Fertility

No effect of saquinavir has been seen on reproductive performance, fertility, or embryo survival in rats. Because of limited bioavailability of saquinavir in animals, the maximal plasma exposures achieved in rats were approximately 26% of those obtained in humans at the recommended clinical dose boosted with ritonavir.¹

Teratogenicity/Developmental Toxicity

No evidence of embryotoxicity or teratogenicity of saquinavir has been found in rabbits or rats. Because of limited bioavailability of saquinavir in animals and/or dosing limitations, the plasma exposures (area under the curve [AUC] values) in the respective species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir.¹

Placental and Breast Milk Passage

Placental transfer of saquinavir in the rat and rabbit was minimal. Saquinavir is excreted in the milk of lactating rats.¹

Human Studies in Pregnancy

Pharmacokinetics

Studies of saquinavir pharmacokinetics (PK) in pregnancy with the original hard-gel capsule formulation demonstrated reduced saquinavir exposures compared to postpartum and dosing recommendations for 800 to 1200 mg saquinavir with 100 mg ritonavir.²⁻⁶ The PK of saquinavir with the current 500-mg tablets boosted with ritonavir at a dose of 1000 mg saquinavir/100 mg ritonavir given twice daily has been studied in pregnant women in two studies.^{7,8} One study performed intensive sampling on HIV-infected pregnant women at 20 weeks' gestation (n = 16), 33 weeks' gestation (n = 31), and 6 weeks postpartum (n = 9). PK parameters were comparable during pregnancy and postpartum.⁷ The second study performed intensive sampling in 14 pregnant women at 24 and 34 weeks' gestation and 6 weeks postpartum. Saquinavir AUC was similar during the second trimester and postpartum. Although there was a 50% reduction in saquinavir AUC in the third trimester compared to postpartum, no subject experienced loss of virologic control and all but one maintained adequate third-trimester trough levels of saquinavir.⁹ In an observational study of saquinavir concentrations collected as part of clinical care between 11 and 13 hours after dosing with the tablet formulation (1000 mg saquinavir/100 mg ritonavir) in HIV-infected pregnant women during the third trimester (n = 20) and at delivery (n = 5), saquinavir plasma concentrations averaged around 1.15 mg/L and exceeded the usual trough drug concentration target for saquinavir of 0.1 mg/L in all but one subject.⁸

One study of 42 pregnant women receiving a combination antiretroviral drug regimen that included ritonavir-boosted saquinavir reported abnormal transaminase levels in 13 women (31%) within 2 to 4 weeks of treatment initiation, although the abnormalities were mild (toxicity Grade 1–2 in most, Grade 3 in 1 woman).¹⁰ In a study of 62 pregnant women on a regimen that included ritonavir-boosted saquinavir, one severe adverse event occurred (maternal Grade 3 hepatotoxicity).⁸

Placental and Breast Milk Passage

In a Phase I study in pregnant women and their infants (PACTG 386), transplacental passage of saquinavir was minimal.¹¹ In addition, in a study of eight women treated with saquinavir during pregnancy, the cord blood concentration of saquinavir was less than the assay limit of detection in samples from all women.¹² It is not known if saquinavir is excreted in human milk.

Teratogenicity/Developmental Toxicity

The 184 first-trimester saquinavir exposures monitored by the Antiretroviral Pregnancy Registry are too few to be able to accurately calculate the prevalence of birth defects in exposed cases.¹³

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Saquinavir (SQV) <i>Invirase</i> Note: Must be combined with low-dose RTV for PK boosting	<u>Tablet:</u> • 500 mg <u>Capsule:</u> • 200 mg	<u>Standard Adult Dose:</u> • SQV 1000 mg plus RTV 100 mg twice a day with food or within 2 hours after a meal <u>PK in Pregnancy:</u> • Based on limited data, SQV exposure may be reduced in pregnancy but not sufficient to warrant a dose change. <u>Dosing in Pregnancy:</u> • No change in dose indicated.	Low placental transfer to fetus. ^b Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be boosted with low-dose RTV. Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with preexisting cardiac conduction system disease.

^a Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult 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 Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic; RTV = ritonavir; SQV = saquinavir

References

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