

Fosamprenavir (Lexiva, FPV)

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Fosamprenavir is classified as Food and Drug Administration Pregnancy Category C. Fosamprenavir **should not** be used during pregnancy.

Animal Studies

Carcinogenicity

Fosamprenavir and amprenavir were neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies of fosamprenavir showed an increase in the incidence of hepatocellular adenomas and hepatocellular carcinomas at all doses tested in male mice and at the highest dose tested in female mice. In rats, the incidence of hepatocellular adenomas and thyroid follicular cell adenomas increased in males at all doses and in females at the two highest doses. Repeat dose studies in rats produced effects consistent with enzyme activation, which predisposes rats, but not humans, to thyroid neoplasms. In rats there was an increase in the risk of interstitial cell hyperplasia at higher doses and an increase in the risk of uterine endometrial adenocarcinoma at the highest dose tested. The incidence of endometrial findings was slightly increased over concurrent controls but was within background range for female rats. Thus, the relevance of the incidence of uterine endometrial adenocarcinomas is uncertain. Exposures in the carcinogenicity studies were

0.3 to 0.7 times (in mice) and 0.7 to 1.4 times (in rats) those seen in humans given fosamprenavir 1400 mg twice daily. Exposures were 0.2 to 0.3 times (in mice) and 0.3 to 0.7 times (in rats) those seen in humans given fosamprenavir 1400 mg once daily plus ritonavir 200 mg once daily or 0.1 to 0.3 times (in mice) and 0.3 to 0.6 times (in rats) those seen in humans given fosamprenavir 700 mg plus ritonavir 100 mg twice daily.¹

Reproduction/Fertility

No impairment of fertility or mating was seen in rats given doses that produced exposures that were three to four times the exposure seen in humans who were given fosamprenavir alone, or exposures that were similar to those seen in humans who received both fosamprenavir and ritonavir. No effect was seen on the development or maturation of sperm in rats at these doses.

Teratogenicity/Adverse Pregnancy Outcomes

Administration of fosamprenavir to pregnant rats and rabbits produced no major effects on embryo-fetal development; however, the incidence of abortion was increased in rabbits that were administered fosamprenavir. Administration of amprenavir to pregnant rabbits was associated with abortions and an

increased incidence of minor skeletal variations from deficient ossification of the femur, humerus, and trochlea. Administration of fosamprenavir to pregnant rats at doses that produced twice the exposure typically seen in humans was associated with a reduction in pup survival and body weights. Female offspring had an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared to controls.

Placental and Breast Milk Passage

Amprenavir is excreted in the milk of lactating rats.

Human Studies in Pregnancy

Pharmacokinetics

Data on the use of fosamprenavir in pregnant women are limited. Fosamprenavir pharmacokinetic (PK) data have been reported in 26 women during pregnancy and postpartum. Following standard dosing with fosamprenavir 700 mg and ritonavir 100 mg twice daily, the fosamprenavir area under the curve and 12-hour trough concentration were somewhat lower during pregnancy and higher postpartum, compared to historical data. Fosamprenavir exposure during pregnancy appeared to be adequate for patients without protease inhibitor resistance mutations.² For the postpartum period, potential PK interactions with hormonal contraceptives should be taken into account (see [Table 3](#) in [Preconception Counseling and Care](#)).

Placental and Breast Milk Passage

In a small study of women who received fosamprenavir during pregnancy, the median amprenavir concentration in cord blood was 0.27 µg/mL (with a range of 0.09–0.60 µg/mL), and the median ratio of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery was 0.24 (with a range of 0.06–0.93).² A second small study in pregnancy yielded a similar mean ratio of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery of 0.27 (95% confidence interval 0.24, 0.30).³ Whether amprenavir is excreted in human breast milk is unknown.

Teratogenicity/Adverse Pregnancy Outcomes

Two birth defects out of 109 live births with first-trimester exposure and two birth defects out of 36 live births with second- or third-trimester exposure have been reported to the Antiretroviral Pregnancy Registry. These numbers are insufficient to draw conclusions regarding the risk of birth defects.⁴

Excerpt from Table 8^a

Generic Name (Abbreviation) <i>Trade Name</i>	Formulation	Dosing Recommendations	Use in Pregnancy
Fosamprenavir (FPV) <i>Lexiva (a prodrug of amprenavir)</i> Note: Must be combined with low-dose RTV boosting in pregnancy.	FPV (Lexiva) <i>Tablets:</i> <ul style="list-style-type: none"> 700 mg <i>Oral Suspension:</i> <ul style="list-style-type: none"> 50 mg/mL 	Standard Adult Doses <i>FPV (Lexiva)</i> <ul style="list-style-type: none"> ARV-Naive Patients: <ul style="list-style-type: none"> FPV 1400 mg twice daily without food, <i>or</i> FPV 1400 mg plus RTV 100 or 200 mg once daily without food, <i>or</i> FPV 700 mg plus RTV 100 mg twice daily without food PI-Experienced Patients: <ul style="list-style-type: none"> Once-daily dosing is not recommended FPV 700 mg plus RTV 100 mg twice daily without food Coadministered with EFV: <ul style="list-style-type: none"> FPV 700 mg plus RTV 100 mg twice daily without food; <i>or</i> FPV 1400 mg plus RTV 300 mg once daily without food PK in Pregnancy: <ul style="list-style-type: none"> With RTV boosting, AUC is reduced during the third trimester. However, exposure is greater during the third trimester with boosting than in nonpregnant adults without boosting, and trough concentrations achieved during the third trimester were adequate for patients without PI resistance mutations. Dosing in Pregnancy: <ul style="list-style-type: none"> Use of unboosted FPV or once-daily FPV with RTV boosting is not recommended during pregnancy. No change is indicated in standard boosted twice-daily dose (FPV 700 mg plus RTV 100 mg twice daily without food). 	FPV should not be used during pregnancy. Low placental transfer to fetus. ^b Insufficient data to assess for teratogenicity in humans. Increased fetal loss in rabbits, but no increase in defect in rats and rabbits.

^a Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent 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 to Acronyms: ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FPV = fosamprenavir; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

References

1. Fosamprenavir [package insert] Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021548s040bledt.pdf.
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3. Cespedes MS, Castor D, Ford SL, et al. Steady-state pharmacokinetics, cord blood concentrations, and safety of ritonavir-boosted fosamprenavir in pregnancy. *J Acquir Immune Defic Syndr*. 2013;62(5):550-554. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23314414>.
4. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: <http://www.apregistry.com/>.