



Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Fosamprenavir (Lexiva, FPV)

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

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

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 in males (all doses tested) and in females (two highest doses tested) was also increased. Repeat dose studies in rats produced effects consistent with enzyme activation, which predisposes rats, but not humans, to thyroid neoplasms. In rats only, there was an increase in interstitial cell hyperplasia at higher doses and an increase in 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 uterine endometrial adenocarcinomas is uncertain. Exposures in the carcinogenicity studies were 0.3- to 0.7 (mice) and 0.7- to 1.4 (rats) times those in humans given 1400 mg twice daily of fosamprenavir alone and were 0.2- to 0.3 (mice) and 0.3- to 0.7 (rats) times those in humans given 1400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily or 0.1- to 0.3 (mice) and 0.3- to 0.6 (rats) times those in humans given 700 mg fosamprenavir plus 100 mg ritonavir twice daily.†

Reproduction/Fertility

No impairment of fertility or mating was seen in rats at doses providing 3 to 4 times the human exposure to fosamprenavir alone or exposure similar to that with fosamprenavir and ritonavir dosing in humans. No effect was seen on the development or maturation of sperm in rats at these doses.

Teratogenicity/Developmental Toxicity

Fosamprenavir was studied in rabbits at 0.8 times and in rats at twice the exposure in humans to fosamprenavir alone and at 0.3 (rabbits) and 0.7 (rats) times the exposure in humans to the combination of fosamprenavir and ritonavir. In rabbits administered fosamprenavir (alone or in combination), the incidence of abortion was increased. In contrast, administration of amprenavir at a lower dose in rabbits was associated with abortions and an increased incidence of minor skeletal variations from deficient ossification of the femur, humerus, and trochlea. Fosamprenavir administered to pregnant rats (at twice human exposure) was associated with a reduction in pup survival and body weights in rats. F1 female rats 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 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, 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 receiving fosamprenavir during pregnancy, the median (range) amprenavir concentration in cord blood was 0.27 (0.09–0.60) µg/mL, and the median (range) ratio of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery was 0.24 (0.06–0.93).² A second small study in pregnancy yielded a similar mean ratio (95% confidence interval) of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery of 0.27 (0.24, 0.30).³ Whether amprenavir is excreted in human breast milk is unknown.

Teratogenicity/Developmental Toxicity

Two birth defects out of 108 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 allow conclusions to be drawn regarding the risk of birth defects.⁴

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Name	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	<u>Tablets:</u> • 700 mg <u>Oral Suspension:</u> • 50 mg/mL	<u>Standard Adult Dose</u> <i>ARV-Naive Patients:</i> <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 <i>PI-Experienced Patients (Once-Daily Dosing Not Recommended):</i> <ul style="list-style-type: none"> • FPV 700 mg plus RTV 100 mg twice daily without food <i>Co-Administered with EFV:</i> <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 <u>PK in Pregnancy:</u> <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 non-pregnant adults without boosting, and trough concentrations achieved during the third trimester were adequate for patients without PI resistance mutations. <u>Dosing in Pregnancy:</u> <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). 	Low placental transfer to fetus. ^b Insufficient data to assess for teratogenicity in humans. Increased fetal loss in rabbits but no increase in defects in rats and rabbits. Must be given as low-dose RTV-boosted regimen in pregnancy.

^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 Acronyms: ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FPV = fosamprenavir; PI = protease inhibitor; PK = pharmacokinetic; RTV= ritonavir

References

1. Fosamprenavir Calcium (Lexiva) [package insert]. Food and Drug Administration. 2016. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021548s037.022116s021lbl.pdf. Accessed April 15, 2016.
2. Capparelli EV, Stek A, Best B, et al. Boosted Fosamprenavir pharmacokinetics during pregnancy. Presented at: The 17th Conference on Retroviruses and Opportunistic Infections. 2010. San Francisco, CA.

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 Jan 1989–31 July 2015. Wilmington, NC: Registry Coordinating Center. 2015. Available at <http://www.apregistry.com/>.