

Lopinavir/Ritonavir (Kaletra, LPV/r)

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No difference in the risk of overall major birth defects has been shown for lopinavir/ritonavir (LPV/r) compared to the background rate for major birth defects in the United States. Treatment-related malformations were not observed when LPV/r was administered to pregnant rats or rabbits, but embryonic and developmental toxicities were seen in rats at maternally toxic doses.

Animal Studies

Carcinogenicity

Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. The LPV/r combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increased incidence of benign hepatocellular adenomas and increased combined incidence of hepatocellular adenomas plus carcinoma in male and female mice and male rats at doses that produced approximately 1.6 to 2.2 times (mice) and 0.5 times (rats) the human exposure at the recommended therapeutic dose of 400 mg/100 mg (based on area under the curve [AUC]_{0–24hr} measurement). Administration of LPV/r did not cause a statistically significant increase in incidence of any other benign or malignant neoplasm in mice or rats.¶

Reproduction/Fertility

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats with exposures approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.¶

Teratogenicity/Developmental Toxicity

No evidence exists of teratogenicity with administration of LPV/r to pregnant rats or rabbits. In rats treated with a maternally toxic dosage (100 mg lopinavir/50 mg ritonavir/kg/day), embryonic and fetal developmental toxicities (e.g., early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations, and skeletal ossification delays) were observed. Drug exposure in the pregnant rats was 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose. In a perinatal and postnatal study in rats, a decrease in survival of pups between birth and postnatal Day 21 occurred with exposure to 40 mg lopinavir/20 mg ritonavir/kg/day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with a maternally toxic dosage, where drug exposure was 0.6-fold for lopinavir and 1-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.¶ In a study of pregnant rats receiving chronic administration of zidovudine, lopinavir, and ritonavir, maternal body weight gain was significantly reduced, but no adverse fetal parameters were observed.² In pregnant mice, ritonavir, lopinavir and atazanavir were associated with significantly lower progesterone levels, and the lower progesterone levels directly correlated with lower fetal weight.³

Placental and Breast Milk Passage

No information is available on placental transfer of lopinavir in animals.¶

Human Studies in Pregnancy

Pharmacokinetics

The original capsule formulation of LPV/r has been replaced by a tablet formulation that is heat-stable, has improved bioavailability characteristics, and does not have to be administered with food.^{4,5} Pharmacokinetic (PK) studies of standard adult LPV/r doses (400 mg/100 mg twice a day) using either the capsule or tablet formulations in pregnant women have demonstrated a reduction in lopinavir plasma concentrations during pregnancy of around 30% compared with that in non-pregnant adults.^{6–8} Further reductions in lopinavir exposure by 33% were demonstrated in food-insecure, malnourished pregnant women in Uganda compared to well-nourished, historical pregnant controls. The authors attributed this reduction to decreased bioavailability.⁹ Increasing the dose of LPV/r during pregnancy to 600 mg/150 mg (tablets) results in lopinavir plasma concentrations equivalent to those seen in non-pregnant adults receiving standard doses.^{10,11}

Reports of clinical experience suggest that most, but not all, pregnant women receiving standard LPV/r tablet dosing during pregnancy will have trough lopinavir concentrations that exceed 1.0 mcg/mL, the usual trough concentration target used in therapeutic drug monitoring programs for antiretroviral-naïve subjects, but not the higher trough concentrations recommended for protease inhibitor (PI)-experienced subjects.^{4,7} A population PK study of LPV/r in 154 pregnant women demonstrated that body weight influences lopinavir clearance and volume, with larger women (>100 kg) or women who missed a dose at higher risk for subtherapeutic trough concentrations when taking the standard dose during pregnancy.¹² Another population PK study in 84 pregnant women and 595 non-pregnant adults found no significant difference in lopinavir concentration in pregnant women taking the more bioavailable tablet formulation compared to non-pregnant adults taking the original capsule formulation.¹³ In one study of 29 women, lopinavir plasma protein binding was reduced during pregnancy, but the resulting increase in free (unbound) drug was insufficient to make up for the reduction in total plasma lopinavir concentration associated with pregnancy.¹⁴ In a study of 12 women, total lopinavir exposure was significantly decreased throughout pregnancy, but unbound AUC and C₁₂ did not differ throughout pregnancy, even with an increased dose of 500/125 mg.¹⁵ A population PK study found a 39% increase in total lopinavir clearance during pregnancy, but measured unbound lopinavir concentrations in pregnancy were within the range of those simulated in nonpregnant adults.¹⁶ Bonafe et al randomized 32 pregnant women to standard dose and 31 pregnant women to the 600/150 mg dose of LPV/r at gestational ages between 14 and 33 weeks. No differences in adverse events (AEs) were seen between groups. In women with baseline viral loads >50 copies/mL, 45% in the standard dose group had plasma viral loads >50 copies/mL during the last 4 weeks of pregnancy, compared to 10.5% in the increased dose group (*P* = 0.01). In women with baseline viral loads <50 copies/mL, no difference was seen between groups in viral load measurements in the last 4 weeks of pregnancy.¹⁷

These studies have led some experts to support use of an increased dose of LPV/r in HIV-infected pregnant women during the second and third trimesters, especially in PI-experienced pregnant women and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. If standard doses of LPV/r are used during pregnancy, virologic response and lopinavir drug concentrations, if available, should be monitored. An alternative strategy to increasing LPV/r dosing during pregnancy by using 3 adult 200/50 mg tablets to provide a dose of 600/150 mg is to add a pediatric LPV/r tablet (100/25 mg) to the standard dose of 2 adult 200/50 mg tablets to provide a dose of 500/125 mg.¹⁵ Once-daily dosing of LPV/r **is not recommended** in pregnancy because no data exist to address whether drug levels are adequate with such administration.

Placental and Breast Milk Passage

Lopinavir crosses the human placenta; in the P1026s PK study, the average ratio of lopinavir concentration in cord blood to maternal plasma at delivery was 0.20 ± 0.13. In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda receiving LPV/r during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested significant in utero transfer: 41% of infants had detectable plasma lopinavir concentrations at birth and mean infant-to-maternal-hair concentrations at 12 weeks postpartum were 0.87 for lopinavir.¹⁸ However, transfer during breastfeeding was not observed, and no infant had detectable plasma lopinavir levels at 12 weeks. Lopinavir concentrations in human breast milk are very low to undetectable and lopinavir concentrations in breastfeeding infants whose mothers received lopinavir are not clinically significant.¹⁸⁻²²

Teratogenicity/Developmental Toxicity

The French Perinatal Cohort found no association between birth defects and lopinavir or ritonavir with 85% power to detect a 1.5-fold increase.²³ The Pediatric HIV/AIDS Cohort Study found no association between lopinavir and congenital anomalies.²⁴ Surveillance data from the United Kingdom and Ireland over a 10 year period showed a 2.9% prevalence of congenital abnormalities (134 children of 4,609 lopinavir-exposed pregnancies), comparable to rates in uninfected populations.²⁵ In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to LPV/r have been monitored for detection of at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with LPV/r. Among cases of first-trimester exposure to LPV/r reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was

2.3% (29 of 1,290; 95% CI, 1.5% to 3.2%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.²⁶

Safety

LPV/r oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol. Reduced hepatic metabolic and kidney excretory function in newborns can lead to accumulation of lopinavir as well as alcohol and propylene glycol, resulting in AEs such as serious cardiac, renal, metabolic, or respiratory problems. Preterm babies may be at increased risk because their metabolism and elimination of lopinavir, propylene glycol, and alcohol are further reduced. Post-marketing surveillance has identified 10 neonates (i.e., babies aged <4 weeks), nine of whom were born prematurely, who received LPV/r and experienced life-threatening events.²⁷ In a separate report comparing 50 HIV-exposed newborns treated with LPV/r after birth to 108 HIV-exposed neonates treated with zidovudine alone, elevated concentrations of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate, consistent with impairment of 21 α -hydroxylase activity, were seen only in the lopinavir-exposed infants. All term infants were asymptomatic but three of eight preterm infants had life-threatening symptoms, including hyponatremia, hyperkalemia, and cardiogenic shock, consistent with adrenal insufficiency.²⁸ LPV/r oral solution should not be administered to neonates before a postmenstrual age (first day of the mother’s last menstrual period to birth, plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained.

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Name.	Formulation	Dosing Recommendations	Use in Pregnancy
Lopinavir/ Ritonavir (LPV/r) Kaletra	<p><u>Tablets (Co-Formulated):</u></p> <ul style="list-style-type: none"> • LPV 200 mg plus RTV 50 mg • LPV 100 mg plus RTV 25 mg <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> • LPV 400 mg plus RTV 100 mg/5 mL 	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • LPV 400 mg plus RTV 100 mg twice daily, <i>or</i> • LPV 800 mg plus RTV 200 mg once daily <p><u>Tablets:</u></p> <ul style="list-style-type: none"> • Take without regard to food. <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> • Take with food. <p><u>With EFV or NVP (PI-Naive or PI-Experienced Patients):</u></p> <ul style="list-style-type: none"> • LPV 500 mg plus RTV 125 mg tablets twice daily without regard to meals (use a combination of two LPV 200 mg plus RTV 50 mg tablets and one LPV 100 mg plus RTV 25 mg tablet), <i>or</i> • LPV 520 mg plus RTV 130 mg oral solution (6.5 mL) twice daily with food <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • With twice-daily dosing, LPV exposure is reduced in pregnant women receiving standard adult doses; increasing the dose by 50% results in exposure equivalent to that seen in non-pregnant adults receiving standard doses. • No PK data are available for once-daily dosing in pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • Once daily dosing is not recommended during pregnancy. • Some experts recommend that an increased dose (i.e., LPV 600 mg plus RTV 150 mg twice daily without regard to meals) should be used in the second and third trimesters, especially in PI- experienced pregnant women and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. • If standard dosing is used, monitor virologic response and LPV drug levels, if available. 	<p>Low placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</p> <p>Oral solution contains 42% alcohol and 15% propylene glycol and is not recommended for use in pregnancy.</p> <p>Once-daily LPV/r dosing is not recommended during pregnancy</p>

^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: EFV = efavirenz; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

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