

# Lopinavir/Ritonavir

**Brand Name: Kaletra**

## Drug Description

Lopinavir/ritonavir is a fixed combination of two HIV protease inhibitors (PIs). Ritonavir, a potent inhibitor of the hepatic cytochrome P450 isoenzyme CYP3A, decreases metabolism of and increases plasma concentrations of lopinavir. [1]

## HIV/AIDS-Related Uses

Lopinavir/ritonavir was approved by the FDA on September 15, 2000, for use in combination with other antiretrovirals in the treatment of HIV infection. Lopinavir/ritonavir should not be used alone in the treatment of HIV infection. The fixed combination of lopinavir and ritonavir and two nucleoside reverse transcriptase inhibitors is one of several preferred regimens for initial antiretroviral therapy in HIV infected adults who are treatment naive.[2] [3]

## Pharmacology

The antiviral activity of lopinavir/ritonavir is due to the lopinavir component. Lopinavir inhibits the human immunodeficiency virus (HIV) protease, preventing cleavage of the Gag-Pol polyprotein and reducing the probability of viral particles reaching a mature, infectious state.[4] [5]

Ritonavir inhibits CYP3A, the principal isoenzyme that metabolizes lopinavir; coadministration results in decreased metabolism and increased plasma concentrations of lopinavir. At low doses (100 mg twice daily), ritonavir acts as a pharmacoenhancer of amprenavir, indinavir, nelfinavir, and saquinavir, as well as lopinavir.[6]

The absorption of the combination of lopinavir and ritonavir is favorably affected by the presence of food. Administration with a high-fat meal increases the area under the curve (AUC) of lopinavir by 97% and C<sub>max</sub> by 43% for the capsules and 130% and 56%, respectively, for the oral solution relative to administration during a fasting state.[7] [8]

Peak plasma concentration of lopinavir was  $9.6 \pm 4.4$  mcg/ml following multiple doses of 400 mg lopinavir and 100 mg ritonavir for 3 to 4 weeks in

HIV infected patients.[9]

Lopinavir/ritonavir is in FDA Pregnancy Category C. No studies using lopinavir/ritonavir have been done in pregnant women. In rats given a maternally toxic dosage, early reabsorption, decreased fetal viability and body weight, and increased incidence of skeletal variation and delayed skeletal ossification occurred. Lopinavir/ritonavir should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to lopinavir/ritonavir and other antiretrovirals. Physicians may register patients by calling (800) 258-4263 or at <http://www.APRegistry.com>. It is not known whether lopinavir is secreted in human milk; it is, however, secreted in the milk of laboratory rats. Because of the potential for HIV transmission and serious adverse effects in nursing infants, mothers should be instructed not to breast-feed if they are taking lopinavir/ritonavir.[10]

Protein binding of lopinavir is 98% to 99%. It binds to both alpha-1-acid glycoprotein and albumin but has a higher affinity for alpha-1-acid glycoprotein. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg lopinavir/ritonavir twice a day and is similar between healthy volunteers and HIV infected patients.[11]

Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isoenzyme. Because ritonavir is a potent CYP3A inhibitor, it inhibits the metabolism of lopinavir and increases plasma levels of lopinavir. At least 13 lopinavir oxidative metabolites have been identified in humans. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Predose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.[12] Following multiple doses of lopinavir/ritonavir, the serum half-life of lopinavir was 5 to 6 hours. Time to peak lopinavir concentration was 4 hours in HIV infected patients.[13]

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## Pharmacology (cont.)

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Following a single 400/100 mg dose of lopinavir/ritonavir, approximately  $10.4 \pm 2.3\%$  of the administered lopinavir excreted in urine and  $82.6 \pm 2.5\%$  excreted in feces was accounted for after 8 days.[14] [15] Unchanged lopinavir accounted for approximately 2.2% and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose was excreted unchanged in the urine.[16]

HIV-1 isolates with reduced susceptibility to lopinavir have been selected in vitro. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses in vitro. Resistance to lopinavir/ritonavir has emerged in patients previously treated with other protease inhibitors (PIs). In studies of 227 antiretroviral treatment-naïve and PI-experienced patients, isolates from 4 of 23 patients with quantifiable viral RNA after 12 to 100 weeks of treatment with lopinavir/ritonavir showed significantly reduced susceptibility to lopinavir. Three of these patients previously had been treated with one PI, and one had been treated with multiple PIs. Following viral rebound, isolates from these patients all contained additional mutations, some of which are associated with PI resistance.[17]

Varying degrees of cross resistance have been observed among HIV PIs. In studies of the in vitro activity of lopinavir against clinical isolates from patients previously treated with a single PI, isolates that displayed a greater than fourfold reduced susceptibility to nelfinavir and saquinavir displayed a less than fourfold reduced susceptibility to lopinavir. Isolates with a greater than fourfold reduced susceptibility to indinavir and ritonavir displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more PIs showed greater reductions in susceptibility to lopinavir.[18]

## Adverse Events/Toxicity

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Pancreatitis has been observed in patients receiving lopinavir/ritonavir, including those who developed marked triglyceride elevations; in some cases,

fatalities have occurred. Although a causal relationship with lopinavir/ritonavir has not been established, marked triglyceride elevation is a risk factor in the development of pancreatitis. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during lopinavir/ritonavir therapy. Pancreatitis should be considered if clinical symptoms suggestive of pancreatitis occur, including nausea, vomiting, abdominal pain, or abnormal laboratory values such as increased serum lipase or amylase. Patients who exhibit these signs or symptoms should be evaluated and lopinavir/ritonavir and/or other antiretroviral therapy should be suspended.[19]

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance of HIV infected patients receiving PI therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemia agents for treatment of these events; in some cases, diabetic ketoacidosis has occurred. In those patients who discontinued PI therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between PI therapy and these events has not been established.[20]

Other clinically observed adverse effects include body fat redistribution and accumulation, increased bleeding in patients with hemophilia type A and B, lipid elevations, and exacerbation of existing hepatitis or other liver disease.[21]

Other adverse effects seen with the use of lopinavir/ritonavir include diabetes mellitus or hyperglycemia, pancreatitis, diarrhea, nausea, abdominal pain, abnormal stools, asthenia, headache, insomnia, pain, rash, vomiting, and redistribution of body fat.[22]

## Drug and Food Interactions

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To enhance bioavailability and minimize pharmacokinetic variability, the manufacturer recommends that lopinavir/ritonavir should be taken with food. Administering lopinavir/ritonavir

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## Drug and Food Interactions (cont.)

capsules or oral solution with food increases absorption. When lopinavir/ritonavir is administered with a high-fat meal, the lopinavir AUC increases by 97% and the C<sub>max</sub> by 43% for capsules and by 130% and 56%, respectively, for the oral solution.[23] Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of lopinavir/ritonavir coformulated capsules and liquid. When administered under fasting conditions, both the mean AUC and C<sub>max</sub> of lopinavir were 22% lower for the lopinavir/ritonavir liquid relative to the capsules.[24]

Lopinavir/ritonavir is an inhibitor of the P450 isoform CYP3A *in vitro*. Coadministration of lopinavir/ritonavir and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects. Lopinavir/ritonavir has also been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.[25]

Concentrations of antiarrhythmic drugs (amiodarone, bepridil, lidocaine, and quinidine) may be increased if taken concurrently with lopinavir/ritonavir; therapeutic monitoring of antiarrhythmic concentration may be necessary. Concomitant use of lopinavir/ritonavir with lipid lowering agents will result in an increase of concentrations of these agents. Levels of atorvastatin or cerivastatin should be lowered to the lowest possible level when used in combination with lopinavir/ritonavir. Pravastatin or fluvastatin should be considered as substitutes for atorvastatin or cerivastatin. Concomitant use of lovastatin or simvastatin with lopinavir/ritonavir is not recommended, as serious reactions such as myopathy, including rhabdomyolysis, may occur. Concurrent use of carbamazepine, dexamethasone, phenobarbital or phenytoin with lopinavir/ritonavir may decrease concentrations of lopinavir and lead to decreased effectiveness of lopinavir.[26]

Serum concentrations of clarithromycin may increase if administered concomitantly with

lopinavir/ritonavir. In patients concurrently taking clarithromycin, doses of lopinavir/ritonavir should be decreased as necessary in patients with renal impairment. Concentrations of cyclosporine, sirolimus, and tacrolimus may increase if administered concomitantly with lopinavir/ritonavir. Therapeutic monitoring is recommended for patients taking any of these immunosuppressants concurrently with lopinavir/ritonavir. Concentrations of dihydropyridine calcium channel blockers (felodipine, nifedipine, and nifedipine) may also increase if taken concomitantly with lopinavir/ritonavir; clinical monitoring is recommended.[27]

Azole antifungals such as itraconazole and ketoconazole are not recommended to be taken concurrently with lopinavir/ritonavir because it may increase azole concentrations. When rifabutin and lopinavir/ritonavir are administered concurrently, increased concentrations of rifabutin and rifabutin metabolite occur. A rifabutin dosage reduction by at least 75% is recommended, with further dose reduction possibly necessary.[28]

Concomitant use of ritonavir and St. John's wort (*Hypericum perforatum*) or products containing St. John's wort is not recommended as St. John's wort may substantially decrease lopinavir/ritonavir concentrations, resulting in suboptimal lopinavir concentrations, loss of virologic response, and possible resistance to lopinavir/ritonavir. Coadministration of lopinavir/ritonavir and sildenafil is expected to substantially increase sildenafil concentration and the risk of sildenafil-associated adverse effects, including hypotension, prolonged erection, syncope, and visual changes. Concomitant use of warfarin with lopinavir/ritonavir may affect warfarin serum concentrations; International Ratio Monitoring is recommended.[29]

Lopinavir concentrations decrease in patients concurrently taking efavirenz, nevirapine, amprenavir, or nelfinavir, due to induction of CYP3A by these drugs; increased dosage of lopinavir/ritonavir may be required.[30] [31] [32]

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## Contraindications

Lopinavir/ritonavir is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir. Coadministration of lopinavir/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events. These drugs include antihistamines (astemizole, terfenadine), ergot derivatives (dihydroergotamine, ergonovine, ergotamine, metylergonovine), the gastrointestinal motility agent cisapride, the neuroleptic pimozide, and sedatives (midazolam, triazolam). Concurrent use of any of these drugs with lopinavir/ritonavir is contraindicated due to the potential for serious and/or life threatening reactions such as cardiac arrhythmias, prolonged or increased sedation, or respiratory depression.[33] [34] Use of rifampin with lopinavir/ritonavir is also contraindicated, as it may lead to the loss of virologic response and possible resistance to lopinavir/ritonavir, other PIs, or any other coadministered antiretroviral agents.[35]

Risk-benefit should be considered if patients also have diabetes mellitus, hepatic function impairment, hepatitis B, hepatitis C, or a history of pancreatitis.[36]

## Clinical Trials

For information on clinical trials that involve Lopinavir/Ritonavir, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Lopinavir/Ritonavir AND HIV Infections.

## Dosing Information

Mode of Delivery: Oral.[37]

Dosage Form: Soft gelatin capsules containing 133.3 mg lopinavir and 33.3 mg ritonavir; oral solution containing 80 mg/ml of lopinavir and 20 mg/ml of ritonavir.[38]

The recommended dose of lopinavir/ritonavir is 400/100 mg (3 capsules or 5.0 ml) twice daily. When lopinavir/ritonavir is used in combination

with efavirenz or nevirapine, the lopinavir/ritonavir dose should be increased to 533/133 mg (4 capsules or 6.5 ml) twice daily. In children age 6 months to 12 years who weigh 7 to 15 kg, the recommended dose is 12/3 mg/kg twice daily; for those children who weigh 15 to 40 kg, the recommended dose is 10/2.5 mg/kg (maximum dose of 400/100 mg twice daily).[39]

Storage: Store capsules and oral solution at 2 C to 8 C (36 F to 46 F) until dispensed. Avoid exposure to excessive heat. Patients can keep refrigerated capsules and oral solution until expiration date. If kept at room temperature, capsules and oral solution should be used within 2 months of dispensing.[40]

## Chemistry

CAS Name: Lopinavir: (alphaS)-Tetrahydro-N-[(alphaS)-alpha-[(2S,3S)-2-hydroxy-4-phenyl-3-[2-(2,6-xylyloxy)acetamido]butyl]phenethyl]-alpha-isopropyl-2-oxo-1(2H)-pyrimidineacetamide[41]

Ritonavir: 5-Thiazolylmethyl [(alphaS)-alpha-[(1S,3S)-1-hydroxy-3-[(2S)-2-[3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido]-3-methylbutyramido]-4-phenylbutyl]phenethyl] carbamate[42]

Lopinavir/ritonavir:  
2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-(2-(1-methylethyl)-4-thiazolyl)-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (aS)-N-((1S,3S,4S)-4-(((2,6-dimethylphenoxy)acetyl)amino)-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl)tetrahydro-a- (1-methylethyl)-2-oxo-1(2H)- pyrimidineacetamide[43]

CAS Number: Lopinavir: 192725-17-0[44]

Ritonavir: 155213-67-5[45]

Lopinavir/ritonavir: 369372-47-4[46]

Molecular formula:  
C37-H48-N4-O5.C37-H48-N6-O5[47]

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## **Chemistry (cont.)**

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Lopinavir: C70.67%, H7.69%, N8.91%, O12.72%; Ritonavir: C61.64%, H6.71%, N11.66%, O11.10%, S8.90%[48]

Molecular weight: Lopinavir: 628.80; Ritonavir: 720.96[49]

Melting point: Lopinavir: 124 to 127 C[50]

Physical Description: Lopinavir: white to light tan powder.[51] Ritonavir: white to light tan powder with bitter metallic taste.[52]

Solubility: Lopinavir: Freely soluble in methanol and ethanol; soluble in isopropanol; practically insoluble in water.[53] Ritonavir: Freely soluble in methanol and ethanol; soluble in isopropanol; practically insoluble in water.[54]

## **Other Names**

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Lopinavir: A 157378.0; ABT 378; ABT-378[55]

Ritonavir: A-84538; Abbott 84538; ABT-538; Norvir[56]

LPV/RTV[57]

## **Further Reading**

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## **Manufacturer Information**

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## **For More Information**

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Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: [http://aidsinfo.nih.gov/live\\_help](http://aidsinfo.nih.gov/live_help) Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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