

<b>LOPINAVIR/RITONAVIR (LPV/R)</b> (Updated April 2010)	
<b>Trade Name</b>	Kaletra
<b>Classification</b>	Protease Inhibitor
<b>Form<sup>a</sup></b>	LPV 200 mg/RTV 50 mg film-coated tablets LPV 100 mg/RTV 25 mg film-coated tablets LPV 80 mg/RTV 20 mg per mL oral solution (contains 42% alcohol)
<b>Dosing Recommendations</b>	LPV 400 mg/RTV 100 mg (2 tablets) twice daily with or without food <i>or</i> LPV 800 mg/RTV 200 mg (4 tablets) once daily* with or without food <sup>b</sup> <i>or</i> LPV 400 mg/RTV 100 mg (5 mL) twice daily with food <i>or</i> LPV 800 mg/RTV 200 mg (10 mL) once daily* with food <sup>b</sup>  * FDA recommended only in patients with <3 LPV resistance-associated substitutions, but some experts would recommend LPV/r 400/100 mg twice-daily in these patients
<b>Hepatic Impairment Dosing</b>	Use with caution in patients with hepatic impairment
<b>Food Effect</b>	<b>Tablets:</b> May take with or without food; swallow whole  <b>Oral solution:</b> Must take with food. To increase absorption by 50%-80%, take with meal containing >15 g of fat
<b>Oral Bioavailability</b>	Not determined in humans
<b>Serum Half-life</b>	5-6 hours
<b>Route of Metabolism</b>	P450 cytochrome 3A4 inhibitor and substrate (may be an inducer at steady-state)
<b>Storage</b>	<b>Tablets:</b> store at room temperature. Do not expose to high humidity outside original container for longer than 2 weeks  <b>Refrigerated oral solution:</b> stable until expiration date on label. If stored at room temperature, stable for 2 months
<b>Adverse Events</b>	GI intolerance, nausea, vomiting, diarrhea, asthenia  Rare: Pancreatitis, including marked triglyceride elevations; in some cases, fatalities have been observed  PR interval prolongation may occur. Second- and third-degree AV block have been reported. Use with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities. The impact on the PR interval of co-administration of LPV/r with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated; co-administration of LPV/r with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A.  QT interval prolongation and torsade de pointes have been reported. Avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval.

	<p>Elevated serum transaminase, hyperglycemia,<sup>c</sup> fat redistribution and lipid abnormalities,<sup>d</sup> possible increased bleeding episodes in patients with hemophilia</p> <p>Increased potential for sildenafil-associated adverse events such as visual abnormalities, hypotension, prolonged erections, and syncope when co-administered when sildenafil is used for the treatment of pulmonary arterial hypertension. Avoid high-dose sildenafil and use with caution.</p>
<b>FDA Pregnancy Category</b>	C
<b>Long-Term Animal Carcinogenicity Studies</b>	Not completed
<b>Animal Teratogen Studies</b>	Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)
<b>Black Box Warnings</b>	None
<b>Drugs to Avoid</b>	<p><b>As part of the ARV regimen:</b>  Darunavir/ritonavir  Tipranavir/ritonavir</p> <p>Alfuzosin, alprazolam, astemizole, cisapride, ergot derivatives, flecainide, fluticasone, garlic supplements, lovastatin, midazolam,<sup>e</sup> pimoziide, propafenone, ranolazine, rifampin,<sup>f</sup> rifapentine, high-dose sildenafil, salmeterol, simvastatin, St. John's wort, terfenadine, triazolam</p>
<b>Cautious Use or Dose Adjustment</b>	
<b>Antiretrovirals</b>	<p><b>Atazanavir:</b> ATV 300 mg once daily plus LPV/r 400/100 mg twice daily. Monitor for PR interval prolongation</p> <p><b>Efavirenz:</b> LPV AUC ↓ 40% – ↑ LPV/r dose to 500/125 mg twice daily with food. LPV/r once daily should not be co-administered with EFV</p> <p><b>Etravirine:</b> Use standard dose</p> <p><b>Fosamprenavir:</b> Not recommended by some. Consider FPV 1400 mg twice daily plus LPV/r 500/125 mg twice daily. Consider therapeutic drug monitoring. LPV/r once daily should not be co-administered with FPV</p> <p><b>Indinavir:</b> ↑ IDV – ↓ IDV dose to 600 mg twice daily or 666 mg twice daily</p> <p><b>Maraviroc:</b> ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily</p> <p><b>Nelfinavir:</b> ↓ NFV AUC – Not recommended by some. ↑ LPV/r dose to 500/125 mg twice daily with food. LPV/r once daily should not be co-administered with NFV</p> <p><b>Nevirapine:</b> LPV Cmin ↓ 55% – ↑ LPV/r dose to 500/125 mg twice daily with food. LPV/r once daily should not be co-administered with NVP</p> <p><b>Raltegravir:</b> Use standard dose</p> <p><b>Saquinavir:</b> SQV AUC and Cmin ↑ – Use SQV 1000 mg twice daily</p>
<b>Antiarrhythmics</b>	<p><b>Amiodarone, bepridil, lidocaine (systemic), quinidine:</b> ↑ antiarrhythmics – Use with caution. Monitor concentrations of antiarrhythmics</p>

<b>Anticonvulsants</b>	<p><b>Carbamazepine, phenobarbital, phenytoin:</b> Levels ↑ when co-administered with RTV – Use with caution; monitor anticonvulsant levels. Do not use with once-daily dosing of LPV/r.</p> <p><b>Valproic acid:</b> May ↓ valproic acid. LPV AUC ↑ 75%</p> <p><b>Lamotrigine:</b> LPV not affected, but lamotrigine AUC ↓ 50%. Titrate to effect</p>
<b>Antidepressants</b>	<p><b>Trazodone:</b> Trazodone AUC ↑ 240%, Cmax ↑ 34% – Use lowest dose; monitor for CNS and CV adverse effects</p> <p><b>Bupropion:</b> Bupropion AUC ↓ 46%. Titrate to effect</p>
<b>Antifungals</b>	<p><b>Itraconazole:</b> Itraconazole ↑ – Use with caution, do not exceed 200 mg itraconazole daily</p> <p><b>Ketoconazole:</b> LPV AUC ↓ 13%; keto ↑ 3-fold – Use with caution, do not exceed 200 mg keto daily</p> <p><b>Voriconazole:</b> Potential for bi-directional inhibition; when boosted with RTV, may significantly ↓ voriconazole – Monitor for toxicities and voriconazole serum concentrations (target trough &gt;2 mcg/mL)</p>
<b>Antigout</b>	<p><b>Colchicine:</b> For treatment of gout flares – 0.6 mg (1 tablet) x 1 dose, then 0.3 mg (½ tablet) 1 h later. Do not repeat dose before 3 days. For prophylaxis of gout flares – adjust dose to ¼ original regimen For treatment of familial Mediterranean fever (FMF) – Max: 0.6 mg daily</p> <p>Do not co-administer in patients with hepatic or renal impairment</p>
<b>Antihypertensive</b>	<p><b>Beta-blocker:</b> May ↑ PR interval; use with close monitoring</p> <p><b>Calcium channel blocker:</b> May ↑ PR interval; use with close monitoring</p>
<b>Antimycobacterials</b>	<p><b>Clarithromycin:</b> CL AUC ↑ 77% – Adjust CL dose for moderate and severe renal impairment. For creatinine clearance 30-60 mL/min, administer clarithromycin 500 mg orally once daily. For creatine clearance &lt;30 mL/min administer clarithromycin 250 mg orally once daily. Monitor for QTc prolongation with co-administration</p> <p><b>Rifabutin:</b> RFB AUC ↑ 3-fold; 25-O-desacetyl metabolite ↑ 47.5-fold – ↓ RFB dose to 150 mg qod. Monitor rifabutin serum concentrations</p>
<b>Bronchodilators</b>	<p><b>Salmeterol:</b> Co-administration not recommended. Consider formoterol</p>
<b>Cardiac Glycosides</b>	<p><b>Digoxin:</b> Digoxin AUC ↑ 81% with LPV/r co-administration. Monitor digoxin serum concentrations and PR interval with co-administration</p>
<b>Erectile Dysfunction Agents</b>	<p><b>Sildenafil:</b> Sildenafil AUC ↑ 11-fold when co-administered with RTV – Use cautiously, start with reduced dose of 25 mg q48h, and monitor for adverse effects</p> <p><b>Tadalafil:</b> Substantial ↑ in tadalafil AUC and half-life – Start with a 5-mg dose, and do not exceed a single 10-mg dose in 72 hours</p> <p><b>Vardenafil:</b> May substantially ↑ vardenafil AUC – Start with a 2.5-mg dose, and do not exceed a single 2.5-mg dose in 72 hours</p>

<b>Lipid-Lowering Agents</b>	<p><b>Atorvastatin:</b> ATO AUC ↑ 5.88-fold – Use lowest possible starting dose of ATO with careful monitoring. Consider pravastatin</p> <p><b>Rosuvastatin:</b> ROS AUC ↑ 108%. Use lowest possible starting dose 5-10 mg/day</p> <p><b>Pravastatin:</b> Pravastatin AUC ↑ 33%. Use standard dose</p>
<b>Oral Contraceptives</b>	<p><b>Ethinyl estradiol:</b> EE ↓ 42% – Use alternative or additional method of contraception</p>
<b>Pulmonary Hypertension Agents</b>	<p><b>Bosentan:</b> LPV/r ↑ bosentan AUC 48-fold on day 4 and 5-fold on day 10 (steady-state). Co-administer bosentan at a reduced dose of 62.5 mg only after RTV dosing has reached steady-state (after 10 days of RTV). If patient is taking bosentan, discontinue bosentan for ≥36 hrs prior to initiating RTV and restart bosentan 62.5 mg 10 days after initiating RTV</p> <p><b>Tadalafil:</b> In patients already taking LPV/r for ≥1 wk, co-administer tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. In patients already taking tadalafil, avoid use of tadalafil during initiation of LPV/r. Stop tadalafil ≥24 h prior to starting LPV/r. At least ≥1 wk after initiating LPV/r, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability.</p>
<p><sup>a</sup> Capsules discontinued in early 2006.</p> <p><sup>b</sup> Lopinavir/ritonavir should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, fosamprenavir, or nelfinavir.</p> <p><sup>c</sup> Cases of worsening glycemic control in patients with preexisting diabetes, and cases of new-onset diabetes including diabetic ketoacidosis have been reported with the use of all protease inhibitors.</p> <p><sup>d</sup> Discontinuation of PIs may be required to reverse fat redistribution. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risks for cardiovascular events and pancreatitis.</p> <p><sup>e</sup> Can be used with caution as a single dose in a monitored situation for procedural sedation.</p> <p><sup>f</sup> In one small study, an increased dose of LPV/r 800/200 mg was used to offset rifampin-inducing activity of LPV; the standard dose of rifampin was used. 28% of patients discontinued this regimen due to increases in LFTs. The safety of this combination has not been established, and if used, close monitoring, including measuring LPV concentrations, is recommended.</p>	