

<b>DARUNAVIR (DRV)</b> (Updated December 2010)	
<b>Trade Name</b>	Prezista
<b>Classification</b>	Protease Inhibitor
<b>Form</b>	75, 150, 300-, 400-, 600-mg tablets
<b>Dosing Recommendations</b>	<p>Must be co-administered with ritonavir (RTV) –</p> <p><b>For ARV-naïve patients:</b> DRV 800 mg + RTV 100 mg once daily with food</p> <p><b>For ARV-experienced patients:</b></p> <p style="padding-left: 40px;">With no darunavir resistance-associated substitutions<sup>a</sup>:  DRV 800 mg + RTV 100 mg once daily with food</p> <p style="padding-left: 40px;">With at least one darunavir-resistance associated substitution<sup>a</sup>:  DRV 600 mg + RTV 100 mg twice daily with food<sup>b</sup></p>
<b>Hepatic Impairment Dosing</b>	No dose adjustment necessary for patients with either mild or moderate hepatic impairment. No data available for patients with severe hepatic impairment – not recommended for use in patients with severe hepatic impairment
<b>Food Effect</b>	Food increases AUC and C <sub>max</sub> 30%
<b>Oral Bioavailability</b>	37-82%
<b>Serum Half-life</b>	15 hours
<b>Route of Metabolism</b>	P450 cytochrome 3A4 inhibitor and substrate (DVR/r co-administration has a net CYP3A4 inhibitory effect)
<b>Storage</b>	Room temperature
<b>Adverse Events</b>	<p>Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with DVR/RTV. Patients with preexisting liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatitis.</p> <p>If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients receiving DRV/RTV, interruption or discontinuation of treatment must be considered.</p> <p>Severe skin rash, including erythema multiforme and Stevens-Johnson Syndrome, has been reported – Discontinue if severe rash develops.</p> <p>Rare events of hypersensitivity including facial edema and rhabdomyolysis associated with co-administration with HMG-CoA reductase inhibitors.</p> <p>Angioedema and urticaria have been reported with DRV/r.</p> <p>Osteonecrosis has been associated with DRV/r-based regimen.</p> <p>PI class adverse effects that include – GI intolerance, headache, nasopharyngitis, lipodystrophy syndrome, hyperglycemia, increased triglycerides and/or cholesterol, transaminase elevation. Contains a sulfonamide moiety – Use with caution in patients with severe sulfa allergy.</p>

<b>FDA Pregnancy Category</b>	C. Not embryotoxic or teratogenic in mice, rats, and rabbits. Based on animal studies, serum concentrations may be significantly decreased in pregnancy
<b>Long-Term Animal Carcinogenicity Studies</b>	Not determined
<b>Animal Teratogen Studies</b>	None
<b>Black Box Warnings</b>	None
<b>Drugs to Avoid</b>	<p><b>As part of the ARV regimen:</b>  Lopinavir/ritonavir  Saquinavir  Tipranavir/ritonavir</p> <p>Alfuzosin, alprazolam, astemizole, cisapride, ergot derivatives, lovastatin, midazolam, phenobarbital, phenytoin, pimozone, ranolazine, rifampin, high-dose sildenafil, simvastatin, St. John's wort, terfenadine, triazolam</p>
<b>Cautious Use or Dose Adjustment</b>	
<b>Antiretrovirals</b>	<p><b>Atazanavir:</b> Dose ATV 300 mg once daily + DRV/r 600/100 mg twice daily</p> <p><b>Didanosine:</b> Administer ddI 1 hr before or 2 hr after DRV/r</p> <p><b>Efavirenz:</b> EFV AUC and Cmin ↑ 21% and 17%, respectively; DRV Cmin ↓ 31% – Studied dose lower than FDA approved dose. Consider DRV/r 600/100 mg twice daily with EFV 600 mg qhs or DRV/r 900/100 mg once daily (PI-naïve only) with EFV 600 mg qhs.</p> <p><b>Etravirine:</b> DRV AUC ↑ 15%. ETR AUC and Cmin ↓ 37% and 49%, respectively. Good clinical data with co-administration. Use standard dose</p> <p><b>Indinavir:</b> IDV AUC and Cmin ↑ 23% and 125%, respectively; DRV AUC and Cmin ↑ 24% and 44%, respectively. Dose not established – Co-administration may ↑ risk of nephrolithiasis</p> <p><b>Maraviroc:</b> ↑ MVC AUC – ↓ MVC dose to 150 mg twice daily</p> <p><b>Nevirapine:</b> DRV and NVP AUC ↑ 24% and 27%, respectively. Limited clinical data; consider standard dose</p> <p><b>Raltegravir:</b> Usual dose</p> <p><b>Ritonavir:</b> DRV AUC ↑, Cmax ↑, Cmin ↑</p>
<b>Antiarrhythmics</b>	May ↑ antiarrhythmics (amiodarone, dofetilide, propafenone, flecainide, quinidine) – Avoid or use with caution. Monitor concentrations of antiarrhythmics
<b>Anticoagulants</b>	<b>Warfarin:</b> ↓ S-warfarin AUC 21% – Monitor INR closely with co-administration
<b>Anticonvulsants</b>	<b>Carbamazepine:</b> No significant ↓ in DRV/r AUC. Carbamazepine serum concentrations may be ↑. Monitor carbamazepine serum concentrations with co-administration

<b>Antidepressants</b>	<p><b>Trazodone:</b> ↑ Trazodone – Use with caution and consider a lower dose of trazodone</p> <p><b>Paroxetine:</b> Paroxetine AUC ↓ 39%</p> <p><b>Sertraline:</b> Sertraline AUC ↓ by 49%</p>
<b>Antifungals</b>	<p><b>Itraconazole:</b> Itraconazole AUC may be ↑. Monitor itraconazole serum concentrations with co-administration</p> <p><b>Ketoconazole:</b> Ketoconazole AUC ↑ 212%; DRV AUC ↑ 42% – Ketoconazole dose should not exceed 200 mg once daily</p> <p><b>Voriconazole:</b> Voriconazole AUC may be ↓. Monitor voriconazole serum concentrations with co-administration</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>Antimycobacterials</b>	<p><b>Clarithromycin:</b> CL AUC ↑ 57%. For patients with: CrCl 30-60 mL/min: dose CL at 250 mg q12h CrCl &lt;30 mL/min: dose CL at 250 mg once daily Avoid with QTc prolongation</p> <p><b>Rifabutin:</b> Administer RFB dose at 150 mg every other day; monitor for adverse events (i.e., uveitis). Consider monitoring rifabutin serum concentrations</p>
<b>Bronchodilators</b>	<b>Salmeterol:</b> Co-administration not recommended. Consider formoterol
<b>Calcium Channel Blockers</b>	May ↑ calcium channel blockers – Use with caution and monitor patients
<b>Corticosteroids</b>	<b>Fluticasone propionate:</b> Use with caution and consider alternatives (beclomethasone) for long-term use
<b>Erectile Dysfunction Agents</b>	<p><b>Sildenafil:</b> do not exceed a single dose of 25 mg in 48 hr. High-dose sildenafil used for pulmonary hypertension is not recommended (but dose-adjusted sildenafil can be considered for pulmonary hypertension)</p> <p><b>Tadalafil:</b> do not exceed a single dose of 10 mg in 72 hr</p> <p><b>Vardenafil:</b> do not exceed a single dose of 2.5 mg in 72 hr</p>
<b>Immunosuppressants</b>	↑ AUC immunosuppressants (cyclosporine, tacrolimus, sirolimus) – Monitor concentration of immunosuppressive agent
<b>Lipid-Lowering Agents</b>	<p><b>Atorvastatin:</b> ATO ↑ by 4-fold – Start with atorvastatin 10 mg once daily titrate slowly, and monitor carefully</p> <p><b>Pravastatin:</b> Pravastatin AUC ↑ 81% – Start with 10 mg and titrate slowly</p>
<b>Oral Contraceptives</b>	<b>Ethinyl estradiol/norethindrone:</b> EE and norethindrone AUC ↓ by 44% and 14% respectively – Use alternative or additional method of contraception

<b>Pulmonary Hypertension Agents</b>	<p><b>Bosentan:</b> In patients already taking boosted DRV for &gt;10 days, co-administer bosentan at a reduced dose of 62.5 mg once daily or qod based on tolerability. If patient is already taking bosentan, discontinue bosentan for &gt;36 hrs prior to initiating boosted DRV. After boosted DRV has been given for &gt;10 days, once daily or qod bosentan can be reintroduced. Limited clinical data. Monitor closely with co-administration</p> <p><b>Tadalafil:</b> In patients already taking boosted DRV for &gt;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 boosted DRV. Stop tadalafil &gt;24 h prior to starting boosted DRV. At least &gt;1 wk after initiating boosted DRV, resume tadalafil at 20 mg once daily; increase to 40 mg once daily based on tolerability. Limited clinical data. Monitor closely with co-administration</p>
<b>Selective Serotonin Reuptake Inhibitors (SSRIs)</b>	<b>Paroxetine, sertraline:</b> ↓ SSRIs (sertraline and paroxetine) – titrate dose to therapeutic effect – Monitor patients starting DRV who are already receiving stable dose of SSRI
<b>Synthetic Narcotics</b>	<b>Methadone:</b> May ↓ R-methadone AUC 26% – Monitor and titrate dose to effect
<p><sup>a</sup> V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.</p> <p><sup>b</sup> DRV 600 mg + RTV 100 mg twice daily recommended if no resistance testing obtained in patients previously treated with PIs and there is a high likelihood of PI-associated resistance.</p>	