

Darunavir

DARUVIR Tablets

COMPOSITION

DARUVIR Tablets

Each tablet contains:

Darunavir 300 mg

DOSAGE FORM

Oral tablet

PHARMACOLOGY

Pharmacodynamics

Darunavir is an inhibitor of the human immunodeficiency virus (HIV)-1 protease. It selectively inhibits the cleavage of HIV-encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles.

Pharmacokinetics

Adults

General

Darunavir is primarily metabolized by Cytochrome 3A (CYP3A). Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir. When a single dose of darunavir 600 mg was given orally in combination with 100 mg ritonavir twice daily, there was an approximate 14-fold increase in the systemic exposure of darunavir. Therefore, **DARUVIR** should only be used in combination with 100 mg of ritonavir to achieve sufficient exposures of darunavir.

The pharmacokinetics of darunavir, co-administered with low-dose ritonavir (100 mg), has been evaluated in healthy adult volunteers and in HIV-1-infected subjects. Table 1 displays the population pharmacokinetic estimates of darunavir after oral administration of darunavir/ritonavir (DRV/RTV) 600/100 mg twice daily (based on sparse sampling in 285 patients in study TMC114-C214 and 119 patients [integrated data] from Studies TMC114-C202 and TMC114-C213) and darunavir/rtv 800/100 mg once daily (based on sparse sampling in 335 patients in Study TMC114-C211) to HIV-1-infected patients.

Table 1: Population pharmacokinetic estimates of darunavir with darunavir/rtv 800/100 mg once daily (Study TMC114-C211, 48-week analysis) and darunavir/rtv 600/100 mg twice daily (Study TMC114-C214, 48-week analysis and integrated data from Studies TMC114-C213 and TMC114-C202, primary 24-week analysis)

Parameter	Study TMC114-C211 DRV/RTV 800/100 mg Once Daily n = 335	Study TMC114-C214 DRV/RTV 600/100 mg Twice Daily n = 285	Studies TMC114- C213 and TMC114- C202 (Integrated Data) DRV/RTV 600/100 mg Twice Daily n =119
AUC_{24h} (ng·h/mL)*			
Mean ± Standard Deviation	93,026 ± 27,050	116,796 ± 33,594	124,698 ± 32,286
Median (Range)	87,854 (45,000–219,240)	111,632 (64,874–355,360)	123,336 (67,714–212,980)
C_{0h} (ng/mL)			
Mean ± Standard Deviation	2282 ± 1168	3490 ± 1401	3578 ± 1151
Median (Range)	2041 (368–7242)	3307 (1517–13,198)	3539 (1255–7368)
n = Number of subjects with data *AUC _{24h} is calculated as AUC _{12h} *2			

Absorption and Bioavailability: Darunavir, co-administered with 100 mg ritonavir twice daily, was absorbed following oral administration with a t_{max} of approximately 2.5–4 hours. The absolute oral bioavailability of a single 600 mg dose of darunavir alone and after co-administration with 100 mg ritonavir twice daily was 37% and 82%, respectively. *In vivo* data suggests that darunavir/ritonavir is an inhibitor of the p-glycoprotein (p-gp) transporters.

Effects of Food on Oral Absorption: When administered with food, the C_{max} and AUC of darunavir, co-administered with ritonavir, is approximately 30% higher relative to the fasting state. Therefore, **DARUVIR** tablets co-administered with ritonavir should always be taken with food. Within the range of meals studied, darunavir exposure is similar. The total caloric content of the various meals evaluated ranged from 240 Kcal (12 gms fat) to 928 Kcal (56 gms fat).

Distribution: Darunavir is approximately 95% bound to plasma proteins. Darunavir binds primarily to plasma alpha 1-acid glycoprotein (AAG).

Metabolism: *In vitro* experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by CYP enzymes, primarily by CYP3A. A mass balance study in healthy volunteers showed that after a single-dose administration of 400 mg ¹⁴C-darunavir, co-administered with 100 mg ritonavir, the majority of the radioactivity in the plasma was due to darunavir. At least three oxidative metabolites of darunavir have been identified

in humans; all showed activity that was at least 90% less than the activity of darunavir against wild-type HIV.

Elimination: A mass balance study in healthy volunteers showed that after single-dose administration of 400 mg ¹⁴C-darunavir, co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose of ¹⁴C-darunavir was recovered in the feces and the urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in the feces and the urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir. After intravenous administration, the clearance of darunavir, administered alone and co-administered with 100 mg twice daily ritonavir, was 32.8 L/h and 5.9 L/h, respectively.

Special Populations

Hepatic Impairment: Darunavir is primarily metabolized by the liver. The steady-state pharmacokinetic parameters of darunavir were similar after multiple dose co-administration of darunavir/ritonavir 600/100 mg b.i.d. to subjects with normal hepatic function (n = 16), mild hepatic impairment (Child-Pugh Class A; n = 8), and moderate hepatic impairment (Child-Pugh Class B; n = 8). The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been evaluated (see **WARNINGS AND PRECAUTIONS, Hepatic Impairment; DOSAGE AND ADMINISTRATION**)

Hepatitis B or Hepatitis C Virus Co-infection: The 48-week analysis of the data from Studies TMC114-C211 and TMC114-C214 in HIV-1-infected subjects indicated that hepatitis B and/or hepatitis C virus co-infection status had no apparent effect on the exposure of darunavir.

Renal Impairment: Results from a mass balance study with ¹⁴C-darunavir/rtv showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine as unchanged drug. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected subjects with moderate renal impairment (CrCL between 30 to 60 mL/min, n = 20). There are no pharmacokinetic data available in HIV-1-infected patients with severe renal impairment or end-stage renal disease.

Gender: Population pharmacokinetic analysis showed higher mean darunavir exposure in HIV-infected females compared to males. This difference is not clinically relevant.

Race: Population pharmacokinetic analysis of darunavir in HIV-infected subjects indicated that race had no apparent effect on the exposure to darunavir.

Geriatric Patients: Population pharmacokinetic analysis in HIV-infected subjects showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV-infected subjects (n = 12, age ≥65) (see **WARNINGS AND PRECAUTIONS**).

INDICATIONS

DARUVIR co-administered with ritonavir (DRV/RTV) and with other antiretroviral agents, are indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

In treatment-experienced adult patients, the following points should be considered when initiating therapy with **DARUVIR**:

- Treatment history and, when available, genotypic or phenotypic testing should guide the use of **DARUVIR**.
- The use of other active agents with **DARUVIR** is associated with a greater likelihood of treatment.

DOSAGE AND ADMINISTRATION

Treatment-Experienced Adult Patients

The recommended oral dose of **DARUVIR Tablets** is 600 mg (two 300 mg tablets) taken with ritonavir 100 mg twice daily and with food.

DARUVIR Tablets must be co-administered with **RITOMUNE Tablets** (ritonavir 100 mg) to exert its therapeutic effect. Failure to correctly co-administer **DARUVIR Tablets** with ritonavir will result in plasma levels of darunavir that will be insufficient to achieve the desired antiviral effect and will alter some drug interactions.

Patients with Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available regarding the use of darunavir/rtv when co-administered to subjects with severe hepatic impairment; therefore, **DARUVIR/rtv** are not recommended for use in patients with severe hepatic impairment (see **PHARMACOLOGY, Pharmacokinetics, Special Populations, Hepatic Impairment**).

CONTRAINDICATIONS

Co-administration of **DARUVIR/rtv** 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 (narrow therapeutic index). These drugs and other contraindicated drugs (which may lead to reduced efficacy of darunavir) are listed in Table 2 (also see **WARNINGS AND PRECAUTIONS, Drug Interactions, Table 3**).

Table 2: Drugs within class that are contraindicated with DARUVIR/rtv Tablets

Drug Class	Drugs Within Class That Are Contraindicated with DARUVIR/RTV	Clinical Comment
Alpha 1adrenoreceptor antagonist	Alfuzosin	Potential for serious and/or life-threatening reactions such as hypotension.
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics	Orally administered midazolam, triazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A. Co-administration of triazolam or orally administered midazolam with DARUVIR /ritonavir may cause large increases in the concentrations of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.

Herbal Products	St. John's wort (<i>Hypericum perforatum</i>)	Patients taking DARUVIR /ritonavir should not use products containing St. John's wort because co-administration may result in reduced plasma concentrations of darunavir. This may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	<p>Potential for serious reactions such as myopathy, including rhabdomyolysis.</p> <p>For dosing recommendation regarding atorvastatin and pravastatin, see WARNINGS AND PRECAUTIONS, Drug Interactions, Table 3</p> <p>Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction.</p>
Antimycobacterial	Rifampin	Rifampin is a potent inducer of CYP450 metabolism. DARUVIR /ritonavir should not be used in combination with rifampin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to darunavir.

PDE-5 inhibitor	Sildenafil for treatment of pulmonary arterial hypertension	A safe and effective dose for the treatment of pulmonary arterial hypertension has not been established with darunavir/ritonavir. There is an increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope).
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Due to the need for co-administration of **DARUVIR** with ritonavir, please refer to the ritonavir prescribing information for a description of ritonavir contraindications.

WARNINGS AND PRECAUTIONS

General

DARUVIR must be co-administered with ritonavir and food to achieve the desired antiviral effect. Failure to administer **DARUVIR** with ritonavir and food may result in a loss of efficacy of darunavir.

Please refer to the ritonavir prescribing information for additional information on precautionary measures.

Hepatotoxicity

Drug-induced hepatitis (eg, acute hepatitis, cytolytic hepatitis) has been reported with darunavir/rtv. During the clinical development program (N = 3063), hepatitis has been reported in 0.5% of patients receiving combination therapy with darunavir/rtv. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities, including severe hepatic adverse events.

Postmarketing cases of liver injury, including some fatalities, have been reported. These have generally occurred in patients with advanced HIV-1 disease who were taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection, and/or developing an immune reconstitution syndrome. A causal relationship with darunavir/rtv therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with **DARUVIR** /rtv and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of **DARUVIR** /rtv treatment.

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 on **DARUVIR**/rtv should prompt consideration of interruption or discontinuation of treatment.

Skin Rash

During the clinical development program (n=3063), severe skin reactions, accompanied by fever and/or elevations of transaminases in some cases, have been reported in 0.4% of subjects. Stevens-Johnson Syndrome was rarely (<0.1%) reported during the clinical development program. During post-marketing experience toxic epidermal necrolysis has been reported. Discontinue **DARUVIR** /rtv immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash (all grades, regardless of causality) occurred in 10.3% of subjects treated with darunavir/rtv [*also see **UNDESIRABLE EFFECTS***]. Rash was mostly mild-to-moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in subjects using darunavir/rtv was 0.5%.

Sulfa Allergy

Darunavir contains a sulfonamide moiety. **DARUVIR** should be used with caution in patients with a known sulfonamide allergy. In clinical studies with darunavir/rtv, the incidence and severity of rash was similar in subjects with or without a history of sulfonamide allergy.

Diabetes Mellitus/Hyperglycemia

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

Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Resistance/Cross-Resistance

Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in darunavir/rtv-treated patients, the effect that therapy with darunavir will have on the activity of subsequently administered protease inhibitors is unknown.

Immune Reconstitution Syndrome

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jirovecii* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment.

Drug Interactions

Please see **CONTRAINDICATIONS, Table 2**, for a listing of drugs that are contraindicated for use with **DARUVIR** /rtv due to potentially life-threatening adverse events, significant drug-drug interactions, or loss of therapeutic effect to **DARUVIR**. Please refer to Table 3 in this section for established and other potentially significant drug-drug interactions

Potential for DARUVIR /Rtv to Affect Other Drugs

DARUVIR, co-administered with ritonavir, are an inhibitor of CYP3A and CYP2D6. Co-administration of **DARUVIR** and ritonavir with drugs that are primarily metabolized by CYP3A and CYP2D6 may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see Table 3).

Potential for Other Drugs to Affect Darunavir

Darunavir and ritonavir are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir/ rtv and other drugs that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (see Table 3).

Established and other potentially significant drug interactions

Table 3 provides dosing recommendations as a result of drug interactions with darunavir/ritonavir. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

**Table 3: Established and other potentially significant drug interactions:
Alterations in dose or regimen may be recommended based on drug interaction studies or predicted interaction**

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir or Concomitant Drug	Clinical Comment
HIV Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Didanosine	↔ darunavir ↔ didanosine	Didanosine should be administered 1 hour before or 2 hours after DARUVIR /rtv (which are administered with food).
HIV Antiviral Agents: HIV Protease Inhibitors (PIs)		
Indinavir (The reference regimen for indinavir was indinavir/ritonavir 800/100 mg b.i.d.)	↑ darunavir ↑ indinavir	The appropriate dose of indinavir in combination with darunavir/rtv has not been established.
Lopinavir/ritonavir	↓ darunavir ↔ lopinavir	Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer lopinavir/ritonavir and DARUVIR , with or without ritonavir.
Saquinavir	↓ darunavir ↔ saquinavir	Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer saquinavir and DARUVIR , with or without ritonavir.

Maraviroc	↑ maraviroc	Maraviroc concentrations are increased when co-administered with darunavir/rtv. When used in combination with darunavir/rtv, the dose of maraviroc should be 150 mg twice daily.
Other Agents		
Anti-Arrhythmics Bepridil, lidocaine (systemic), quinidine, amiodarone, propafenone	↑ anti-arrhythmics	Concentrations of bepridil, lidocaine, quinidine and amiodarone may be increased when co-administered with DARUVIR /rtv. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for anti-arrhythmics when co-administered with DARUVIR /rtv.
Digoxin	↑ digoxin	The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.
Anticoagulant Warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations are decreased when co-administered with DARUVIR /rtv. It is recommended that the international normalized ratio (INR) be monitored when warfarin is

		combined with DARUVIR /rtv.
<p>Anticonvulsants Carbamazepine</p> <p>Phenobarbital, phenytoin</p>	<p>↔ darunavir ↑ carbamazepine</p> <p>↔ darunavir ↓ phenytoin ↓ phenobarbital</p>	<p>The dose of either darunavir/rtv or carbamazepine does not need to be adjusted when initiating co-administration with darunavir/rtv and carbamazepine. Clinical monitoring of carbamazepine concentrations and its dose titration is recommended to achieve the desired clinical response.</p> <p>Co-administration of darunavir/rtv may cause a decrease in the steady-state concentrations of phenytoin and phenobarbital. Phenytoin and phenobarbital levels should be monitored when co-administering with DARUVIR /rtv.</p>
<p>Antidepressants Trazodone, desipramine</p>	<p>↑ trazodone ↑ desipramine</p>	<p>Concomitant use of trazodone or desipramine and DARUVIR /rtv may increase plasma concentrations of trazodone or desipramine, which may lead to adverse events</p>

		such as nausea, dizziness, hypotension, and syncope. If trazodone or desipramine is used with DARUVIR /rtv, the combination should be used with caution and a lower dose of trazodone or desipramine should be considered.
Anti-Infective Clarithromycin	↔ darunavir ↑ clarithromycin	No dose adjustment of darunavir or clarithromycin is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: <ul style="list-style-type: none"> • For subjects with CL_{cr} of 30–60 mL/min, the dose of clarithromycin should be reduced by 50%. • For subjects with CL_{cr} of <30 mL/min, the dose of clarithromycin should be reduced by 75%.
Antifungals Ketoconazole itraconazole voriconazole	↑ ketoconazole ↑ darunavir ↑ itraconazole (not studied) ↓ voriconazole (not studied)	Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole, and darunavir/rtv may increase plasma concentration of darunavir. Plasma concentrations of ketoconazole or itraconazole may be increased in the

		<p>presence of darunavir/rtv. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Plasma concentration of voriconazole may be decreased in presence of darunavir/ritonavir. Voriconazole should not be administered to patients receiving darunavir/rtv unless an assessment of the benefit/risk ratio justifies the use of voriconazole.</p>
<p>Anti-gout: colchicine</p>	<p>↑ colchicine</p>	<p>Treatment of gout-flares – co-administration of colchicine in patients on darunavir/ritonavir: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days.</p> <p>Prophylaxis of gout-flares – co-administration of colchicine in patients on darunavir/ritonavir: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.</p> <p>Treatment of familial</p>

		<p>Mediterranean fever – co-administration of colchicine in patients on darunavir/ritonavir: maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day). Patients with renal or hepatic impairment should not be given colchicine with darunavir/ritonavir.</p>
<p>Antimycobacterial Rifabutin</p> <p>The reference regimen for rifabutin was 300 mg once daily</p>	<p>↑ darunavir ↑ rifabutin ↑ 25-O-desacetyl-rifabutin</p>	<p>Dose reduction of rifabutin by at least 75% of the usual dose (300 mg once daily) is recommended (ie, a maximum dose of 150 mg every other day). Increased monitoring for adverse events is warranted in patients receiving this combination and a further dose reduction of rifabutin may be necessary.</p>
<p>Beta-Blockers Metoprolol, timolol</p>	<p>↑ beta-blockers</p>	<p>Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with DARUVIR /rtv.</p>
<p>Benzodiazepines Parenterally administered midazolam</p>	<p>↑ midazolam</p>	<p>Concomitant use of parenteral midazolam with darunavir/rtv may increase plasma concentrations of midazolam. Co-administration should be done in a setting which ensures close clinical monitoring and appropriate medical</p>

		management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Co-administration of oral midazolam with DARUVIR /rtv is CONTRAINDICATED .
Calcium Channel Blockers Felodipine nifedipine nicardipine	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (eg, felodipine, nifedipine, nicardipine) may increase when darunavir/rtv are co-administered. Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid Systemic: Dexamethasone Corticosteroid Inhaled/Nasal: Fluticasone	↓ darunavir ↑ fluticasone	Systemic dexamethasone induces CYP3A and can thereby decrease darunavir plasma concentrations. This may result in loss of therapeutic effect to darunavir. Concomitant use of inhaled fluticasone and darunavir may increase plasma concentrations of fluticasone propionate. Alternatives should be considered, particularly for long-term use.

<p>Endothelin receptor antagonists: bosentan</p>	<p>↑ bosentan</p>	<p><u>Co-administration of bosentan in patients on darunavir/ritonavir:</u> In patients who have been receiving darunavir/ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.</p> <p><u>Co-administration of darunavir/ritonavir in patients on bosentan:</u> Discontinue use of bosentan at least 36 hours prior to initiation of darunavir/ritonavir. After at least 10 days following the initiation of darunavir/ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.</p>
<p>HMG-CoA Reductase Inhibitors Pravastatin atorvastatin rosuvastatin</p>	<p>↑ pravastatin ↑ atorvastatin ↑ rosuvastatin</p>	<p>Use the lowest possible dose of atorvastatin, pravastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin in combination with darunavir/rtv.</p>

<p>Immunosuppressants Cyclosporine tacrolimus sirolimus</p>	<p>↑ immunosuppressants</p>	<p>Plasma concentrations of cyclosporine, tacrolimus or sirolimus may be increased when co-administered with darunavir/ritonavir. Therapeutic concentration monitoring of the immunosuppressive agent is recommended for immunosuppressant agents when co-administered with darunavir/ritonavir.</p>
<p>Inhaled beta agonist: salmeterol</p>	<p>↑ salmeterol</p>	<p>Concurrent administration of salmeterol and darunavir/ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.</p>
<p>Narcotic Analgesic Methadone Buprenorphine, Buprenorphine/naloxone</p>	<p>↓ methadone ↔ buprenorphine, naloxone ↑ norbuprenorphine (metabolite)</p>	<p>No adjustment of methadone dosage is required when initiating co-administration of darunavir/ritonavir. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.</p> <p>No dose adjustment for buprenorphine or buprenorphine/naloxone is required with</p>

		concurrent administration of darunavir/ritonavir. Clinical monitoring is recommended if darunavir/ritonavir and buprenorphine or buprenorphine/naloxone are co-administered.
Neuroleptics Risperidone, thioridazine	↑ neuroleptics	A dose decrease may be needed for these drugs when co-administered with darunavir/rtv.
Oral Contraceptives/Estrogen Ethinyl estradiol, norethindrone	↓ ethinyl estradiol ↓ norethindrone	Plasma concentrations of ethinyl estradiol are decreased due to induction of its metabolism by ritonavir. Alternative methods of non-hormonal contraception are recommended.
PDE-5 Inhibitors Sildenafil, vardenafil, tadalafil	↑ PDE-5 inhibitors (only the use of sildenafil at doses used for treatment of erectile dysfunction has been studied with darunavir/ritonavir)	Co-administration with darunavir/ritonavir may result in an increase in PDE-5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances and priapism. <u>Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):</u> •Use of sildenafil is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) [see Contraindications (4)]. • The following dose adjustments are recommended for use of

		<p>tadalafil with darunavir/ritonavir: <u>Co-administration of tadalafil in patients on darunavir/ritonavir:</u> In patients receiving darunavir/ritonavir for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><u>Co-administration of darunavir/ritonavir in patients on tadalafil:</u> Avoid use of tadalafil during the initiation of darunavir/ritonavir. Stop tadalafil at least 24 hours prior to starting darunavir/ritonavir. After at least one week following the initiation of darunavir/ritonavir, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><u>Use of PDE-5 inhibitors for erectile dysfunction:</u> Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse events.</p>
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<p>Selective Serotonin Reuptake Inhibitors (SSRIs) Sertraline, paroxetine</p>	<p>↔ darunavir ↓ sertraline ↓ paroxetine</p>	<p>If sertraline or paroxetine is co-administered with DARUVIR Tablets, the recommended approach is a careful dose titration of the SSRI, based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with DARUVIR tablets should be monitored for antidepressant response.</p>
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In addition to the drugs included in Table 3, the interaction between darunavir/rtv and the following drugs were evaluated in clinical studies and no dose adjustments are needed for either drug: Atazanavir, efavirenz, etravirine, nevirapine, omeprazole, ranitidine, and tenofovir disoproxil fumarate.

Other NRTIs

Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine, and abacavir) that are primarily renally excreted, no drug interactions are expected for these drugs and darunavir/rtv.

Other protease inhibitors

The co-administration of darunavir/rtv and protease inhibitors other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir has not been studied. Therefore, such co-administration is not recommended.

Pregnancy

Pregnancy Category C

DARUVIR should be used during pregnancy only if the potential benefit justifies the potential risk.

No adequate and well-controlled studies have been conducted in pregnant women. Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice, rats and rabbits. However, due to limited bioavailability and/or dosing limitations, animal exposures (based on AUC) were only 50% (mice and rats) and 5% (rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the rat prenatal and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of the pups to drug substances via the milk. Sexual development, fertility and the mating performance of the offspring were not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the juvenile toxicity study where rats were directly dosed with darunavir, deaths occurred from postnatal day 5 through 11 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on postnatal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) of 0.1 of the human plasma exposure levels.

Lactation

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known whether darunavir is secreted in human milk, darunavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving DARUVIR Tablets.**

Geriatric Use

Clinical studies of darunavir did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of darunavir in elderly patients reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy [**see Pharmacology, Special Populations**].

Hepatic Impairment

No dose adjustment of darunavir/rtv is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of darunavir/rtv in subjects with severe hepatic impairment; therefore, **DARUVIR Tablets/rtv** are not recommended for use in patients with severe hepatic impairment (see **DOSAGE AND ADMINISTRATION** and **PHARMACOLOGY, Pharmacokinetics, Special Populations, Hepatic Impairment**).

Renal Impairment

Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected subjects with moderate renal impairment (CrCL between 30 to 60 mL/min, n = 20). No pharmacokinetic data are available in HIV-1-infected patients with severe renal impairment or end-stage renal disease; however, because the renal clearance of darunavir is limited, a decrease in the total body clearance is not expected in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed

by hemodialysis or peritoneal dialysis (see **PHARMACOLOGY, Pharmacokinetics, Special Populations, Renal Impairment**).

UNDESIRABLE EFFECTS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Due to the need for co-administration of darunavir with ritonavir, please refer to the ritonavir prescribing information for ritonavir-associated adverse reactions.

Clinical Trials Experience: Treatment-Experienced Adults

Study TMC114-C214: The safety assessment is based on all safety data from the Phase 3 trial TMC114-C214 comparing darunavir/rtv 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in 595 antiretroviral treatment-experienced HIV-1-infected adult subjects. The total mean exposure for subjects in the darunavir/rtv 600/100 mg twice daily arm and in the lopinavir/ritonavir 400/100 mg twice daily arm was 53.5 and 51.5 weeks, respectively.

The majority of the adverse drug reactions (ADRs) reported during treatment with darunavir/rtv 600/100 mg twice daily were mild in severity. The most common ADRs to darunavir/rtv 600/100 mg twice daily ($\geq 5\%$) of at least moderate intensity (\geq Grade 2) were diarrhea, nausea, rash, and abdominal pain. In the darunavir/rtv arm, 3.7% of subjects in the darunavir /rtv arm discontinued treatment due to ADRs.

ADRs to darunavir/rtv 600/100 mg twice daily of at least moderate intensity (\geq Grade 2) in antiretroviral treatment-experienced HIV-1-infected adult subjects are presented in Table 4.

Table 4: Selected Adverse Drug Reactions to darunavir/rtv 600/100 mg twice daily* of at least moderate intensity (\geqGrade 2) in antiretroviral treatment-experienced HIV-1-infected adult subjects		
	Randomized Study TMC114-C214	
System Organ Class, Preferred Term, %	Darunavir/Rtv 600/100 mg Twice Daily + OBR n = 298	Lopinavir/Ritonavir 400/100 mg Twice Daily + OBR n = 297
Gastrointestinal Disorders		
Abdominal distension	2%	<1%
Abdominal pain	6%	3%
Diarrhea	14%	20%
Dyspepsia	2%	1%
Nausea	7%	6%
Vomiting	5%	3%

General Disorders and Administration Site Conditions		
Asthenia	3%	1%
Fatigue	2%	1%
Metabolism and Nutrition Disorders		
Anorexia	2%	2%
Diabetes mellitus	2%	<1%
Nervous System Disorders		
Headache	3%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	7%	3%

N = Total number of subjects per treatment group

OBR = Optimized background regimen

* Excluding laboratory abnormalities reported as ADRs

Less Common Adverse Reactions

Treatment-emergent ADRs of at least moderate intensity (\geq Grade 2) occurring in less than 2% of antiretroviral treatment-experienced subjects receiving darunavir/ritonavir 600/100 mg twice daily are listed below by body system:

Gastrointestinal Disorders: acute pancreatitis, flatulence

Musculoskeletal and Connective Tissue Disorders: myalgia

Psychiatric Disorders: abnormal dreams

Skin and Subcutaneous Tissue Disorders: pruritus, urticaria

Laboratory Abnormalities

Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir 600/100 mg twice daily are presented in Table 5.

Table 5: Grade 2 to 4 laboratory abnormalities observed in antiretroviral treatment-experienced HIV-1-infected adult subjects*			
		Randomized Study TMC114-C214	
Laboratory Parameter Preferred Term, %	Limit	Darunavir/ritonavir 600/100 mg Twice Daily + OBR	Lopinavir/Ritonavir 400/100 mg Twice Daily + OBR
Biochemistry			
Alanine Aminotransferase			
Grade 2	>2.5 to \leq 5.0 X	7%	5%

	ULN		
Grade 3	>5.0 to \leq 10.0 X ULN	2%	2%
Grade 4	>10.0 X ULN	1%	2%
Aspartate Aminotransferase			
Grade 2	>2.5 to \leq 5.0 X ULN	6%	6%
Grade 3	>5.0 to \leq 10.0 X ULN	2%	2%
Grade 4	>10.0 X ULN	<1%	2%
Alkaline Phosphatase			
Grade 2	>2.5 to \leq 5.0 X ULN	<1%	0%
Grade 3	>5.0 to \leq 10.0 X ULN	<1%	<1%
Grade 4	>10.0 X ULN	0%	0%
Hyperbilirubinemia			
Grade 2	>1.5 to \leq 2.5 X ULN	<1%	2%
Grade 3	>2.5 to \leq 5.0 X ULN	<1%	<1%
Grade 4	>5.0 X ULN	<1%	0%
Triglycerides			
Grade 2	5.65-8.48 mmol/L 500-750 mg/dL	10%	11%
Grade 3	8.49-13.56mmol/L 751-1200mg/dL	7%	10%
Grade 4	>13.56 mmol/L >1200 mg/dL	3%	6%
Total Cholesterol			
Grade 2	6.20-7.77mmol/L 240-300 mg/dL	25%	23%
Grade 3	>7.77 mmol/L >300 mg/dL	10%	14%
Low-Density lipoprotein Cholesterol			
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	14%	14%
Grade 3	\geq 4.91 mmol/L > 191 mg/dL	8%	9%
Elevated Glucose Levels			
Grade 2	6.95-13.88 mmol/L 126-250 mg/dL	10%	11%

Grade 3	13.89-27.75 mmol/L 251-500 mg/dL	<1%	0%
Grade 4	>27.75 mmol/L > 500 mg/dL	<1%	0%
Pancreatic Lipase			
Grade 2	>1.5 to ≤ 3.0 X ULN	3%	4%
Grade 3	>3.0 to ≤ 5.0 X ULN	2%	<1%
Grade 4	>5.0 X ULN	<1%	0%
Pancreatic Amylase			
Grade 2	>1.5 to < 2.0 X ULN	6%	7%
Grade 3	>2.0 to < 5.0 X ULN	7%	3%
Grade 4	>5.0 X ULN	0%	0%
N= Total number of subjects per treatment group OBR= optimized background regimen *Grade 4 data not applicable in division of AIDS grading scale.			

Serious ADRs

The following serious ADRs of at least moderate intensity (≥Grade 2) occurred in the Phase 2b studies (Studies TMC114-C213, TMC114-C202, TMC114-C215, and TMC114-C208) and Phase 3 studies (TMC114-C211, TMC114-C214, TMC114-C209, DUET-1 (TMC125-C206), and DUET-2 (TMC125-C216)) with darunavir/rtv: Abdominal pain, acute hepatitis, acute pancreatitis, anorexia, asthenia, diabetes mellitus, diarrhea, fatigue, headache, hepatic enzyme increased, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, immune reconstitution syndrome, low-density lipoprotein increased, nausea, pancreatic enzyme increased, rash, Stevens-Johnson Syndrome, and vomiting.

Additional ADRs to Darunavir/R Identified in Adult Subjects in Other Clinical Trials

The additional ADR of interest identified from other clinical trials was osteonecrosis.

Patients Co-Infected with Hepatitis B and/or Hepatitis C Virus

In subjects co-infected with hepatitis B or C virus receiving darunavir/rtv, the incidence of adverse events and clinical chemistry abnormalities was not higher than in subjects receiving darunavir/rtv who were not co-infected, except for increased hepatic enzymes (see **WARNINGS AND PRECAUTIONS, Hepatotoxicity**). The pharmacokinetic exposure in co-infected subjects was comparable to that in subjects without co-infection.

Postmarketing Experience

The following events have been identified during postmarketing use of darunavir. Because these events are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Redistribution of body fat has been reported.

Rarely, rhabdomyolysis (associated with co-administration with HMG-CoA reductase inhibitors and darunavir/ritonavir) and toxic epidermal necrolysis have been reported [see **WARNINGS AND PRECAUTIONS**]

OVERDOSAGE

Human experience of acute overdose with darunavir/rtv is limited. Single doses up to 3200 mg of the oral solution of darunavir alone and up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

No specific antidote is available for overdose with darunavir. Treatment of overdose with darunavir consists of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since darunavir is highly protein-bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

PACKAGING INFORMATION

DARUVIR Tablets.....Bottle of 60 tablets

Last updated: October 2010

