DARUVIR 600 Tablets (Darunavir)

Composition

Each film-coated tablet contains:

Darunavir Ethanolate equivalent to Darunavir 600 mg

Colours: Titanium Dioxide & Sunset Yellow FCF

Dosage Form

Oral tablet

Pharmacology

Pharmacodynamics

Mechanism of Action

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

Cardiac Electrophysiology

In a thorough QT/QTc study in 40 healthy subjects, darunavir/ritonavir doses of 1.33 times the maximum recommended dose did not affect the QT/QTc interval.

Pharmacokinetics

Pharmacokinetics in Adults

General

Darunavir is primarily metabolized by 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, darunavir 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 600/100 mg twice daily (based on sparse sampling in 285 patients in trial TMC114-C214, 278 patients in trial TMC114-C229 and 119 patients [integrated data] from trials TMC114-C202 and TMC114-C213).

Table 1: Population pharmacokinetic estimates of darunavir at darunavir/ritonavir 600/100 mg twice

daily (Trial TMC114-C214, 48-week analysis, Trial TMC114-C229, 48-week analysis and integrated data from Trials TMC114-C213 and TMC114-C202, primary 24-week analysis)

Parameter	**Darunavir/ritonavir 600/100 mg twice daily**		
	Study TMC114-C214 N = 285	**Study TMC114-C229 N = 278**	**Studies TMC114-C213 and TMC114-C202 (integrated data) N =119**
AUC_{24h} (ng·h/mL)*			
Mean ± Standard Deviation	116796 ± 33594	114302 ± 32681	124698 ± 32286
Median (Range)	111632 (64874–355360)	109401 (48934-323820)	123336 (67714–212980)
C_{0h} (ng/mL)			
Mean ± Standard Deviation	3490 ± 1401	3386 ± 1372	3578 ± 1151
Median (Range)	3307 (1517–13198)	3197 (250-11865)	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 suggest that darunavir/ritonavir is an inhibitor of the p-glycoprotein (p-gp) transporters.

Effects of Food on Oral Absorption

When darunavir tablets were administered with food, the C_{max} and AUC of darunavir, co-administered with ritonavir, is approximately 40% higher relative to the fasting state. 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 ^{14}C-darunavir, co-administered with 100 mg ritonavir, the majority of the radioactivity in the plasma was due to darunavir. At least 3 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-1.

Elimination

A mass balance study in healthy volunteers showed that after single-dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir was recovered in the feces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when co-administered 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 daruanvir/ritonavir 600/100 mg twice daily 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 ^{14}C-darunavir/ritonavir 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-1-infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n = 20). There are no pharmacokinetic data available in HIV-1-infected patients with severe renal impairment or end-stage renal disease (see **WARNINGS AND PRECAUTIONS**).

Gender

Population pharmacokinetic analysis showed higher mean darunavir exposure in HIV-1-infected females compared to males. This difference is not clinically relevant.

Race

Population pharmacokinetic analysis of darunavir in HIV-1-infected subjects indicated that race had no apparent effect on the exposure to darunavir.

Geriatric Patients

Population pharmacokinetic analysis in HIV-1-infected subjects showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV-

1-infected subjects (n = 12, age greater than or equal to 65) (see **WARNINGS AND PRECAUTIONS**).

Pregnancy and Postpartum

The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 600/100 mg twice daily and darunavir/ritonavir 800/100 mg once daily as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum (see Table 2, Table 3 and Figure 1).

Table 2: Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 600/100 mg twice daily as part of an antiretroviral regimen, during the 2nd trimester of pregnancy, the 3rd trimester of pregnancy and postpartum

Pharmacokinetics of total darunavir (mean ± standard deviation)	**2nd Trimester of pregnancy (n=11)***	**3rd Trimester of pregnancy (n=11)**	**Postpartum (6-12 Weeks) (n=11)**
C_{max}, ng/mL	4601 ± 1125	5111 ± 1517	6499 ± 2411
AUC_{24h}, ng.h/mL‡	77900 ± 20020	87400 ± 32800	110600 ± 54040
C_{min}, ng/mL†	1980 ± 839.9	2498 ± 1193	2711 ± 2268

* n=10 for AUC24h

† excluding Cmin value below LLOQ, n=10 for reference

‡ AUC24h is calculated as AUC12h*2.

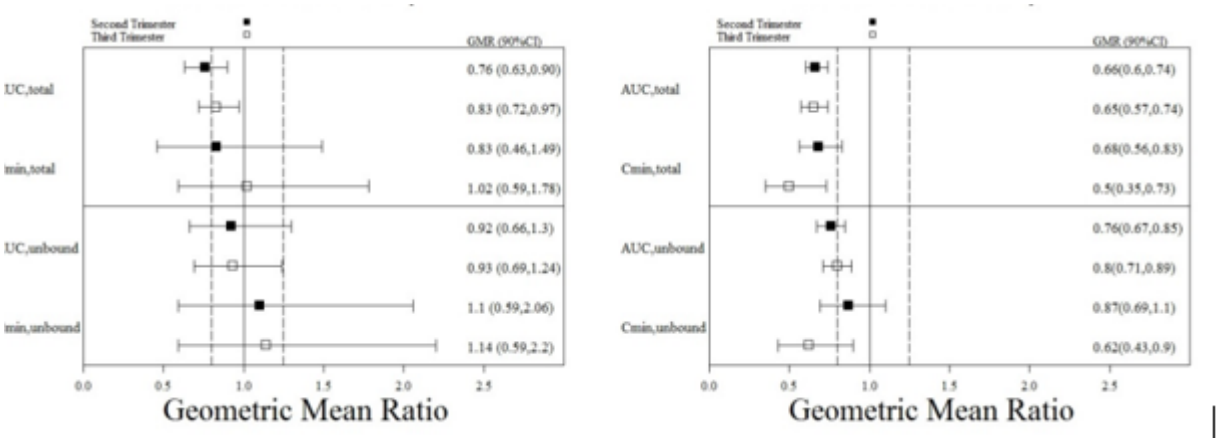
Table 3: Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 800/100 mg once daily as part of an antiretroviral regimen, during the 2nd trimester of pregnancy, the 3rd trimester of pregnancy and postpartum

Pharmacokinetics of total darunavir (mean ± standard deviation)	**2nd Trimester of pregnancy (n=16)**	**3rd Trimester of pregnancy (n=14)**	**Postpartum (6-12 Weeks) (n=15)**
C_{max}, ng/mL	4988 ± 1551	5138 ± 1243	7445 ± 1674
AUC_{24h}, ng.h/mL‡	61303 ± 16232	60439 ± 14052	94529 ± 28572
C_{min}, ng/mL†	1193 ± 509	1098 ± 609	1572 ± 1108

* N=12 for postpartum, N=15 for 2nd trimester and N=14 for 3rd trimester

Due to an increase in the unbound fraction of darunavir during pregnancy compared to postpartum, unbound darunavir exposures were less reduced during pregnancy as compared to postpartum. Exposure reductions during pregnancy were greater for the once daily regimen as compared to the twice daily regimen (see Figure 1).

Figure 1: Pharmacokinetic results (within-subject comparison) of total and unbound darunavir after administration of darunavir/ritonavir at 600/100 mg twice daily or 800/100 mg once daily as part of an antiretroviral regimen, during the 2nd and 3rd trimester of pregnancy compared to postpartum



Legend: 90% CI: 90% confidence interval; GMR: geometric mean ratio. Solid vertical line: ratio of 1.0; dotted vertical lines: reference lines of 0.8 and 1.25.

Indications

DARUVIR is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those patients with HIV-1 strains resistant to more than one protease inhibitor when co-administered with 100 mg ritonavir, and with other antiretroviral agents.

Dosage and Administration

Testing Prior to Initiation of DARUVIR/Ritomune

In treatment-experienced patients, treatment history, genotypic and/or phenotypic testing is recommended to assess drug susceptibility of the HIV-1 virus.

Appropriate laboratory testing such as serum liver biochemistries should be conducted prior to initiating therapy with Darunavir/ritonavir (see **WARNINGS AND PRECAUTIONS**).

Monitoring During Treatment with DARUVIR/Ritomune

Patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases should be monitored for elevation in serum liver biochemistries, especially during the first several months of Darunavir/ritonavir treatment (see **WARNINGS AND PRECAUTIONS**).

Recommended Dosage in Adult Patients

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.

Treatment-Experienced Adult Patients

The recommended oral dosage for treatment-experienced adult patients is summarized below:

Treatment-Experienced Adult Patients

With at least one darunavir resistance associated substitution* or with no baseline resistance information	One 600 mg Darunavir tablet twice daily taken with one ritonavir 100 mg tablet taken twice daily and with food

* V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V

Baseline genotypic testing is recommended for dose selection. However, when genotypic testing is not feasible, **DARUVIR 600** mg taken with ritonavir 100 mg twice daily is recommended.

Recommended Dosage During Pregnancy

The recommended dosage in pregnant patients is Darunavir 600 mg taken with ritonavir 100 mg twice daily with food.

Not recommended in Patients with Severe Hepatic Impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment. No data are available regarding the use of darunavir/ritonavir when co-administered to subjects with severe hepatic impairment; therefore, **DARUVIR/Ritomune**is not recommended for use in patients with severe hepatic impairment (see **PHARMACOLOGY, WARNING AND PRECAUTIONS**).

Contraindications

Co-administration of **DARUVIR/Ritomune** 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 below (also see **WARNINGS AND PRECAUTIONS, Drug Interactions, Table 4**). Due to the need for co-administration of Darunavir with ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: dronedarone
- Anti-gout: colchicine, in patients with renal/and or hepatic impairment
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide
- Ergot derivatives, e.g. dihydroergotamine, ergotamine, methylergonovine
- GI motility agent: cisapride
- Herbal product: St. John’s wort (Hypericum perforatum)
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir
- Lipid modifying agents: lomitapide, lovastatin, simvastatin
- Sedatives/hypnotics: orally administered midazolam, triazolam
- PDE-5 inhibitor: sildenafil when used for treatment of pulmonary arterial hypertension

Warnings and Precautions

Importance of Co-administration with Ritonavir

Darunavir must be co-administered with ritonavir and food to achieve the desired antiviral effect.

Failure to administer darunavirwith 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/ritonavir. During the clinical development program (N = 3063), hepatitis was reported in 0.5% of patients receiving combination therapy with darunavir/ritonavir. 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.

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

Appropriate laboratory testing should be conducted prior to initiating therapy with Darunavir/ritonavir 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 Darunavir/ritonavir 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 Darunavir/ritonavir should prompt consideration of interruption or discontinuation of treatment.

Severe Skin Reactions

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 (less than 0.1%) reported during the clinical development program. During post-marketing experience toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis has been reported. Discontinue Darunavi**r**/ritonavir 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/ritonavir [*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/ritonavir was 0.5%.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing darunavir/ritonavir + raltegravir compared to subjects receiving darunavir/ritonavir without raltegravir or raltegravir without darunavir/ritonavir. However, rash that was considered drug related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

Sulfa Allergy

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

Risk of Serious Adverse Reactions due to Drug Interactions

Initiation of darunavir/ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving darunavir/ritonavir, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of darunavir/ritonavir, respectively. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life threatening, or fatal events from greater exposures of concomitant medications.
- Clinically significant adverse reactions from greater exposures of darunavir/ritonavir.
- Loss of therapeutic effect of darunavir/ritonavir and possible development of resistance.

See **Table 3** for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during darunavir/ritonavir therapy; review concomitant medications during darunavir/ritonavir therapy; and monitor for the adverse reactions associated with the concomitant drugs [*see* **CONTRAINDICATIONS**].

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.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including darunavir. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of antiretroviral treatment.

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.

Not Recommended in Pediatric Patients Below 3 Years of Age

Darunavir/ritonavir in pediatric patients below 3 years of age is not recommended in view of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age [see **USE IN SPECIFIC POPULATIONS**].

Drug Interactions

Potential for Darunavir/ritonavir to Affect Other Drugs:

Darunavir, co-administered with ritonavir is an inhibitor of CYP3A and CYP2D6 and P-gp. Co-administration of Darunavi**r** and ritonavir with drugs that are primarily metabolized by CYP3A and CYP2D6 or are transported by P-gp may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see Table 4).

Potential for Other Drugs to Affect Darunavir:

Darunavir and ritonavir are metabolized by CYP3A. *In vitro* data indicate that darunavir may be a P-gp substrate. 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 and ritonavir and other drugs that inhibit CYP3A, or P-gp may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (see Table 4).

Established and other potentially significant drug interactions:

Table 4 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. (see **CONTRAINDICATIONS**)

Table 4: 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-1-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		

Didanosine	↔ darunavir ↔ didanosine	Didanosine should be administered 1 hour before or 2 hours after **darunavir**/ritonavir (which are administered with food).
HIV-1-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/ritonavir 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 **darunavir**, 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 **darunavir**, with or without ritonavir.
Other HIV protease inhibitors, except atazanavir		As coadministration with darunavir/ritonavir has been studied, coadministration is not recommended
HIV-1-Antiviral Agents: CCR5 co-receptor antagonists		
Maraviroc	↑ maraviroc	When used in combination with darunavir/ritonavir, the dose of maraviroc should be 150 mg twice daily.
Other Agents		
Alpha 1-adrenoreceptor antagonist: Alfuzosin Antianginal: ranolazine	↑ alfuzosin ↑ ranolazine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension. Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
Anti-arrhythmics: dronedarone e.g. amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine digoxin	↑ dronedarone ↑ antiarrhythmics ↑ digoxin	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. Therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with darunavir/ritonavir. 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.

Antibacterial: clarithromycin	↔ darunavir ↑ clarithromycin	No dose adjustment of the combination is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: · 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%.
Anticoagulant: <u>Direct Oral Anticoagulants (DOACs)</u> Apixaban Rivaroxaban Betrixaban Dabigatran Edoxaban Other Anticoagulants warfarin	↑ apixaban ↑ rivaroxaban ↔ betrixaban ↔ dabigatran ↔ edoxaban ↓ warfarin ↔ darunavir	Due to potentially increased bleeding risk, dosing recommendations for coadministration of apixaban with darunavir depends on the apixaban dose. Refer to apixaban dosing instructions for coadministration with strong CYP3A and P-gp inhibitors in apixaban prescribing information Co-administration of darunavir /ritonavir and rivaroxaban is not recommended because it may lead to an increased bleeding risk No dose adjustment is needed when betrixaban, dabigatran, or edoxaban is co-administered with darunavir Warfarin concentrations are decreased when co-administered with **darunavir**/ritonavir. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with **darunavir**/ritonavir.
Anticonvulsant: Carbamazepine Clonazepam Phenobarbital, phenytoin	↔ darunavir ↑ carbamazepine ↑ clonazepam ↔ darunavir ↓ phenytoin ↓ phenobarbital	The dose of either darunavir/ritonavir or carbamazepine does not need to be adjusted when initiating co-administration with darunavir/ritonavir and carbamazepine. Clinical monitoring of carbamazepine concentrations and its dose titration is recommended to achieve the desired clinical response. Clinical monitoring of anticonvulsants that are metabolized by CYP3A is recommended. Phenytoin and phenobarbital levels should be monitored when co-administering with darunavir/ritonavir

Antidepressant: Selective Serotonin Reuptake Inhibitors (SSRIs): Paroxetine, sertraline	↓ paroxetine, ↓ sertraline	If either sertraline or paroxetine is initiated in patients receiving darunavir/ritonavir, dose titrating the SSRI based on a clinical assessment of antidepressant response is recommended. Monitor for antidepressant response in patients on a stable dose of sertraline or paroxetine who start treatment with darunavir/ritonavir.
Tricyclic Antidepressants (TCAs) Amitriptyline, desipramine, imipramine, nortriptyline Other: trazodone,	↑ amitriptyline ↑ desipramine ↑ imipramine ↑ nortriptyline ↑ trazodone	Use a lower dose of the tricyclic antidepressants and trazodone due to potential increased adverse events such as nausea, dizziness, hypotension and syncope.
Antifungals: Itraconazole, ketoconazole, Posaconazole	↑ darunavir ↑ itraconazole ↑ ketoconazole ↔ posaconazole (not studied)	Monitor for increased darunavir/ritonavir adverse events with concomitant use of itraconazole, ketoconazole, or posaconazole. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg with monitoring for increased antifungal adverse events.
voriconazole	↓ voriconazole	Voriconazole is not recommended for patients receiving darunavir/ritonavir unless an assessment comparing predicted benefit to risk ratio justifies the use of voriconazole.

Anti-gout: Colchicine	↑ colchicine	The coadministration of darunavir/ritonavir with colchinine in patients with renal or hepatic impairnment is contraindicated. (see **CONTRAINDICATIONS**) For patients without renal or hepatic impairment · Treatment of gout-flares – coadministration 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. Prophylaxis of gout-flares–c--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. Treatment of familial 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).
Antimalarials: artemether/lumefantrine	↓ artemether ↓ dihydroartemisinin ↑ lumefantrine ↔ darunavir	The combination of darunavir/ritonavir and artemether/lumefantrine can be used without dose adjustments. However, the combination should be used with caution as increased lumefantrine exposure may increase the risk of QT prolongation.
Antimycobacterials: Rifampin rifabutin (The reference regimen for rifabutin was 300 mg once daily) Rifapentine	↓ darunavir ↓ cobicistat ↑ darunavir ↑ rifabutin ↑ 25-*O*-desacetylrifabutin ↓ darunavir	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance. Dose reduction of rifabutin by at least 75% of the usual dose (300 mg once daily) is recommended (i.e., 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. Co-administration of darunavir/ ritonavir with rifapentine is not recommended

Antineoplastics: Dasatinib, nilotinib vinblastine, vincristine	↑ antineoplastics	A decrease in the dosage or an adjustment of the dosing interval of dasatinib and nilotinib may be necessary for patients. Please refer to the dasatinib and nilotinib prescribing information for dosing instructions. For vincristine and vinblastine, consideration should be given to temporarily withholding the ritonavir containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when darunavir/ritonavir is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consideration should be given to initiating a revised regimen that does not include a CYP3A or P-gp inhibitor.
Antipsychotics: Lurasidone pimozide Quetiapine e.g. perphenazine, risperidone, thioridazine	↑ lurasidone ↑ pimozide ↑ quetiapine ↑ antipsychotics	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions. Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. Initiation of darunavir with ritonavir in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures. If co-administration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. Initiation of quetiapine in patients taking darunavir with ritonavir: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine. A decrease in the dose of antipsychotics that are metabolized by CYP3A or CYP2D6 may be needed when co-administered with darunavir/ritonavir

β-blockers: e.g. Carvedilol, metoprolol, timolol	↑ beta-blockers	Clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with darunavir/ritonavir and a lower dose of the beta blocker should be considered.
Calcium Channel Blockers: e.g. amlodipine, diltiazem, felodipine, nifedipine, nicardipine, verapamil	↑ calcium channel blockers	Clinical monitoring of patients is recommended.
Systemic/Inhaled/Nasal/Ophthalmic Corticosteroid e.g. Betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, prednisone, triamcinolone	↓ darunavir ↑ corticosteroid	Co-administration of darunavir/ritonavir with systemic dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss of therapeutic effect and development of resistance to darunavir. Consider alternative corticosteroids Co-administration with corticosteroids of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone (for which PK and/or PD are less affected by strong CYP3A inhibitors relative to other steroids) should be considered, particularly for long term use.
Endothelin receptor antagonists: Bosentan	↑ bosentan	Co-administration of bosentan in patients on darunavir/ritonavir: 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. Co-administration of darunavir/ritonavir in patients on bosentan: 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.
Ergot derivatives: e.g. dihydroergotamine, ergotamine, methylergonovine	↑ ergot derivatives	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.

GI motility agent: cisapride	↑ cisapride	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Hepatitis C Virus (HCV) Direct-Acting Agents: elbasvir/grazoprevir simeprevir	↑elbasvir/grazoprevir ↑ simeprevir ↑ darunavir	Co-administration is contraindicated due to potential for the increased risk of alanine transaminase (ALT) elevations. Co-administration of darunavir/ritonavir and simeprevir is not recommended.
Herbal Product St. John's wort (Hypericum perforatum)	↓ darunavir ↓ cobicistat	Co-administration is contraindicated due to potential for reduced plasma concentrations of darunavir, which may result in loss of therapeutic effect and development of resistance.
Lipid Modifying Agents: **HMG-CoA Reductase Inhibitors:** Lovastatin,simvastatin Pravastatin, atorvastatin, Rosuvastatin Other lipid modifying agents: lomitapide	↑ lovastatin ↑ simvastatin ↑ HMG-CoA reductase inhibitors ↑ lomitapide	Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis. Co-administration of darunavir/ritonavir with HMG-Co A reductase inhibitors may lead to adverse events such as myopathy. Titrate atorvastatin, pravastatin or rosuvastatin dose carefully and use the lowest necessary dose while monitoring for adverse events. Do not exceed atorvastatin 20 mg/day. Co-administration is contraindicated due to potential for markedly increased transaminases.
Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus Immunosuppressant/neoplastic: Everolimus	↑ immunosuppressants	Therapeutic concentration monitoring of the immunosuppressive agent is recommended when co-administered with darunavir/ritonavir. Co-administration of everolimus and darunavir/ritonavir is not recommended.

Inhaled beta agonist: salmeterol	↑ salmeterol	Co-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.
Narcotic analgesics metabolized by CYP3A: e.g. fentanyl, oxycodone Tramadol	↑ fentanyl ↑ oxycodone ↑ tramadol	Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A-metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended with co-administration. A dose decrease may be needed for tramadol with concomitant use.
Narcotic Analgesic/Treatment of Opioid Dependence: Buprenorphine, buprenorphine/naloxone methadone	↔ buprenorphine, naloxone ↑ norbuprenorphine (metabolite) ↓ methadone	No dose adjustment for buprenorphine or buprenorphine /naloxone is required with concurrent administration of darunavir/ritonavir. Clinical monitoring is recommended if darunavir/ritonavir and buprenorphine or buprenorphine/naloxone are co-administered. No adjustment of methadone dosage is required when initiating co-administration of darunavir/ritonavir. However, clinical monitoring is recommended as the dose of methadone maintenance therapy may need to be adjusted in some patients.
Oral Contraceptives/estrogen: ethinyl estradiol, norethindrone,drospirenone	↓ ethinyl estradiol ↓ norethindrone Drospirenone effects unknown	Effective alternative contraceptive methods or barrier method of contraception are recommended. For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia. No data are available to make recommendations on co-administration with other hormonal contraceptives.

PDE-5 inhibitors: e.g. Avanafil, 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. Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH): Co-administration with sildenafil used for PAH is contraindicated due to potential for sildenafil associated adverse reactions (which include visual disturbances, hypotension, prolonged erection, and syncope). The following dose adjustments are recommended for use of tadalafil with darunavir/ritonavir: Co-administration of tadalafil in patients on darunavir/ritonavir: 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. Co-administration of darunavir /ritonavir in patients on tadalafil: 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. Use of PDE-5 inhibitors for erectile dysfunction: 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. Co-administration of darunavir/ritonavir and avanafil is not recommended
Platelet aggregation inhibitor: ticagrelor	↑ ticagrelor	Co-administration of darunavir/ritonavir and ticagrelor is not recommended.

Proton pump inhibitor: Omeprazole	↓ omeprazole ↔ darunavir	When omeprazole is co-administered with darunavir/ritonavir, monitor patients for decreased efficacy of omeprazole. Consider increasing the omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg per day of omeprazole.
Sedatives/Hypnotics: Orally administered midazolam triazolam Metabolized by CYP3A e.g. buspirone, diazepam, estazolam, zoldipem parenterally administered midazolam	↑ midazolam ↑ triazolam ↑ sedative/hypnotics	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. Triazolam and orally administered midazolam are extensively metabolized by CYP3A. Co-administration of triazolam or orally administered midazolam with darunavir may cause large increases in the concentrations of these benzodiazepines. Titration is recommended when co-administering darunavir/ritonavir with sedatives/hypnotics metabolized by CYP3A and a lower dose of the sedatives/hypnotics should be considered with monitoring for adverse events. Co-administration of parenteral midazolam should be done in a setting which ensures close clinical monitoring and appropriate medical 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.

Drugs without Clinically Significant Interactions with Darunavir

No dosage adjustments are recommended when darunavir/ritonavir is co-administered with the following medications: atazanavir, dolutegravir, efavirenz, etravirine, nevirapine, nucleoside reverse transcriptase inhibitors (abacavir, emtricitabine, emtricitabine/tenofoviralafenamide lamivudine, stavudine, tenofovir disoproxil fumarate, zidovudine), pitavastatin, raltegravir, ranitidine, and rilpivirine.

Pregnancy

Risk Summary

Available limited data from the APR show no difference in rate of overall birth defects for darunavir (2.7%) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) [see Data]. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The

MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks gestation

The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Studies in animals did not show evidence of developmental toxicity. Exposures (based on AUC) in rats were 3-fold higher, whereas in mice and rabbits, exposures were lower (less than 1-fold) than human exposures at the recommended daily dose (see Data).

Clinical Considerations

The recommended dosage in pregnant patients is PREZISTA 600 mg taken with ritonavir 100 mg twice daily with food.

Data

Human Data

Darunavir/ritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 34 pregnant women during the second and third trimesters, and postpartum. Seventeen subjects were enrolled in each BID and QD treatment arms. Twenty-seven subjects completed the trial through the postpartum period (6-12 weeks after delivery) and 7 subjects discontinued before trial completion, 5 subjects in the BID arm and 2 subjects in the QD arm.

The pharmacokinetic data demonstrate that exposure to darunavir and ritonavir as part of an antiretroviral regimen was lower during pregnancy compared with postpartum (6-12 weeks). Exposure reductions during pregnancy were greater for the once daily regimen as compared to the twice daily regimen.

Virologic response was preserved. In the BID arm, the proportion of subjects with HIV-1 RNA <50 copies/mL were 35% (6/17) at baseline, 59% (10/17) through the third trimester visit, and 59% (10/17) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥50 copies/mL for 12% (2/17) of subjects and were missing for 5 subjects (1 subject discontinued prematurely due to virologic failure). In the QD arm, the proportion of subjects with HIV-1 RNA <50 copies/mL were 59% (10/17) at baseline, 82% (14/17) through the third trimester visit, and 82% (14/17) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥50 copies/mL for none of the subjects and were missing for 3 subjects (1 subject discontinued prematurely due to virologic failure).

Darunavir/ritonavir was well tolerated during pregnancy and postpartum. There were no new clinically relevant safety findings compared with the known safety profile of darunavir/ritonavir in HIV-1 infected adults.Among the 29 infants with HIV test results available data, born to the 29 HIV-infected pregnant women who completed trial through delivery or postpartum period, all 29 infants had test results that were negative for HIV-1 at the time of delivery and/or through 16 weeks postpartum. All 29 infants received antiretroviral prophylactic treatment containing zidovudine.

Based on prospective reports to the APR of 615 live births following exposure to darunavir-containing regimens during pregnancy (including 385 exposed in the first trimester and 230 exposed in the second/third trimester), there was no difference in rate of overall birth defects for darunavir compared with the background rate for major birth defects in a U.S. reference population of the

MACDP.The prevalence of birth defects in live births was 2.6% (95% CI: 1.2% to 4.7%) with first trimester exposure to darunavir containing regimens and 1.7% (95% CI: 0.3% to 4.4%) with second/third trimester exposure to darunavir containing regimens.

Animal Data

Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice (doses up to 1000 mg/kg from gestation day (GD) 6-15 with darunavir alone) and rats (doses up to 1000 mg/kg from GD 7-19 in the presence or absence of ritonavir) as well as in rabbits (doses up to 1000 mg/kg/day from GD 8-20 with darunavir alone). In these studies, darunavir exposures (based on AUC) were higher in rats (3-fold), whereas in mice and rabbits, exposures were lower (less than 1-fold) compared to those obtained in humans at the recommended clinical dose of darunavir boosted with ritonavir.

Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

There are no data on the presence of darunavir in human milk, the effects on the breastfed infant, or the effects on milk production. Darunavir is present in the milk of lactating rats (see Data). Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving darunavir.

Data

Animal Data

Studies in rats (with darunavir alone or with ritonavir) have demonstrated that darunavir is secreted in the milk. In the rat pre-and postnatal development study, a reduction in pup body weight gain was observed due to exposure of pups to drug substances via milk. The maximal maternal plasma exposures achieved with darunavir (up to 1000 mg/kg with ritonavir) were approximately 50% of those obtained in humans at the recommended clinical dose with ritonavir.

Females and Males of Reproductive Potential

Contraception

Use of darunavir may reduce the efficacy of combined hormonal contraceptives and the progestin only pill. Advise patients using combined hormonal contraceptives or the progestin only pill to use an effective alternative contraceptive method or add a barrier method of contraception. For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia.[See **WARNINGS AND PRECAUTIONS: Drug Interaction**]

Pediatric Use

Darunavir/ritonavir is not recommended in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age.

The safety, pharmacokinetic profile, and virologic and immunologic responses of darunavir/ritonavir administered twice daily were evaluated in treatment-experienced HIV-1 infected pediatric subjects 3 to less than 18 years of age and weighting at least 10 kg. These subjects were evaluated in clinical trials TMC114-C212 (80 subjects, 6 to less than 18 years of age) and TMC114-228 (21 subjects, 3 to less than 6 years of age). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults.

In clinical trial TMC114-C230, the safety, pharmacokinetic profile and virologic and immunologic responses of darunavir/ritonavir administered once daily were evaluated in treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age (12 subjects). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults. Once daily dosing recommendations for pediatric patients 3 to less than 12 years of age were derived using population pharmacokinetic modeling and simulation. Although a darunavir/ritonavir once daily dosing pediatric trial was not conducted in children less than 12 years of age, there is sufficient clinical safety data to support the predicted darunavir exposures for the dosing recommendations in this age group.

Juvenile Animal Data

In a juvenile toxicity study where rats were directly dosed with darunavir (up to 1000 mg/kg), deaths occurred from post-natal day 5 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 post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) 2 times the human plasma exposure levels.

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, Pharmacokinetics- *Special Populations***].

Hepatic Impairment

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

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**).

Undesirable Effects

The following adverse reactions are discussed in other sections of labeling:

- Hepatotoxicity (see **WARNING AND PRECAUTIONS**)
- Severe Skin Reactions (see **WARNING AND PRECAUTIONS**)
- Diabetes Mellitus/Hyperglycemia (see **WARNING AND PRECAUTIONS**)
- Fat Redistribution (see **WARNING AND PRECAUTIONS**)
- Immune Reconstitution Syndrome (see **WARNING AND PRECAUTIONS**)
- Hemophilia (see **WARNING AND PRECAUTIONS**)

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

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 clinical practice.

Treatment-Experienced Adults

Study TMC114-C214

The safety assessment is based on all safety data from the Phase 3 trial TMC114-C214 comparing darunavir/ritonavir 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/ritonavir 600/100 mg twice daily arm and in the lopinavir/ritonavir 400/100 mg twice daily arm was 80.7 and 76.4 weeks, respectively.

The majority of the adverse drug reactions (ADRs) reported during treatment with darunavir/ritonavir 600/100 mg twice daily were mild in severity. The most common clinical ADRs to darunavir/ritonavir 600/100 mg twice daily (greater than or equal to 5%) of at least moderate intensity (greater than or equal to Grade 2) were diarrhea, nausea, rash, abdominal pain and vomiting. 4.7% of subjects in the darunavir /ritonavir arm discontinued treatment due to ADRs.

ADRs to darunavir/ritonavir 600/100 mg twice daily of at least moderate intensity (greater than or equal to Grade 2) in antiretroviral treatment-experienced HIV-1-infected adult subjects are presented in Table 5.

Table 5: Selected clinical adverse drug reactions to darunavir/ritonavir 600/100 mg twice daily* of at least moderate intensity (≥grade 2) occurring in ≥2% of antiretroviral treatment-experienced HIV---infected adult subjects (Trial TMC114-C214)

System Organ Class, Preferred Term, %	**Darunavir/ritonavir 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 (greater than or equal to 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 6.

Table 6: Grade 2 to 4 laboratory abnormalities observed in antiretroviral treatment-experienced HIV-1-infected adult subjects* (Trial 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 ≤ 5.0 X ULN	7%	5%
Grade 3	>5.0 to ≤ 10.0 X ULN	2%	2%
Grade 4	>10.0 X ULN	1%	2%
Aspartate Aminotransferase			
Grade 2	>2.5 to ≤ 5.0 X ULN	6%	6%
Grade 3	>5.0 to ≤ 10.0 X ULN	2%	2%
Grade 4	>10.0 X ULN	<1%	2%
Alkaline Phosphatase			
Grade 2	>2.5 to ≤ 5.0 X ULN	<1%	0%
Grade 3	>5.0 to ≤ 10.0 X ULN	<1%	<1%
Grade 4	>10.0 X ULN	0%	0%
Hyperbilirubinemia			
Grade 2	>1.5 to ≤ 2.5 X ULN	<1%	2%
Grade 3	>2.5 to ≤ 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	8.49-13.56 mmol/L 751-1200 mg/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	≥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 (greater than or equal to Grade 2) occurred in the Phase 2b studies and Phase 3 studies with darunavir/ritonavir: 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.

Patients co-infected with hepatitis B and/or hepatitis C virus

In subjects co-infected with hepatitis B or C virus receiving darunavir/ritonavir, the incidence of adverse events and clinical chemistry abnormalities was not higher than in subjects receiving darunavir/ritonavir who were not co-infected, except for increased hepatic enzymes (*see* **WARNINGS AND PRECAUTIONS**). 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 post approval use of darunavir. Because these events are reported voluntarily from a population of uncertain 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) has been reported.

In addition, toxic epidermal necrolysis, acute generalized exanthematous pustulosis and drug rash with eosinophilia and systemic symptoms have been reported rarely (*see* **WARNINGS AND PRECAUTIONS**).

If you experience any side effects, talk to your doctor or pharmacist or write to **drugsafety@cipla.com**. You can also report side effects directly via the national pharmacovigilance program of India by calling on **1800 180 3024.**

By reporting side effects you can help provide more information on the safety of this product.

Overdosage

Human experience of acute overdose with darunavir/ritonavir is limited. 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.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

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