ZADURNA
Darunavir/Ritonavir Film-coated Tablets 400 mg/50 mg

1. NAME OF THE MEDICINAL PRODUCT

ZADURNA (Darunavir/Ritonavir Film-coated Tablets 400 mg/50 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film-coated Tablet contains:
Darunavir Ethanolate equivalent to Darunavir……..400 mg
Ritonavir USP……..50 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-Coated Tablets

A light yellow film-coated, ovaloid, biconvex, beveled edge tablet debossed with “M” on one side of the tablet and “DRL” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Darunavir/ritonavir tablets, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection in:
• treatment-naïve adults;
• treatment-experienced adults for whom once-daily darunavir/ritonavir 800 mg/100 mg is appropriate; and
• treatment-naïve paediatric patients weighing at least 40 kg with no darunavir resistance-associated substitutions.
Selection of patients should be based on treatment history, resistance profile and the recommended dosing criteria (see Posology and method of administration).

4.2 Posology and method of administration

HIV genotypic testing is recommended for antiretroviral treatment-experienced patients. However, when HIV genotypic testing is not feasible, darunavir and ritonavir tablets can be used in protease inhibitor-naïve patients but is not recommended in protease inhibitor-experienced patients.

Appropriate laboratory testing such as serum liver biochemistries, triglyceride, and cholesterol should be conducted prior to initiating therapy with darunavir and ritonavir tablets (see Warnings and Precautions).

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 treatment with darunavir and ritonavir tablets (see Warnings and Precautions).

<u>Posology</u>

Darunavir and ritonavir tablets is a fixed-dose combination product containing 400 mg of darunavir and 50 mg of ritonavir. In adults patients who are treatment-naïve or treatment-experienced, and pediatric patients weighing at least 40 kg who are treatment-naïve with no darunavir resistance-associated substitutions, the recommended dosage of darunavir and ritonavir tablets is 800 mg/100 mg (two 400 mg/50 mg tablets) taken once daily orally with food. Do not chew, split, or crush darunavir and ritonavir tablets. Administer darunavir and ritonavir tablets in conjunction with other antiretroviral agents.

Advice on missed doses

Advise patients to take darunavir and ritonavir tablets with food every day on a regular dosing schedule, as missed doses can result in development of resistance. Advise patients not to alter the dose or discontinue therapy with darunavir and ritonavir tablets without consulting their physician.

Special populations

Elderly

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

Hepatic impairment

No dosage adjustment of darunavir and ritonavir tablets is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of darunavir and ritonavir tablets in subjects with severe hepatic impairment. Therefore, darunavir and ritonavir tablets is not recommended for use in patients with severe hepatic impairment

Renal impairment

Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir, one component of darunavir and ritonavir tablets, were not significantly affected in HIV-infected subjects with moderate renal impairment (CrCL between 30-60 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 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.

Paediatric population

The pharmacokinetics of darunavir in combination with ritonavir in 12 antiretroviral treatment-naïve HIV-1-infected pediatric subjects 12 to less than 18 years of age and weighing at least 40 kg receiving darunavir/ritonavir 800/100 mg once daily resulted in similar darunavir exposures when compared to the darunavir exposure achieved in treatment- naïve adults receiving darunavir/ritonavir 800/100 mg once daily.

Pregnancy and postpartum

The recommended dosage in pregnant patients is another formulation of darunavir 600 mg taken with ritonavir 100 mg twice daily with food.

Darunavir and ritonavir tablets 800 mg/100 mg (two 400 mg/50 mg tablets) once daily should only be considered in certain pregnant patients who are already on a stable darunavir 800 mg with ritonavir 100 mg once daily regimen prior to pregnancy, are virologically suppressed (HIV- 1 RNA less than 50 copies per mL), and in whom a change to another formulation of darunavir 600 mg with ritonavir 100 mg administered twice daily may compromise tolerability or compliance.

Method of administration

Darunavir and ritonavir tablets is a fixed-dose combination product containing 400 mg of darunavir and 50 mg of ritonavir. In adults patients who are treatment-naïve or treatment-experienced and pediatric patients weighing at least 40 kg who are treatment-naïve with no darunavir resistance-associated substitutions, the recommended dosage of darunavir and ritonavir tablets is 800 mg/100 mg

(two 400 mg/50 mg tablets) taken once daily orally with food. Do not chew, split, or crush darunavir and ritonavir tablets. Administer darunavir and ritonavir tablets in conjunction with other antiretroviral agents.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Co-administration of darunavir and ritonavir tablets 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). Examples of these drugs and other contraindicated drugs (which may lead to reduced efficacy of darunavir and/or ritonavir) are listed below (see Drug Interactions).

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Anticancer Agents: apalutamide
- Anti-gout: colchicine, in patients with renal and/or hepatic impairment
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide
- Cardiac Disorders: dronedarone, ivabradine, ranolazine
- 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
- Opioid Antagonist: naloxegol
- PDE-5 inhibitor: sildenafil when used for treatment of pulmonary arterial hypertension
- Sedatives/hypnotics: orally administered midazolam, triazolam

4.4 Special warnings and precautions for use

Hepatotoxicity

Drug-induced hepatitis (e.g., 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 and ritonavir tablets 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 and ritonavir tablet 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 and ritonavir tablets 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 have been reported. Discontinue darunavir and ritonavir tablets 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 *(see Adverse Reactions)*. 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 and ritonavir tablets should be used with caution in patients with a known sulfonamide allergy. In clinical studies with darunavir/ritonavir, the incidence and severity of rash were similar in subjects with or without a history of sulfonamide allergy.

Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of darunavir and ritonavir tablets, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving darunavir and ritonavir tablets, may increase plasma concentrations of medications metabolized by CYP3A and reduce plasma concentrations of active metabolite(s) formed by CYP3A.

Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of darunavir and ritonavir tablets, 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 and ritonavir tablets.
- Loss of therapeutic effect of the concomitant medications from lower exposures of active metabolite(s).
- Loss of therapeutic effect of darunavir and ritonavir tablets and possible development of resistance from lower exposures of darunavir and ritonavir tablets.

See Table 1 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *(see Drug Interactions)*. Consider the potential for drug interactions prior to and during darunavir and ritonavir tablet therapy; review concomitant medications during darunavir and ritonavir tablet therapy; and monitor for the adverse reactions associated with the concomitant drugs *(see Contraindications and Drug Interactions)*.

Pancreatitis

Pancreatitis has been observed in patients receiving ritonavir, one component of darunavir and ritonavir tablets, including those who developed hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis *(see Warnings and Precautions)*. Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and darunavir and ritonavir tablets and/or other antitretroviral therapy should be discontinued if a diagnosis of pancreatitis is made.

PR Interval Prolongation

Ritonavir, one component of darunavir and ritonavir tablets, prolongs the PR interval in some patients. Post marketing cases of second or third degree atrioventricular block have been reported in patients.

Darunavir and ritonavir tablets should be used with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease, cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities.

The impact on the PR interval of co-administration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated. As a result, co-administration of ritonavir with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. Clinical monitoring is recommended (see Drug Interactions and Pharmacological Properties).

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 (PI) 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 PI 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 PI therapy and these events have not been established.

Lipid Disorders

Treatment with ritonavir, one component of darunavir and ritonavir tablets, alone or in combination with saquinavir has resulted in substantial increases in the concentration of total cholesterol and triglycerides *(see Adverse Reactions)*. Triglyceride and cholesterol testing should be performed prior to initiating darunavir and ritonavir tablets and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with darunavir and ritonavir tablets and HMG CoA reductase inhibitors (see Contraindications and Drug Interactions).

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 and ritonavir. 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, Guillain-Barré syndrome, and autoimmune hepatitis) 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 PIs. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued or reintroduced if treatment had been discontinued. A causal relationship between PI therapy and these episodes has not been established.

Laboratory Tests

Ritonavir, one component of darunavir and ritonavir tablets, has been shown to increase triglycerides, cholesterol, SGOT (AST), SGPT (ALT), GGT, CPK, and uric acid. Appropriate laboratory testing should be performed prior to initiating ritonavir therapy and at periodic intervals or if any clinical signs or symptoms occur during therapy.

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV. Appropriate precautions should continue to be employed

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Table 1 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. The table includes examples of potentially significant interactions but is not all inclusive (see Contraindications), and therefore the label of each drug that is co-administered with darunavir and ritonavir tablets should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regard to co-administration.

Table 1: 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 Examples	**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 one hour before or two hours after darunavir and ritonavir tablets (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 twice daily.)	↑ darunavir ↑ indinavir	The appropriate dose of indinavir in combination with darunavir/ritonavir tablets 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 and ritonavir tablets.
saquinavir	↓ darunavir ↔ saquinavir	Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer saquinavir and darunavir and ritonavir tablets.
Other HIV protease inhibitors, except atazanavir		As co-administration with darunavir/ritonavir has not been studied, co-administration is not recommended.
HIV-1-Antiviral Agents: CCR5 Co-receptor Antagonists		
maraviroc	↑ maraviroc	When used in combination with darunavir and ritonavir tablets, the dose of maraviroc should be 150 mg twice daily.
Other Agents		
Alpha 1-adrenoreceptor Antagonist:		
alfuzosin	↑ alfuzosin	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.
Antibacterial:		
clarithromycin	↔ darunavir ↑ clarithromycin	No dose adjustment of the combination is required for patients with normal renal

		function. For co- administration of clarithromycin and darunavir and ritonavir tablets in patients with renal impairment, the following dose adjustments should be considered: –For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%. –For subjects with CLcr of < 30 mL/min, the dose of clarithromycin should be reduced by 75%.
Anticoagulants:		
Direct Oral Anticoagulants (DOACs) apixaban	↑ apixaban	Due to potentially increased bleeding risk, dosing recommendations for co- administration of apixaban with darunavir and ritonavir tablets depend on the apixaban dose. Refer to apixaban dosing instructions for co-administration with P-gp and strong CYP3A inhibitors in apixaban prescribing information.
rivaroxaban	↑ rivaroxaban	Co-administration of darunavir and ritonavir tablets and rivaroxaban is not recommended because it may lead to an increased bleeding risk.
Dabigatran etexilate edoxaban	↑ dabigatran ↑ edoxaban	Refer to the dabigatran etexilate or edoxaban prescribing information for recommendations regarding co- administration. The specific recommendations are based on indication, renal function, and effect of the co-administered P-gp inhibitors on the concentration of dabigatran or edoxaban. Clinical monitoring is recommended when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with darunavir and ritonavir tablets.
Other Anticoagulants:		
warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations are decreased when co-administered with darunavir/ritonavir tablets. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with darunavir and ritonavir tablets.
Anticonvulsants:		
carbamazepine	↔ darunavir ↑ carbamazepine	The dose of either darunavir and ritonavir tablets or carbamazepine does not need to be adjusted when initiating co-administration with darunavir and ritonavir tablets and carbamazepine. Clinical monitoring of carbamazepine concentrations and its dose titration is recommended to achieve the desired clinical response.
clonazepam	↑ clonazepam	Clinical monitoring of anticonvulsants that are metabolized by CYP3A is recommended.
phenobarbital, phenytoin	↔ darunavir	Phenytoin and phenobarbital levels should be

	↓ phenytoin ↓ phenobarbital	monitored when co- administering with darunavir and ritonavir tablets.
Antidepressants:		
Selective Serotonin Reuptake Inhibitors (SSRIs): paroxetine, sertraline	↓ paroxetine ↓ sertraline	If either sertraline or paroxetine is initiated in patients receiving darunavir and ritonavir tablets, 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 and ritonavir tablets.
Tricyclic Antidepressants (TCAs):		
amitriptyline, desipramine, imipramine, nortriptyline	↑ amitriptyline ↑ desipramine ↑ imipramine ↑ nortriptyline	Use a lower dose of the tricyclic antidepressants and trazodone due to potential increased adverse events such as nausea, dizziness, hypotension and syncope.
Other Antidepressants:		
trazodone	↑ trazodone	
bupropion	↓ bupropion ↓ active metabolite, hydroxybupropion	Patients receiving darunavir and ritonavir tablets and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antifungals:		
itraconazole, isavuconazole, ketoconazole, posaconazole	↑ darunavir ↑ itraconazole ↑ isavuconazole ↑ ketoconazole ↔ posaconazole	Monitor for increased darunavir and ritonavir and/or antifungal adverse events with concomitant use of these antifungals. 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 and ritonavir tablets unless an assessment comparing predicted benefit to risk ratio justifies the use of voriconazole.
Anti-gout:		
colchicine	↑ colchicine	Co-administration is contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions. For patients without renal or hepatic impairment: –Treatment of gout-flares – co-administration of colchicine in patients on darunavir and ritonavir tablets: 0.6 mg (1 tablet) × 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 – co-administration of colchicine in patients on darunavir and ritonavir tablets:

		– 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 and ritonavir tablets: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimalarial:		
artemether/lumefantrine	↓ artemether ↓ dihydroartemisinin ↑ lumefantrine ↔ darunavir	The combination of darunavir and ritonavir tablets 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	↓ darunavir ↓ ritonavir	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
rifabutin **(The reference regimen for rifabutin was 300 mg once daily.)**	↑ darunavir ↑ rifabutin ↑ 25-O-desacetylrifabutin	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 further dose reduction of rifabutin may be necessary.
rifapentine	↓ darunavir ↓ ritonavir	Co-administration of darunavir and ritonavir tablets with rifapentine is not recommended.
Anticancer Agents:		
abemaciclib apalutamide dasatinib encorafenib ibrutinib irinotecan ivosidenib neratinib nilotinib venetoclax vinblastine vincristine	↑ antineoplastics With apalutamide: ↓ darunavir ↓ ritonavir	Apalutamide is contraindicated due to potential for loss of virologic response and possible resistance to darunavir or to the class of protease inhibitors. A decrease in the dosage or an adjustment of the dosing interval of dasatinib and nilotinib may be necessary. Please refer to the dasatinib and nilotinib prescribing information for dosing instructions. Discontinue darunavir and ritonavir tablets at least 1 week prior to starting irinotecan therapy. Do not administer darunavir and ritonavir tablets with irinotecan unless there are no therapeutic alternatives. Avoid co-administration of encorafenib or ivosidenib with darunavir and ritonavir tablets due to potential risk of serious adverse events

		such as QT interval prolongation. If co-administration of encorafenib with darunavir and ritonavir tablets cannot be avoided, modify dose as recommended in encorafenib USPI. If coadministration of ivosidenib with darunavir and ritonavir tablets cannot be avoided, reduce ivosidenib dose to 250 mg once daily. Avoid use of neratinib, venetoclax or ibrutinib with darunavir and ritonavir tablets. 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 and ritonavir tablets 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	↑ lurasidone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
pimozide	↑ pimozide	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
quetiapine	↑ quetiapine	Initiation of darunavir and ritonavir tablets 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 and ritonavir tablets: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
e.g., perphenazine, risperidone, thioridazine	↑ antipsychotics	A decrease in the dose of antipsychotics that are metabolized by CYP3A or CYP2D6 may be needed when co-administered with darunavir and ritonavir tablets.
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 and ritonavir tablets and a lower dose of the beta blocker should be considered.

Calcium Channel Blockers:		
amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	↑ calcium channel blockers	Clinical monitoring of patients is recommended.
Cardiac Disorders:		
ranolazine, ivabradine dronedarone	↑ ranolazine ↑ ivabradine ↑ dronedarone	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.
digoxin	↑ digoxin	The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Other antiarrhythmics:		
e.g., amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↑ antiarrhythmics	Therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with darunavir and ritonavir tablets.
Corticosteroids:		
dexamethasone (systemic) (also see Corticosteroids primarily metabolized by CYP3A below)	↓ darunavir ↑ dexamethasone	Co-administration of darunavir and ritonavir tablets 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.
Corticosteroids primarily metabolized by CYP3A:		
betamethasone budesonide ciclesonide fluticasone methylprednisolone mometasone triamcinolone	↑ corticosteroids	Co-administration with corticosteroids (all routes of administration) 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, prednisone, 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 Antagonist:		
bosentan	↑ bosentan	Co-administration of bosentan in patients on darunavir and ritonavir tablets: In patients who have been receiving darunavir and ritonavir tablets 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 and ritonavir tablets in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of darunavir and ritonavir

		tablets. After at least 10 days following the initiation of darunavir and ritonavir tablets, 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.
GnRH Receptor Antagonists:		
elagolix	↑ elagolix ↓ darunavir ↓ ritonavir	Concomitant use of elagolix 200 mg twice daily and darunavir and ritonavir tablets for more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and darunavir and ritonavir to 6 months.
Hepatitis C Virus (HCV):		
Direct-Acting Antivirals **elbasvir/grazoprevir**	↑ elbasvir/grazoprevir	Co-administration is contraindicated due to potential for the increased risk of alanine transaminase (ALT) elevations.
glecaprevir/pibrentasvir **simeprevir**	↑ glecaprevir ↑ pibrentasvir ↑ simeprevir	Co-administration of darunavir and ritonavir tablets with glecaprevir/pibrentasvir, or simeprevir is not recommended.
Herbal Product:		
St. John's wort (Hypericum perforatum)	↓ darunavir ↓ ritonavir	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.
Hormonal contraceptives:		
ethinyl estradiol, norethindrone, drospirenone	↓ ethinyl estradiol ↓ norethindrone drospirenone: effects unknown	Effective alternative (non- hormonal) contraceptive method or a barrier method of contraception is recommended (see Use in Specific Populations). 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.
Immunosuppressants: **e.g., cyclosporine, tacrolimus, sirolimus**	↑ immunosuppressants	Therapeutic concentration monitoring of the immunosuppressive agent is recommended when co-administered with darunavir and

Immunosuppressant/ Anticancer Agent: **everolimus** **irinotecan**		ritonavir tablets. Co-administration of everolimus and darunavir and ritonavir tablets is not recommended. Discontinue darunavir and ritonavir tablets at least 1 week prior to starting irinotecan therapy. Do not administer darunavir and ritonavir tablets with irinotecan unless there are no therapeutic alternatives.
Inhaled Beta Agonist: **salmeterol**	↑ salmeterol	Co-administration of salmeterol and darunavir and ritonavir tablets is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Kinase Inhibitors: fostamatinib (also see anticancer agents above)	↑ fostamatinib metabolite R406	Monitor for toxicities of R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required.
Lipid Modifying Agents:		
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis.
atorvastatin, pravastatin, rosuvastatin	↑ HMG-CoA reductase inhibitors	Co-administration of darunavir and ritonavir tablets with HMG-CoA 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.
Other Lipid Modifying Agents: lomitapide	↑ lomitapide	Co-administration is contraindicated due to potential for markedly increased transaminases.
Narcotic Analgesics Metabolized by CYP3A:		
e.g., fentanyl, oxycodone	↑ fentanyl ↑ oxycodone	Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A-metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended with co-administration.
tramadol meperidine	↑ tramadol	A dose decrease may be needed for tramadol with concomitant use.
	↓ meperidine ↑ normeperidine (metabolite)	Dosage increase and long-term use of meperidine with ritonavir are not recommended due to the increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity

		(e.g., seizures).
Narcotic Analgesics/Treatment of Opioid Dependence:		
buprenorphine, buprenorphine/naloxone	↔ buprenorphine, naloxone ↑ norbuprenorphine (metabolite)	No dose adjustment for buprenorphine or buprenorphine/naloxone is required with concurrent administration of darunavir and ritonavir tablets. Clinical monitoring is recommended if darunavir and ritonavir tablets and buprenorphine or buprenorphine/naloxone are co-administered.
methadone	↓ methadone	No adjustment of methadone dosage is required when initiating co- administration of darunavir and ritonavir tablets. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients.
Opioid Antagonist:		
naloxegol	↑ naloxegol	Co-administration of darunavir and ritonavir tablets and naloxegol is contraindicated due to potential for precipitating opioid withdrawal symptoms.
PDE-5 Inhibitors:		
e.g., avanafil, sildenafil, tadalafil, vardenafil	↑ 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 and ritonavir tablets 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 and ritonavir tablets: –Co-administration of tadalafil in patients on darunavir and ritonavir tablets: In patients receiving darunavir and ritonavir tablets 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 and ritonavir tablets in patients on tadalafil: Avoid use of tadalafil during the initiation of darunavir and ritonavir tablets. Stop tadalafil at least 24 hours

		prior to starting darunavir/ritonavir. After at least one week following the initiation of darunavir and ritonavir tablets, 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 and ritonavir tablets and avanafil is not recommended.
Platelet Aggregation Inhibitor:		
ticagrelor	↑ ticagrelor	Co-administration of darunavir and ritonavir tablets and ticagrelor is not recommended.
clopidogrel	↓ clopidogrel active metabolite	Co-administration of darunavir and ritonavir tablets and clopidogrel is not recommended due to potential reduction of the antiplatelet activity of clopidogrel.
prasugrel	↔ prasugrel active metabolite	No dose adjustment is needed when prasugrel is co-administered with darunavir and ritonavir tablets.
Proton Pump Inhibitor:		
omeprazole	↓ omeprazole ↔ darunavir	When omeprazole is co-administered with darunavir and ritonavir tablets, 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.
orally administered midazolam, triazolam	↑ midazolam ↑ triazolam	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 and ritonavir tablets, may cause large increases in the concentrations of these benzodiazepines.
Sedatives/Hypnotics:		
metabolized by CYP3A e.g., buspirone, diazepam, estazolam, zolpidem	↑ sedatives/hypnotics	Titration is recommended when co-administering darunavir and ritonavir tablets with sedatives/hypnotics metabolized by CYP3A and a lower dose of the sedatives/hypnotics should be considered with monitoring for adverse events.

parenterally administered midazolam		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.
Stimulant		
methamphetamine	↑ methamphetamine	Use with caution. A dose decrease of methamphetamine may be needed when co-administered with darunavir and ritonavir tablets.
Urinary antispasmodics		
fesoterodine	↑ fesoterodine	When fesoterodine is co- administered with darunavir and ritonavir tablets, do not exceed a fesoterodine dose of 4 mg once daily.
solifenacin	↑ solifenacin	When solifenacin is co-administered with darunavir and ritonavir tablets, do not exceed a solifenacin dose of 5 mg once daily.

Drugs without Clinically Significant Interactions with Darunavir

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary: Prospective pregnancy data from the Antiretroviral Pregnancy Registry (APR) are not sufficient to adequately assess the risk of birth defects or miscarriage. Available limited data from the APR show no statistically significant difference in the overall risk of major birth defects for darunavir or ritonavir 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 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.
In animal reproduction studies with darunavir, no evidence of adverse developmental outcomes was observed with oral administration to pregnant mice, rats and rabbits. During organogenesis, systemic exposure (AUC) to darunavir was less than 1 (mice and rabbits) and 3 (rat) times human exposure at the recommended daily dose *(see Data)*.

In animal reproduction studies with ritonavir, no evidence of adverse developmental outcomes was observed with oral administration to pregnant rats and rabbits. During organogenesis in the rat and rabbit, systemic exposure (AUC) to ritonavir was approximately 8 times higher than human exposure at the recommended daily dose. In the rat pre- and postnatal developmental study, maternal systemic exposure to ritonavir was approximately 6 times the exposure in humans at the recommended daily dose, based on a body surface area conversion factor *(see Data)*.

Clinical Considerations: The recommended dosage in pregnant patients is another formulation of darunavir 600 mg taken with ritonavir 100 mg twice daily with food.

Darunavir 800 mg taken with ritonavir 100 mg once daily should only be considered in certain pregnant patients who are already on

a stable darunavir 800 mg with ritonavir 100 mg once daily regimen prior to pregnancy, are virologically suppressed (HIV-1 RNA less than 50 copies per mL), and in whom a change to another formulation of darunavir 600 mg with ritonavir 100 mg administered twice daily may compromise tolerability or compliance *(see Dosage and Administration and Pharmacological Properties)*.

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 36 pregnant women during the second and third trimesters, and postpartum. Eighteen subjects were enrolled in each BID and QD treatment arms. Twenty-nine 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 *(see Pharmacological Properties).*

Virologic response was preserved. In the BID arm, the proportion of subjects with HIV-1 RNA < 50 copies/mL were 39% (7/18) at baseline, 61% (11/18) through the third trimester visit, and 61% (11/18) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥ 50 copies/mL for 11% (2/18) 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 61% (11/18) at baseline, 83% (15/18) through the third trimester visit, and 78% (14/18) 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 31 infants with HIV test results available data, born to the 31 HIV-infected pregnant women who completed trial through delivery or postpartum period, all 31 infants had test results that were negative for HIV-1 at the time of delivery and/or through 16 weeks postpartum. All 31 infants received antiretroviral prophylactic treatment containing zidovudine.

Darunavir: Based on prospective reports to the APR of over 980 exposures to darunavir- containing regimens during pregnancy resulting in live births (including over 660 exposed in the first trimester and over 320 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.6% (95% CI: 2.3% to 5.3%) with first trimester exposure to darunavir- containing regimens and 2.5% (95% CI: 1.1% to 4.8%) with second/third trimester exposure to darunavir-containing regimens.

Ritonavir: Based on prospective reports to the APR of approximately 6100 live births following exposure to ritonavir-containing regimens (including over 2800 live births exposed in the first trimester and over 3200 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.3% (95% CI: 1.7%-2.9%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.3%-3.5%) following second and third trimester exposure to ritonavir-containing regimens.

While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

Animal Data

Darunavir: 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.

Ritonavir: Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day), and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on gestation days 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at doses producing systemic exposures (AUC) equivalent to approximately 8 times higher

than human exposure at the recommended daily dose. Developmental toxicity observed in rats (early resorptions, decreased fetal body weight and ossification delays and developmental variations) occurred at a maternally toxic dose at an exposure equivalent to approximately 8 times higher than human exposure at the recommended daily dose. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 3 times higher than human exposure at the recommended daily dose. Developmental toxicity was observed in rabbits (resorptions, decreased litter size and decreased fetal weights) at maternally toxic dosage equivalent to 22 times higher than the recommended daily dose, based on a body surface area conversion factor. In pre-and postnatal development study in rats, ritonavir was administered at doses of 0, 15, 35, and 60 mg/kg/day from gestation day 6 through postnatal day 20. At doses of 60 mg/kg/day, no developmental toxicity was noted with ritonavir dosage equivalent to 6 times the recommended daily dose, based on a body surface area conversion factor.

Breast-feeding

Risk Summary
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)*.

Limited published data reports that ritonavir is present in human milk.

Potential risks of breastfeeding include: (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) adverse reactions in a breastfed infant similar to those seen in adults.

Data
Animal Data:
Darunavir: 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 of darunavir with ritonavir.
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Fertility

Contraception: Use of darunavir and ritonavir tablets may reduce the efficacy of combined hormonal contraceptives and darunavir, one component of darunavir and ritonavir tablets, may reduce the efficacy of the progestin only pill. Advise patients to use an effective alternative (non- hormonal) 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 Drug Interactions).

4.7 Effects on ability to drive and use machines

Darunavir in combination with ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing Darunavir co-administered with low dose ritonavir and should be borne in mind when considering a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

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 Naïve-Adults: TMC114-C211: The safety assessment is based on all safety data from the Phase 3 trial TMC114-C211 comparing darunavir/ritonavir 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day in 689 antiretroviral treatment-naïve HIV-1-infected adult subjects. The total mean exposure for subjects in the darunavir/ritonavir 800/100 mg once daily arm and in the lopinavir/ritonavir 800/200 mg per day arm was 162.5 and 153.5 weeks, respectively.

The majority of the adverse drug reactions (ADRs) reported during treatment with darunavir/ritonavir 800/100 mg once daily were mild in severity. The most common clinical ADRs to darunavir/ritonavir 800/100 mg once daily (greater than or equal to 5%) of at least

moderate intensity (greater than or equal to Grade 2) were diarrhea, headache, abdominal pain and rash. Treatment discontinuation due to ADRs occurred in 2.3% of subjects in the darunavir/ritonavir arm.

ADRs to darunavir/ritonavir 800/100 mg once daily of at least moderate intensity (greater than or equal to Grade 2) in antiretroviral treatment-naïve HIV-1-infected adult subjects are presented in Table 2 and subsequent text below the table.

Table 2: Selected Clinical Adverse Drug Reactions to Darunavir/ritonavir 800/100 mg Once Dailya of at Least Moderate Intensity (≥ Grade 2) Occurring in ≥ 2% of Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects (Trial TMC114-C211)

System organ class, preferred term, %	Darunavir/ritonavir 800/100 mg once daily + TDF/FTC N = 343	Lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346
Gastrointestinal Disorders		
Abdominal pain	6%	6%
Diarrhea	9%	16%
Nausea	4%	4%
Vomiting	2%	4%
General Disorders and Administration Site Conditions		
Fatigue	< 1%	3%
Metabolism and Nutrition Disorders		
Anorexia	2%	< 1%
Nervous System Disorders		
Headache	7%	6%
Skin and Subcutaneous Tissue Disorders		
Rash	6%	7%

N = total number of subjects per treatment group; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate

[a] 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-naïve subjects receiving darunavir/ritonavir 800/100 mg once daily are listed below by body system:

Gastrointestinal Disorders: acute pancreatitis, dyspepsia, flatulence

General Disorders and Administration Site Conditions: asthenia

Hepatobiliary Disorders: acute hepatitis (e.g., acute hepatitis, cytolytic hepatitis, hepatotoxicity)

Immune System Disorders: (drug) hypersensitivity, immune reconstitution syndrome

Metabolism and Nutrition Disorders: diabetes mellitus

Musculoskeletal and Connective Tissue Disorders: myalgia, osteonecrosis

Psychiatric Disorders: abnormal dreams

Skin and Subcutaneous Tissue Disorders: angioedema, pruritus, Stevens-Johnson Syndrome, urticaria

Laboratory Abnormalities: Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-naïve adult subjects treated with darunavir/ritonavir 800/100 mg once daily are presented in Table 3.

Table 3: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjectsa (Trial TMC114-C211)

Laboratory parameter %	Limit	Darunavir/ritonavir 800/100 mg once daily + TDF/FTC	Lopinavir/ritonavir 800/200 mg per day + TDF/FTC
Biochemistry			
Alanine Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	9%	9%
Grade 3	> 5.0 to ≤ 10.0 X ULN	3%	3%
Grade 4	> 10.0 X ULN	< 1%	3%
Aspartate Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	7%	10%
Grade 3	> 5.0 to ≤ 10.0 X ULN	4%	2%
Grade 4	> 10.0 X ULN	1%	3%
Alkaline Phosphatase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	1%	1%
Grade 3	> 5.0 to ≤ 10.0 X ULN	0%	< 1%
Grade 4	> 10.0 X ULN	0%	0%
Hyperbilirubinemia			
Grade 2	> 1.5 to ≤ 2.5 X ULN	< 1%	5%
Grade 3	> 2.5 to ≤ 5.0 X ULN	< 1%	< 1%
Grade 4	> 5.0 X ULN	0%	0%
Triglycerides			
Grade 2	5.65-8.48 mmol/L 500-750 mg/dL	3%	10%
Grade 3	8.49-13.56 mmol/L 751-1200 mg/dL	2%	5%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	1%	1%
Total Cholesterol			
Grade 2	6.20-7.77 mmol/L 240-300 mg/dL	23%	27%
Grade 3	> 7.77 mmol/L > 300 mg/dL	1%	5%
Low-Density Lipoprotein Cholesterol			
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	14%	12%
Grade 3	≥ 4.91 mmol/L ≥ 191 mg/dL	9%	6%
Elevated Glucose Levels			
Grade 2	6.95-13.88 mmol/L 126-250 mg/dL	11%	10%
Grade 3	13.89-27.75 mmol/L 251-500 mg/dL	1%	< 1%
Grade 4	> 27.75 mmol/L > 500 mg/dL	0%	0%
Pancreatic Lipase			
Grade 2	> 1.5 to ≤ 3.0 X ULN	3%	2%
Grade 3	> 3.0 to ≤ 5.0 X ULN	< 1%	1%
Grade 4	> 5.0 X ULN	0%	< 1%
Pancreatic Amylase			
Grade 2	> 1.5 to ≤ 2.0 X ULN	5%	2%
Grade 3	> 2.0 to ≤ 5.0 X ULN	5%	4%
Grade 4	> 5.0 X ULN	0%	< 1%

N = total number of subjects per treatment group; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate
[a] 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 and Phase 3 trials 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.

Pancreatitis has been observed in patients receiving high-dose ritonavir therapy, including those who developed hypertriglyceridemia. In some cases, fatalities have been observed.

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.

Clinical Trials Experience: Pediatric Patients: Darunavir/ritonavir has been studied in combination with other antiretroviral agents in TMC114-C230 in which 12 antiretroviral treatment-naïve HIV-1 infected pediatric patients aged from 12 to less than 18 years and weighing at least 40 kg were included. The TMC114-C230 trial evaluated darunavir/ritonavir once daily dosing *(see Use in Specific Populations and Clinical Studies)*.

Frequency, type, and severity of ADRs in pediatric subjects were comparable to those observed in adults.

TMC114-C230: Clinical ADRs to darunavir/ritonavir (all grades, greater than or equal to 3%), were vomiting (33%), nausea (25%), diarrhea (16.7%), abdominal pain (8.3%), decreased appetite (8.3%), pruritus (8.3%), and rash (8.3%).

There were no Grade 3 or 4 laboratory abnormalities considered as ADRs in this trial.

Although a causal relationship has not been definitively established, protease inhibitors may contribute to increase in blood sugar levels and even diabetes in HIV patients. Close monitoring of blood glucose level is recommended

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

For reporting of adverse events and PV related queries please write to Email: ProductSafety@viatris.com

4.9 Overdose

Human experience of acute overdose with darunavir and ritonavir tablets is limited. No specific antidote is available for overdose with darunavir and ritonavir. Treatment of overdose with darunavir and ritonavir tablets consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed ritonavir should be achieved by gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed ritonavir.

Since both darunavir and ritonavir are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitors, ATC code: J05AR26

Mechanism of action

Darunavir is an inhibitor of the 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.

Ritonavir is a peptidomimetic inhibitor of the HIV-1 protease. Ritonavir, at the recommended dose, is not intended for use as an inhibitor of the HIV-1 protease.

Darunavir and ritonavir tablets is a fixed-dose combination of HIV-1 antiviral drugs darunavir and ritonavir. As co-formulated in darunavir and ritonavir tablets, ritonavir inhibits the CYP3A-mediated metabolism of darunavir, thereby providing increased systemic exposure of darunavir.

Antiviral activity *in vitro*

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC50 values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity in cell culture against a broad panel of HIV-1 group M (A, B, C, D, E, F, G), and group O primary isolates with EC_{50} values ranging from less than 0.1 to 4.3 nM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir did not show antagonism when studied in combination with the PIs amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine, the NNRTIs delavirdine, rilpivirine, efavirenz, etravirine, or nevirapine, and the fusion inhibitor enfuvirtide.

Resistance

Cell Culture: HIV-1 isolates with a decreased susceptibility to darunavir have been selected in cell culture and obtained from subjects treated with darunavir/ritonavir. Darunavir- resistant virus derived in cell culture from wild-type HIV-1 had 21- to 88-fold decreased susceptibility to darunavir and developed 2 to 4 of the following amino acid substitutions S37D, R41E/T, K55Q, H69Q, K70E, T74S, V77I, or I85V in the protease. Selection in cell culture of darunavir resistant HIV-1 from nine HIV-1 strains harboring multiple PI resistance-associated mutations resulted in the overall emergence of 22 mutations in the protease gene, coding for amino acid substitutions L10F, V11I, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S, and Q92R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease substitutions and exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC50 values ranging from 125 nM to 3461 nM.

Clinical Trials of Darunavir/Ritonavir in Treatment-Experienced Subjects: In the 48-week analysis of the Phase 3 trial TMC114-C229, the number of virologic failures (including those who discontinued before suppression after Week 4) was 26% (75/294) in the group of subjects receiving darunavir/ritonavir 800/100 mg once daily compared to 19% (56/296) of subjects receiving darunavir/ritonavir 600/100 mg twice daily. Examination of isolates from subjects who failed on darunavir/ritonavir 800/100 mg once daily and had post-baseline genotypes showed that 8 subjects (8/60; 13%) had isolates that developed IAS-USA defined PI resistance- associated substitutions compared to 5 subjects (5/39; 13%) on darunavir/ritonavir 600/100 mg twice daily. Isolates from 2 subjects developed PI resistance associated substitutions associated with decreased susceptibility to darunavir; 1 subject isolate in the darunavir/ritonavir 800/100 mg once daily arm developed substitutions V32I, M46I, L76V and I84V associated with a 24-fold decreased susceptibility to darunavir, and 1 subject isolate in the darunavir/ritonavir 600/100 mg twice daily arm developed substitutions L33F and I50V associated with a 40-fold decreased susceptibility to darunavir. In the darunavir/ritonavir 800/100 mg once daily and darunavir/ritonavir 600/100 mg twice daily groups, isolates from 7 (7/60; 12%) and 4 (4/42; 10%) virologic failures, respectively, developed decreased susceptibility to an NRTI included in the treatment regimen.

Clinical Trials of Darunavir/Ritonavir in Treatment-Naïve Subjects: Clinical trials of darunavir/ritonavir in treatment-naïve subjects: In the 192-week as-treated analysis censoring those who discontinued before Week 4 of the Phase 3 trial TMC114-C211, the percentage of virologic failures (never suppressed, rebounders and discontinued before achieving suppression) was 22% (64/288) in the group of subjects receiving darunavir/ritonavir 800/100 mg once daily compared to 29% (76/263) of subjects receiving lopinavir/ritonavir 800/200 mg per day. In the darunavir/ritonavir arm, emergent PI resistance-associated substitutions were identified in 11 of the virologic failures with post-baseline genotypic data (n = 43). However, none of the darunavir virologic failures had a decrease in darunavir susceptibility (greater than 7-fold change) at failure. In the comparator lopinavir/ritonavir arm, emergent PI resistance-

associated substitutions were identified in 17 of the virologic failures with post-baseline genotypic data (n = 53), but none of the lopinavir/ritonavir virologic failures had decreased susceptibility to lopinavir (greater than 10-fold change) at failure. The reverse transcriptase M184V substitution and/or resistance to emtricitabine, which was included in the fixed background regimen, was identified in 4 virologic failures from the darunavir/ritonavir arm and 7 virologic failures in the lopinavir/ritonavir arm.

Cross-resistance

Cross-resistance among PIs has been observed. Darunavir has a less than 10- fold decreased susceptibility in cell culture against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to these PIs remain susceptible to darunavir.

Darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir in cell culture. However, six of nine darunavir-resistant viruses selected in cell culture from PI-resistant viruses showed a fold change in EC50 values less than 3 for tipranavir, indicative of limited cross-resistance between darunavir and tipranavir.

Cross-resistance between darunavir and nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, fusion inhibitors, CCR5 co-receptor antagonists, or integrase inhibitors is unlikely because the viral targets are different.

Clinical results

Description of Adult Clinical Trial

The evidence of efficacy of darunavir/ritonavir is based on the analyses of 192-week data from a randomized, controlled open-label Phase 3 trial in treatment-naïve (TMC114-C211) HIV-1- infected adult subjects.

Treatment-Naïve Adult Subjects

TMC114-C211: TMC114-C211 is a randomized, controlled, open-label Phase 3 trial comparing darunavir/ritonavir 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day (given as a twice daily or as a once daily regimen) in antiretroviral treatment-naïve HIV-1-infected adult subjects. Both arms used a fixed background regimen consisting of tenofovir disoproxil fumarate 300 mg once daily (TDF) and emtricitabine 200 mg once daily (FTC).

HIV-1-infected subjects who were eligible for this trial had plasma HIV-1 RNA greater than or equal to 5000 copies/mL. Randomization was stratified by screening plasma viral load (HIV-1 RNA less than 100,000 copies/mL or greater than or equal to 100,000 copies/mL) and screening CD4+ cell count (less than 200 cells/mm^3 or greater than or equal to 200 cells/mm^3). Virologic response was defined as a confirmed plasma HIV-1 RNA viral load less than 50 copies/mL. Analyses included 689 subjects in trial TMC114-C211 who had completed 192 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the darunavir/ritonavir arm and the lopinavir/ritonavir arm (see Table 4). Table 4 compares the demographic and baseline characteristics between subjects in the darunavir/ritonavir 800/100 mg once daily arm and subjects in the lopinavir/ritonavir 800/200 mg per day arm in trial TMC114-C211.

Table 4: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C211

	Darunavir/Ritonavir 800/100 mg once daily + TDF/FTC N = 343	**Lopinavir/Ritonavir 800/200 mg per day + TDF/FTC N = 346**
Demographic characteristics		
Median age (years) (range, years)	34 (18-70)	33 (19-68)
Sex		
Male	70%	70%
Female	30%	30%
Race		
White	40%	45%

Black	23%	21%
Hispanic	23%	22%
Asian	13%	11%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA (log10 copies/mL)	4.86	4.84
Median baseline CD4+ cell count (cells/mm3) (range, cells/mm3)	228 (4-750)	218 (2-714)
Percentage of patients with baseline viral load ≥ 100,000 copies/mL	34%	35%
Percentage of patients with baseline CD4+ cell count < 200 cells/mm3	41%	43%

FTC = emtricitabine; TDF = tenofovir disoproxil fumarate

Week 192 outcomes for subjects on darunavir/ritonavir 800/100 mg once daily from trial TMC114-C211 are shown in Table 10.

Table 5: Virologic Outcome of Randomized Treatment of Trial TMC114-C211 at 192 Weeks

	Darunavir/Ritonavir 800/100 mg once daily + TDF/FTC N = 343	**Lopinavir/Ritonavir 800/200 mg per day + TDF/FTC N = 346**
Virologic success HIV-1 RNA < 50 copies/mL	70%[a]	61%
Virologic failure[b]	12%	15%
No virologic data at Week 192 window[c]		
Reasons		
Discontinued trial due to adverse event or death[d]	5%	13%
Discontinued trial for other reasons[e]	13%	12%
Missing data during window[c] but on trial	< 1%	0%

N = total number of subjects with data; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate

[a] 95% CI: 1.9; 16.1

[b] Includes patients who discontinued prior to Week 192 for lack or loss of efficacy and patients who are ≥ 50 copies in the 192-week window and patients who had a change in their background regimen that was not permitted by the protocol.

[c] Window 186-198 Weeks.

[d] Includes patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

[e] Other includes: withdrew consent, loss to follow-up, etc., if the viral load at the time of discontinuation was < 50 copies/mL.

In trial TMC114-C211 at 192 weeks of treatment, the median increase from baseline in CD4+ cell counts was 258 cells/mm^3 in the darunavir/ritonavir 800/100 mg once daily arm and 263 cells/mm^3 in the lopinavir/ritonavir 800/200 mg per day arm. Of the darunavir/ritonavir subjects with a confirmed virologic response of < 50 copies/mL at Week 48, 81% remained undetectable at Week 192 versus 68% with lopinavir/ritonavir. In the 192 week analysis, statistical superiority of the darunavir/ritonavir regimen over the lopinavir/ritonavir regimen was demonstrated for both ITT and OP populations.

Treatment-Experienced Adult Subjects

TMC114-C229: TMC114-C229 is a randomized, open-label trial comparing darunavir/ritonavir 800/100 mg once daily to darunavir/ritonavir 600/100 mg twice daily in treatment-experienced HIV-1-infected patients with screening genotype resistance test showing no darunavir resistance associated substitutions (i.e., V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V) and a screening viral load of greater than 1,000 HIV-1 RNA copies/mL. Both arms used an optimized background regimen consisting of greater than or equal to 2 NRTIs selected by the investigator.

HIV-1-infected subjects who were eligible for this trial were on a highly active antiretroviral therapy regimen (HAART) for at least 12 weeks. Virologic response was defined as a confirmed plasma HIV-1 RNA viral load less than 50 copies/mL. Analyses included 590 subjects who had completed 48 weeks of treatment or discontinued earlier.

Table 6 compares the demographic and baseline characteristics between subjects in the darunavir/ritonavir 800/100 mg once daily arm and subjects in the darunavir/ritonavir 600/100 mg twice daily arm in trial TMC114-C229. No imbalances between the 2 arms were noted.

Table 6: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C229

	Darunavir/Ritonavir 800/100 mg once daily + OBR N = 294	**Darunavir/Ritonavir 600/100 mg twice daily + OBR N = 296**
Demographic characteristics		
Median age (years) (range, years)	40 (18-70)	40 (18-77)
Sex		
Male	61%	67%
Female	39%	33%
Race		
White	35%	37%
Black	28%	24%
Hispanic	16%	20%
Asian	16%	14%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA (log10 copies/mL)	4.19	4.13
Median baseline CD4+ cell count (cells/mm^3) (range, cells/mm^3)	219 (24-1306)	236 (44-864)
Percentage of patients with baseline viral load ≥ 100,000 copies/mL	13%	11%
Percentage of patients with baseline CD4+ cell count < 200 cells/mm^3	43%	39%
Median darunavir fold change (range)[a]	0.50 (0.1-1.8)	0.50 (0.1-1.9)
Median number of resistance- associatedb:		
PI mutations	3	4
NNRTI mutations	2	1
NRTI mutations	1	1
Percentage of subjects susceptible to all available PIs at baseline	88%	86%
Percentage of subjects with number of baseline primary protease inhibitor mutationsb:		
0	84%	84%
1	8%	9%
2	5%	4%
≥ 3	3%	2%
Median number of ARVs previously usedc:		
NRTIs	3	3
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	1	1

OBR = optimized background regimen

[a] Based on phenotype (Antivirogram®).

[b] Johnson VA, Brun-Vézinet F, Clotet B, et al. Update of the drug resistance mutations in HIV- 1: December 2008. Top HIV Med 2008; 16(5): 138-145.

[c] Only counting ARVs, excluding low-dose ritonavir.

Week 48 outcomes for subjects on darunavir/ritonavir 800/100 mg once daily from trial TMC114-C229 are shown in Table 7.

Table 7: Virologic Outcome of Randomized Treatment of Trial TMC114-C229 at 48 Weeks

	Darunavir/Ritonavir 800/100 mg once daily + OBR N = 294	**Darunavir/Ritonavir 600/100 mg twice daily + OBR N = 296**
Virologic success HIV-1 RNA < 50 copies/mL	69%	69%
Virologic failure[a]	26%	23%
No virologic data at Week 48 window[b]		
Reasons		
Discontinued trial due to adverse event or death[c]	3%	4%
Discontinued trial for other reasons[d]	2%	3%
Missing data during window[b] but on trial	0%	< 1%

N = total number of subjects with data; OBR = optimized background regimen

[a] Includes patients who discontinued prior to Week 48 for lack or loss of efficacy, patients who are ≥ 50 copies in the 48-week window, patients who had a change in their background regimen that was not permitted in the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of trial medication) and patients who discontinued for reasons other than AEs/death and lack or loss of efficacy (provided their last available viral load was detectable (HIV RNA ≥ 50 copies/mL).

[b] Window 42-54 Weeks

[c] Patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

[d] Other includes: withdrew consent, loss to follow-up, etc., if the viral load at the time of discontinuation was < 50 copies/mL.

The mean increase from baseline in CD4+ cell counts was comparable for both treatment arms (108 cells/mm^3 and 112 cells/mm^3 in the darunavir/ritonavir 800/100 mg once daily arm and the darunavir/ritonavir 600/100 mg twice daily arm, respectively).

Pediatric Patients

The pharmacokinetic profile, safety and antiviral activity of darunavir/ritonavir were evaluated in a randomized, open-label, multicenter study.

TMC114-C230: Treatment-naïve pediatric subjects between the ages of 12 and less than 18 years and weighing at least 40 kg received the adult recommended dose of darunavir/ritonavir 800/100 mg once daily plus background therapy consisting of at least two non-protease inhibitor antiretroviral drugs.

The 12 randomized pediatric subjects had a median age of 14.4 years (range 12.6 to 17.3 years), and were 33.3% male, 58.3% Caucasian and 41.7% Black. The mean baseline plasma HIV-1 RNA was 4.72 log10 copies/mL, and the median baseline CD4+ cell count was 282 cells/mm^3 (range: 204 to 515 cells/mm^3). Overall, 41.7% of pediatric subjects had baseline plasma HIV-1 RNA ≥ 100,000 copies/mL.

All subjects completed the 48 week treatment period.

The proportion of subjects with HIV-1 RNA less than 50 copies/mL and less than 400 copies/mL was 83.3% and 91.7%, respectively. The mean increase in CD4+ cell count from baseline was 221×10^6 cells/L.

5.2 Pharmacokinetic properties

Pharmacokinetics in Adults:
Darunavir and Ritonavir Tablets: The mean systemic exposures of darunavir and ritonavir from the combination tablets (2 x 400 mg/50 mg) were comparable to that from PREZISTA® tablets of Janssen (containing darunavir 800 mg) and NORVIR® tablets of AbbVie (containing ritonavir 100 mg), respectively, when single doses were administered to healthy subjects under fasted and fed conditions.

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 4 displays the population pharmacokinetic estimates of darunavir after oral administration of darunavir/ritonavir 800/100 mg once daily (based on sparse sampling in 335 patients in trial TMC114-C211 and 280 patients in trial TMC114-C229) to HIV-1-infected patients.

Table 8: Population Pharmacokinetic Estimates of Darunavir at Darunavir/Ritonavir 800/100 mg Once Daily (Trial TMC114-C211, 48-Week Analysis and Trial TMC114-C229, 48-Week Analysis)

	Darunavir/Ritonavir 800/100 mg Once Daily	
Parameter	**TMC114-C211 N = 335**	**TMC114-C229 N = 280**
AUC_{24h} (ng.h/mL)		
Mean ± Standard Deviation	93026 ± 27050	93334 ± 28626
Median (Range)	87854 (45000-219240)	87788 (45456-236920)
C_{0h} (ng/mL)		
Mean ± Standard Deviation	2282 ± 1168	2160 ± 1201
Median (Range)	2041 (368-7242)	1896 (184-7881)

N = number of subjects with data

Absorption and Bioavailability:
Darunavir, co-administered with 100 mg ritonavir twice daily, was absorbed following oral administration with a Tmax 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 Cmax 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 g fat) to 928 Kcal (56 g 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.

Specific 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 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 and ritonavir has not been evaluated *(see Dosage and Administration and Use in Specific Populations)*.

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 Use in Specific Populations)*.

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 Use in Specific Populations)*.

Pediatric Patients: The pharmacokinetics of darunavir in combination with ritonavir in 12 antiretroviral treatment-naïve HIV-1-infected pediatric subjects 12 to less than 18 years of age and weighing at least 40 kg receiving darunavir/ritonavir 800/100 mg once daily resulted in similar darunavir exposures when compared to the darunavir exposure achieved in treatment- naïve adults receiving darunavir/ritonavir 800/100 mg once daily.

The population pharmacokinetic parameters in pediatric subjects with darunavir/ritonavir administered once daily are summarized in the table below:

Table 9: Population Pharmacokinetic Estimates of Darunavir Exposure (Trial TMC114-C230) Following Administration of Doses

Parameter	**Darunavir/Ritonavir once daily**
	TMC114-C230$_a$ N = 12
AUC24h (ng·h/mL)	
Mean ± Standard Deviation	84390 ± 23587
Median (Range)	86741 (35527–123325)
C_{0h} (ng/mL)	
Mean ± Standard Deviation	2141 ± 865

Median (Range)	2234 (542–3776)

N = number of subjects with data

[a] Summary statistics for population pharmacokinetic parameter estimates for DRV after administration of DRV/rtv at 800/100 mg once daily in treatment-naïve HIV-1 infected subjects from 12 to < 18 years of age – Week-48 Analyses.

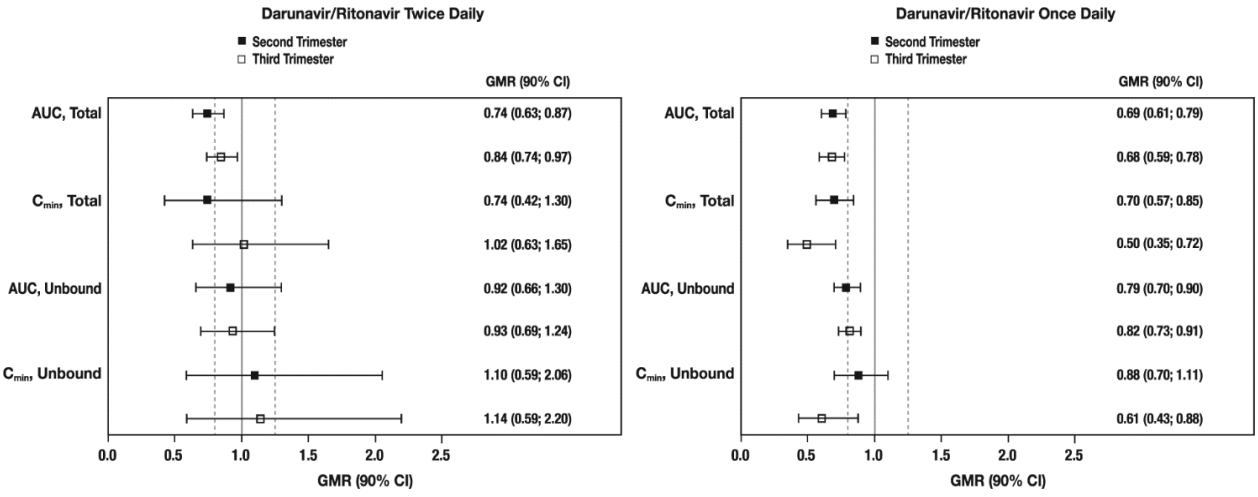
Pregnancy and Postpartum: The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 800/100 mg once daily as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum (see Table 6 and Figure 1).

Table 10: 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 = 17)**	**3rd Trimester of pregnancy (n = 15)**	**Postpartum (6-12 Weeks) (n = 16)**
C_{max}, ng/mL	4964 ± 1505	5132 ± 1198	7310 ± 1704
AUC_{24h}, ng.h/mL	62289 ± 16234	61112 ± 13790	92116 ± 29241
C_{min}, ng/mL	1248 ± 542	1075 ± 594	1473 ± 1141

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.

5.3 Preclinical safety data

Carcinogenesis

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg was administered to rats. A dose-related

increase in the incidence of hepatocellular adenomas and carcinomas were observed in males and females of both species as well as an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on AUC) were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg once daily).

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4 times for males that of the exposure in humans with the recommended therapeutic dose (100 mg daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 7 times for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 7 times that of the exposure in humans with the recommended therapeutic dose. Based on the exposures achieved in the animal studies, the significance of the observed effects should be of low concern.

Mutagenesis

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reserve mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Impairment of Fertility

No effects on fertility or early embryonic development were observed with darunavir in rats.

Ritonavir produced no effects on fertility in rats at drug exposures approximately 5 times (male) and 7 times (female) higher than the 100 mg daily clinical dose. Higher dosages were not feasible due to hepatic toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline Cellulose, Crospovidone, Copovidone, Colloidal Silicon Dioxide, Ferric Oxide Yellow, Sodium Stearyl Fumarate, Sorbitan Monolaurate, Sodium Chloride.

Tablet film-coat

Hypromellose, Titanium Dioxide, Macrogols, Talc, Hydroxypropyl Cellulose, Polysorbate 80, Colloidal anhydrous silica, Iron Oxide Yellow, Iron Oxide Red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from light.

6.5 Nature and contents of container

Round, opaque high-density polyethylene (HDPE) bottle with opaque polypropylene closure with wad containing aluminium induction sealing liner along with silica gel desiccant, containing 60 tablets.

6.6 Special precautions for disposal

No special requirements.

7. Manufacturer

Mylan Laboratories Limited
F-4 & F-12, MIDC, Malegaon, Sinnar,
Nashik - 422 113, Maharashtra, INDIA

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