

## 1. NAME OF THE MEDICINAL PRODUCT

Darunavir Tablets 400 mg  
Darunavir Tablets 600 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Darunavir tablets 400 mg

Each film-coated tablet contains darunavir ethanolate equivalent to darunavir.....400 mg

### Darunavir tablets 600 mg

Each film-coated tablet contains darunavir ethanolate equivalent to darunavir.....600 mg

Excipient with known effect: Sunset Yellow FCF Aluminium Lake

## 3. PHARMACEUTICAL FORM

Film-coated tablet

### **Description**

Darunavir Tablet 400mg

Light orange coloured, oval shaped, biconvex, film coated tablet, debossed with 'DNL' on one side and '400' on other side.

### **Darunavir Tablet 600mg**

Orange coloured, oval shaped, biconvex, film coated tablet, debossed with 'DNL' on one side and '600' on other side.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Darunavir tablets, co-administered with ritonavir (darunavir/ritonavir), in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adult and pediatric patients 3 years of age and older or weighing  $\geq 15$  kg (see section 5.1).

Darunavir tablets, co-administered with ritonavir (darunavir/ritonavir), in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adult and pediatric patients 3 years of age and older (see section 5.1).

### 4.2. Posology and method of administration

#### **Testing Prior to Initiation of Darunavir/ritonavir**

In treatment-experienced patients, treatment history, genotypic and/or phenotypic testing is recommended to assess drug susceptibility of the HIV-1 virus (see section 5.1). Refer *below* for dosing recommendations.

Appropriate laboratory testing such as serum liver biochemistries should be conducted prior to initiating therapy with darunavir/ritonavir (see section 4.4).

#### **Monitoring During Treatment with Darunavir/ritonavir**

Patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases should be monitored for elevation in serum liver

biochemistries, especially during the first several months of darunavir/ritonavir treatment (see section 4.4).

### **Recommended Dosage in Adult Patients**

Darunavir must be co-administered with ritonavir to exert its therapeutic effect. Failure to correctly co-administer darunavir with ritonavir will result in plasma levels of darunavir that will be insufficient to achieve the desired antiviral effect and will alter some drug interactions.

#### Treatment-Naïve Adult Patients

The recommended oral dose of darunavir is 800 mg (two 400 mg tablet) taken with ritonavir 100 mg (one 100 mg tablet or capsule or 1.25 mL of a 80 mg per mL ritonavir oral solution) once daily and with food.

#### Treatment-Experienced Adult Patients

The recommended oral dosage for treatment-experienced adult patients is summarized in Table 1.

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

**Table 1: Recommended Darunavir/ritonavir Dosage in Treatment-Experienced Adult Patients**

<b>Baseline Resistance</b>	<b>Darunavir tablets with ritonavir tablets or capsule</b>
With no darunavir resistance associated substitutions*	800 mg (two 400 mg darunavir tablet) with one 100 mg ritonavir tablet/capsule, taken once daily with food
With at least one darunavir resistance associated substitutions*, or with no baseline resistance information	One 600 mg darunavir tablet with one 100 mg ritonavir tablet/capsule, taken twice daily with food

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

### **Recommended Dosage During Pregnancy**

The recommended dosage in pregnant patients is 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 twice daily darunavir 600 mg with ritonavir 100 mg may compromise tolerability or compliance.

### **Recommended Dosage in Pediatric Patients (age 3 to less than 18 years)**

Healthcare professionals should pay special attention to accurate dose selection of darunavir tablets, transcription of the medication order, dispensing information and dosing instruction to minimize risk for medication errors, overdose, and underdose.

Prescribers should select the appropriate dose of darunavir/ritonavir for each individual child based on body weight (kg) and should not exceed the recommended dose for adults.

Before prescribing darunavir, children weighing greater than or equal to 15 kg should be assessed for the ability to swallow tablets.

The recommended dose of darunavir/ritonavir for pediatric patients (3 to less than 18 years of age and weighing  $\geq 15$  kg is based on body weight (see Tables 2 and 3) and should not exceed the recommended adult dose. Darunavir should be taken with ritonavir and with food.

The recommendations for the darunavir/ritonavir dosage regimens were based on pediatric clinical trial data and population pharmacokinetic modelling and simulation (see sections 5.1 and 5.2).

Dosing Recommendations for Treatment-Naïve Pediatric Patients or Antiretroviral Treatment-Experienced Pediatric Patients with No Darunavir Resistance Associated Substitutions

*Pediatric patients weighing at least 15 kg*

Pediatric patients weighing at least 15 kg can be dosed with darunavir oral tablet(s) using the following table:

**Table 2: Recommended Dose for Pediatric Patients Weighing At Least 15 kg who are Treatment-Naïve or Treatment-Experienced with No Darunavir Resistance Associated Substitutions\***

<b>Body weight (kg)</b>	<b>Darunavir tablet(s) and ritonavir capsules or tablets (100 mg)</b>
	<b>Dose: once daily with food</b>
Greater than or equal to 15 kg to less than 30 kg	Darunavir 600 mg with ritonavir 100 mg
Greater than or equal to 30 kg to less than 40 kg	Darunavir 675 mg with ritonavir 100 mg
Greater than or equal to 40 kg	Darunavir 800 mg with ritonavir 100 mg

\* darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

Dosing Recommendations for Treatment-Experienced Pediatric Patients with At Least One Darunavir Resistance Associated Substitutions

*Pediatric patients weighing at least 40 kg*

Pediatric patients weighing at least 40 kg can be dosed with darunavir oral tablet(s) using the following table:

**Table 3: Recommended Dose for Pediatric Patients Weighing At Least 40 kg Who are Treatment-Experienced with At Least One Darunavir Resistance Associated Substitution\***

	<b>Formulation: Darunavir tablet(s) and ritonavir tablets, capsules (100 mg) or oral solution (80 mg/mL)</b>
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<b>Body weight (kg)</b>	<b>Dose: twice daily with food</b>
Greater than or equal to 40 kg	Darunavir 600 mg with ritonavir 100 mg

\* darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The use of darunavir/ritonavir in pediatric patients below 3 years of age is not recommended (see sections 4.4 and 5.1).

### **Not Recommended in Patients with Severe Hepatic Impairment**

No dosage adjustment is required in patients with mild or moderate hepatic impairment. No data are available regarding the use of darunavir/ritonavir when co-administered to subjects with severe hepatic impairment; therefore, darunavir/ritonavir is not recommended for use in patients with severe hepatic impairment (see sections 5.1 and 5.2).

### **4.3. Contraindications**

Co-administration of darunavir/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These drugs and other contraindicated drugs (which may lead to reduced efficacy of darunavir) are listed in Table 4 (see section 4.5). Due to the need for co-administration of darunavir with ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

**Table 4: Drugs That Are Contraindicated with Darunavir/Ritonavir**

<b>Drug class</b>	<b>Drugs within class that are contraindicated with Darunavir/ritonavir</b>
Alpha 1-adrenoreceptor antagonist	alfuzosin
Antianginal	ranolazine
Antiarrhythmic	dronedaron
Anti-gout	colchicine
Antimycobacterial	rifampin
Antipsychotics	lurasidone
	pimozide
Ergot derivative	dihydroergotamine, ergotamine, methylergonovine
GI motility agent	cisapride
Sedative/hypnotics	Orally administered midazolam, triazolam
Herbal product	St. John's wort ( <i>Hypericum perforatum</i> )
Hepatitis C direct-acting antiviral	elbasvir/grazoprevir
HMG-CoA reductase inhibitors	lovastatin, simvastatin
PDE-5 inhibitor	sildenafil for treatment of pulmonary arterial hypertension

#### **4.4. Special warnings and precautions for use**

##### **Importance of Co-administration with Ritonavir**

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

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

##### **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/ritonavir and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of darunavir/ritonavir treatment.

Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, and hepatomegaly) in patients on darunavir/ritonavir should prompt consideration of interruption or discontinuation of treatment.

##### **Severe Skin Reactions**

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

Rash (all grades, regardless of causality) occurred in 10.3% of subjects treated with darunavir/ritonavir (see section 4.8). 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 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/ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving darunavir/ritonavir, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of darunavir/ritonavir, respectively. These interactions may lead to:

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

See Table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations (see section 4.5). Consider the potential for drug interactions prior to and during darunavir/ritonavir therapy; review concomitant medications during darunavir/ritonavir therapy; and monitor for the adverse reactions associated with the concomitant drugs (see sections 4.3 and 4.5).

### **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.

### **Fat Redistribution**

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

### **Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including darunavir. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as

*Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

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

### **Hemophilia**

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with 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.

### **Not Recommended in Pediatric Patients Below 3 Years of Age**

Darunavir/ritonavir in pediatric patients below 3 years of age is not recommended in view of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age (see sections 5.1 and 5.2).

### **Excipient**

This medicine contains sunset yellow FCF aluminium lake which may cause allergic reactions.

## **4.5. Interaction with other medicinal products and other forms of interaction**

### **Potential for Darunavir/ritonavir to Affect Other Drugs**

Darunavir co-administered with ritonavir is an inhibitor of CYP3A, CYP2D6, and P-gp. Co-administration of darunavir and ritonavir with drugs that are primarily metabolized by CYP3A and CYP2D6, or are transported by P-gp may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see Table 5).

### **Potential for Other Drugs to Affect Darunavir**

Darunavir and ritonavir are metabolized by CYP3A. *In vitro* data indicate that darunavir may be a P-gp substrate. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir and ritonavir and other drugs that inhibit CYP3A, or P-gp may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (see Table 5).

### **Established and Other Potentially Significant Drug Interactions**

Table 5 provides dosing recommendations as a result of drug interactions with darunavir/ritonavir. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy (see sections 4.3 and 5.2).

### **Table 5: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction**

**(see sections 4.3 for a complete list of contraindicated drugs)**

[see section 5.2 for Magnitude of Interaction, Tables 24 and 25]

Concomitant Drug Class Drug Name	Effect on Concentration of Darunavir Or Concomitant	Clinical Comment
<b>HIV-1-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</b>		
didanosine	↔ darunavir ↔ didanosine	Didanosine should be administered one hour before or two hours after darunavir/ritonavir (which are administered with food).
<b>HIV-1-Antiviral Agents: HIV-Protease Inhibitors (PIs)</b>		
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 has not been established.
lopinavir/ritonavir	↓ darunavir ↔ lopinavir	Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer lopinavir/ritonavir and darunavir, with or without ritonavir.
saquinavir	↓ darunavir ↔ saquinavir	Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer saquinavir and darunavir, with or without ritonavir.
Other HIV protease inhibitors, except atazanavir (see section 4.5)		As coadministration with darunavir/ritonavir has not been studied, coadministration is not recommended.
<b>HIV-1-Antiviral Agents: CCR5 co-receptor antagonists</b>		
maraviroc	↑ maraviroc	When used in combination with darunavir/ritonavir, the dose of maraviroc should be 150 mg twice daily.
<b>Other Agents</b>		



<p><b>Alpha 1-adrenoreceptor antagonist:</b></p> <p><b>alfuzosin</b></p> <p><b>Antianginal:</b></p> <p><b>ranolazine</b></p> <p><b>Antiarrhythmics:</b></p> <p><b>dronedarone</b></p> <p>e.g. amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine</p> <p>digoxin</p>	<p>↑ alfuzosin</p> <p>↑ ranolazine</p> <p>↑ dronedarone</p> <p>↑ antiarrhythmics</p> <p>↑ digoxin</p>	<p>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.</p> <p>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.</p> <p>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias</p> <p>Therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with darunavir/ritonavir.</p> <p>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.</p>
<p><b>Antibacterial:</b></p> <p>clarithromycin</p>	<p>↔ darunavir</p> <p>↑ clarithromycin</p>	<p>No dose adjustment of the combination is required for patients with normal renal function. For co-administration of clarithromycin and darunavir/ritonavir in patients with renal impairment, the following dose adjustments should be considered:</p> <ul style="list-style-type: none"><li>• For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%.</li><li>• For subjects with CLcr of &lt;30 mL/min, the dose of clarithromycin should be reduced by 75%.</li></ul>

<p><b>Anticoagulants:</b>  <u>Direct Oral Anticoagulants (DOACs)</u>  apixaban</p> <p>rivaroxaban</p> <p>betrixaban  dabigatran  edoxaban</p> <p><u>Other Anticoagulants</u>  warfarin</p>	<p>↑ apixaban</p> <p>↑ rivaroxaban</p> <p>↔ betrixaban  ↔ dabigatran  ↔ edoxaban</p> <p>↓ warfarin  ↔ darunavir</p>	<p>Due to potentially increased bleeding risk, dosing recommendations for coadministration of apixaban with darunavir depends on the apixaban dose. Refer to apixaban dosing instructions for coadministration with strong CYP3A and P-gp inhibitors in apixaban prescribing information.</p> <p>Co-administration of darunavir /ritonavir and rivaroxaban is not recommended because it may lead to an increased bleeding risk.</p> <p>No dose adjustment is needed when betrixaban, dabigatran, or edoxaban is co-administered with darunavir.</p> <p>Warfarin concentrations are decreased when co-administered with darunavir/ritonavir. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with darunavir/ritonavir.</p>
<p><b>Anticonvulsants:</b>  carbamazepine</p>	<p>↔ darunavir  ↑ carbamazepine</p>	<p>The dose of either darunavir/ritonavir or carbamazepine does not need to be adjusted when initiating co-administration with darunavir/ritonavir and carbamazepine. Clinical monitoring of carbamazepine concentrations and its dose titration is recommended to achieve the desired clinical</p>
<p>clonazepam</p> <p>phenobarbital, phenytoin</p>	<p>↑ clonazepam</p> <p>↔ darunavir  ↓ phenytoin  ↓ phenobarbital</p>	<p>Clinical monitoring of anticonvulsants that are metabolized by CYP3A is recommended.</p> <p>Phenytoin and phenobarbital levels should be monitored when co-administering with darunavir/ritonavir.</p>

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

<p><b>Anti-gout:</b> colchicine</p>	<p>↑ colchicine</p>	<p>Co-administration is contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions.</p> <p><u>For patients without renal or hepatic impairment:</u></p> <ul style="list-style-type: none"> <li>• <u>Treatment of gout-flares – co-administration of colchicine in patients on darunavir/ritonavir:</u> 0.6 mg (1 tablet) <math>\times</math> 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days.</li> <li>• <u>Prophylaxis of gout-flares – co-administration of colchicine in patients on darunavir/ritonavir:</u> 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.</li> <li>• <u>Treatment of familial Mediterranean fever – co-administration of colchicine in patients on darunavir/ritonavir:</u></li> <li>• maximum daily dose of 0.6 mg (one tablet) once a day</li> </ul>
<p><b>Antimalarial:</b> artemether/lumefantrine</p>	<p>↓ artemether ↓ dihydroartemisinin ↑ lumefantrine ↔ darunavir</p>	<p>The combination of darunavir/ritonavir and artemether/lumefantrine can be used without dose adjustments. However, the combination should be used with caution as increased lumefantrine exposure may increase the risk of QT prolongation.</p>
<p><b>Antimycobacterials:</b> rifampin</p>	<p>↓ darunavir ↓ cobicistat</p>	<p>Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance</p>

<p>rifabutin</p> <p>(The reference regimen for rifabutin was 300 mg once daily.)</p> <p>rifapentine</p>	<p>↑ darunavir ↑ rifabutin ↑ 25-O-desacetyl-rifabutin</p> <p>↓ darunavir</p>	<p>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.</p> <p>Co-administration of darunavir/ritonavir with rifapentine is not</p>
<p><b>Antineoplastics:</b> dasatinib, nilotinib</p> <p>vinblastine, vincristine</p>	<p>↑ antineoplastics</p>	<p>A decrease in the dosage or an adjustment of the dosing interval of dasatinib and nilotinib may be necessary for patients. Please refer to the dasatinib and nilotinib prescribing information for dosing instructions.</p> <p>For vincristine and vinblastine, consideration should be given to temporarily withholding the ritonavir-containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when darunavir/ritonavir is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consideration should be given to initiating a revised</p>

<p><b>Antipsychotics:</b></p> <p>lurasidone</p> <p>pimozide</p> <p>quetiapine</p> <p>e.g. perphenazine, risperidone, thioridazine</p>	<p>↑lurasidone</p> <p>↑pimozide</p> <p>↑ quetiapine</p> <p>↑antipsychotics</p>	<p>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.</p> <p>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.</p> <p>Initiation of darunavir with ritonavir in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures. If co-administration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring.</p> <p><u>Initiation of quetiapine in patients taking darunavir with ritonavir:</u> Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.</p> <p>A decrease in the dose of antipsychotics that are metabolized by CYP3A or CYP2D6 may be needed when co-administered with darunavir/ritonavir.</p>
<p><b>β-Blockers:</b> e.g. carvedilol, metoprolol, timolol</p>	<p>↑ beta-blockers</p>	<p>Clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with darunavir/ritonavir and a lower dose of the beta blocker should be considered.</p>
<p><b>Calcium Channel Blockers:</b> amlodipine, diltiazem, felodipine, nifedipine, verapamil</p>	<p>↑ calcium channel blockers</p>	<p>Clinical monitoring of patients is recommended.</p>

<p><b>Systemic/Inhaled/ Nasal/ Ophthalmic Corticosteroids:</b>  <b>e.g.</b>  betamethasone  budesonide  ciclesonide  dexamethasone  fluticasone  methylprednisolone  mometasone  prednisone  triamcinolone</p>	<p>↓ darunavir  ↑ corticosteroids</p>	<p>Co-administration of darunavir/ritonavir with systemic dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss of therapeutic effect and development of resistance to darunavir. Consider alternative corticosteroids.</p> <p>Co-administration with corticosteroids of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression.</p> <p>Alternative corticosteroids including beclomethasone and prednisolone (for which PK and/or PD are less affected by strong CYP3A inhibitors relative to other steroids) should be considered as alternatives for</p>
<p><b>Endothelin receptor antagonist:</b>  bosentan</p>	<p>↑ bosentan</p>	<p><u>Co-administration of bosentan in patients on darunavir/ritonavir:</u>  In patients who have been receiving darunavir/ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.</p> <p><u>Co-administration of darunavir/ritonavir in patients on bosentan:</u>  Discontinue use of bosentan at least 36 hours prior to initiation of darunavir/ritonavir. After at least 10 days following the initiation of darunavir/ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.</p>
<p><b>Ergot derivatives:</b>  e.g. dihydroergotamine, ergotamine, methylergonovine</p>	<p>↑ ergot derivatives</p>	<p>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.</p>

<p><b>GI motility agent:</b> cisapride</p>	<p>↑cisapride</p>	<p>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.</p>
<p><b>Hepatitis C virus (HCV):</b> <u>Direct-Acting Antivirals:</u> elbasvir/grazoprevir  simeprevir</p>	<p>↑elbasvir/ grazoprevir  ↑ simeprevir ↑ darunavir</p>	<p>Co-administration is contraindicated due to potential for the increased risk of alanine transaminase (ALT) elevations.  Co-administration of darunavir/ritonavir and</p>
<p><b>Herbal product:</b> St. John's wort (<i>Hypericum perforatum</i>)</p>	<p>↓darunavir ↓cobicistat</p>	<p>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.</p>
<p><b>Immunosuppressants:</b> e.g. cyclosporine, tacrolimus, sirolimus  <b>Immunosuppressant/ neoplastic:</b> everolimus</p>	<p>↑ immunosuppressants</p>	<p>Therapeutic concentration monitoring of the immunosuppressive agent is recommended when co-administered with darunavir/ritonavir.  Co-administration of everolimus and darunavir/ritonavir is not</p>
<p><b>Inhaled beta agonist:</b> salmeterol</p>	<p>↑ salmeterol</p>	<p>Co-administration of salmeterol and darunavir/ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations</p>



<p><b>Lipid Modifying Agents:</b></p> <p><u>HMG-CoA reductase inhibitors:</u> lovastatin, simvastatin</p> <p>atorvastatin, pravastatin, rosuvastatin</p> <p><u>Other lipid modifying agents:</u> lomitapide</p>	<p>↑ lovastatin ↑ simvastatin</p> <p>↑ HMG-CoA reductase inhibitors</p> <p>↑ lomitapide</p>	<p>Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis.</p> <p>Co-administration of darunavir /ritonavir with HMG-Co A reductase inhibitors may lead to adverse events such as myopathy. Titrate atorvastatin, pravastatin or rosuvastatin dose carefully and use the lowest necessary dose while monitoring for adverse events. Do not exceed atorvastatin 20 mg/ day.</p> <p>Co-administration is contraindicated due to potential for markedly increased transaminase</p>
<p><b>Narcotic analgesics metabolized by CYP3A:</b> e.g. fentanyl, oxycodone</p>	<p>↑ fentanyl ↑ oxycodone</p>	<p>Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A-metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended with co-administration</p>
<p>tramadol</p>	<p>↑ tramadol</p>	<p>A dose decrease may be needed for tramadol with concomitant use.</p>
<p><b>Narcotic analgesics/ treatment of opioid dependence:</b> buprenorphine, buprenorphine/naloxone</p>	<p>↔ buprenorphine, naloxone ↑ norbuprenorphine (metabolite)</p>	<p>No dose adjustment for buprenorphine or buprenorphine/naloxone is required with concurrent administration of darunavir/ ritonavir. Clinical monitoring is recommended if darunavir/ ritonavir and buprenorphine or buprenorphine/naloxone are coadministered.</p>
<p>methadone</p>	<p>↓ methadone</p>	<p>No adjustment of methadone dosage is required when initiating co-administration of darunavir/ritonavir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients.</p>

<p><b>Oral contraceptives / estrogen:</b> ethinyl estradiol, norethindrone, drospirenone</p>	<p>↓ ethinyl estradiol ↓ norethindrone drospirenone: effects unknown</p>	<p>Effective alternative (non-hormonal) contraceptive method or barrier method of contraception is recommended [see <i>Use in Specific Populations (8.3)</i>]. 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.</p>
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<p><b>PDE-5 inhibitors:</b> e.g. avanafil, sildenafil, tadalafil, vardenafil</p>	<p>↑ PDE-5 inhibitors (only the use of sildenafil at doses used for treatment of erectile dysfunction has been studied with darunavir/ritonavir)</p>	<p>Co-administration with darunavir/ritonavir may result in an increase in PDE-5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances and priapism.</p> <p><u>Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):</u> Co-administration with sildenafil used for PAH is contraindicated due to potential for sildenafil associated adverse reactions (which include visual disturbances, hypotension, prolonged erection, and syncope). The following dose adjustments are recommended for use of tadalafil with darunavir/ritonavir:</p> <ul style="list-style-type: none"> <li>• <u>Co-administration of tadalafil in patients on darunavir/ritonavir:</u> In patients receiving darunavir/ritonavir for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</li> <li>• <u>Co-administration of darunavir/ritonavir in patients on tadalafil:</u> Avoid use of tadalafil during the initiation of darunavir/ritonavir. Stop tadalafil at least 24 hours prior to starting darunavir/ritonavir. After at least one week following the initiation of darunavir/ritonavir, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</li> </ul> <p><u>Use of PDE-5 inhibitors for erectile dysfunction:</u> Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for</p>
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<b>Platelet aggregation inhibitor: ticagrelor</b>	↑ ticagrelor	Co-administration of darunavir/ritonavir and ticagrelor is not
<b>Proton pump inhibitor: omeprazole</b>	↓ omeprazole ↔ darunavir	When omeprazole is co-administered with darunavir/ritonavir, monitor patients for decreased efficacy of omeprazole. Consider increasing the omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg per day of omeprazole.
<p><b>Sedatives/hypnotics:</b></p> <p>orally administered midazolam, triazolam</p> <p>metabolized by CYP3A e.g. buspirone, diazepam, estazolam, zolpidem</p> <p>parenterally administered midazolam</p>	<p>↑ midazolam ↑ triazolam</p> <p>↑ sedatives/hypnotics</p>	<p>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. Triazolam and orally administered midazolam are extensively metabolized by CYP3A. Co-administration of triazolam or orally administered midazolam with darunavir may cause large increases in the concentrations of these benzodiazepines.</p> <p>Titration is recommended when co-administering darunavir/ritonavir with sedatives/hypnotics metabolized by CYP3A and a lower dose of the sedatives/hypnotics should be considered with monitoring for adverse events.</p> <p>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</p>

### Drugs without Clinically Significant Interactions with Darunavir

No dosage adjustments are recommended when darunavir/ritonavir is co-administered with the following medications: atazanavir, dolutegravir, efavirenz, etravirine, nevirapine,

nucleoside reverse transcriptase inhibitors (abacavir, emtricitabine, emtricitabine/tenofovir alafenamide, lamivudine, stavudine, tenofovir disoproxil fumarate, zidovudine), pitavastatin, raltegravir, ranitidine, or rilpivirine.

#### 4.6. Fertility, pregnancy and lactation

##### **Pregnancy**

###### Risk Summary

Available limited data from the APR show no difference in rate of overall birth defects for darunavir (2.7%) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) [see Data]. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks gestation.

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

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

###### Clinical Considerations

The recommended dosage in pregnant patients is 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 twice daily darunavir 600 mg with ritonavir 100 mg may compromise tolerability or compliance (see sections 4.2 and 5.2).

###### Data

###### *Human Data*

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

The pharmacokinetic data demonstrate that exposure to darunavir and ritonavir as part of an antiretroviral regimen was lower during pregnancy compared with postpartum (6-12 weeks). Exposure reductions during pregnancy were greater for the once daily regimen as compared to the twice daily regimen (see section 5.2).

Virologic response was preserved. In the BID arm, the proportion of subjects with HIV-1 RNA <50 copies/mL were 35% (6/17) at baseline, 59% (10/17) through the third trimester visit, and 59% (10/17) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥50 copies/mL for 12% (2/17) of subjects and were missing for 5 subjects (1 subject discontinued prematurely due to virologic failure). In the QD arm, the proportion of subjects with HIV-1 RNA <50

copies/mL were 59% (10/17) at baseline, 82% (14/17) through the third trimester visit, and 82% (14/17) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA  $\geq$ 50 copies/mL for none of the subjects and were missing for 3 subjects (1 subject discontinued prematurely due to virologic failure).

Darunavir/ritonavir was well tolerated during pregnancy and postpartum. There were no new clinically relevant safety findings compared with the known safety profile of darunavir/ritonavir in HIV-1-infected adults.

Among the 29 infants with HIV test results available data, born to the 29 HIV-infected pregnant women who completed trial through delivery or postpartum period, all 29 infants had test results that were negative for HIV-1 at the time of delivery and/or through 16 weeks postpartum. All 29 infants received antiretroviral prophylactic treatment containing zidovudine.

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

The prevalence of birth defects in live births was 2.6% (95% CI: 1.2% to 4.7%) with first trimester exposure to darunavir containing regimens and 1.7% (95% CI: 0.5% to 4.4%) with second/third trimester exposure to darunavir containing regimens.

#### *Animal Data*

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

#### **Lactation**

##### Risk Summary

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

There are no data on the presence of darunavir in human milk, the effects on the breastfed infant, or the effects on milk production. Darunavir is present in the milk of lactating rats [see *Data*]. Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving darunavir (see section 5.1).

##### Data

#### *Animal Data*

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

## **Females and Males of Reproductive Potential**

### Contraception

Use of darunavir may reduce the efficacy of combined hormonal contraceptives and the progestin only pill. Advise patients 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 section 4.5).

### **4.7. Effects on ability to drive and use machines**

Darunavir in combination with cobicistat or 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 cobicistat or low dose ritonavir and should be borne in mind when considering a patient's ability to drive or operate machinery

### **4.8. Undesirable effects**

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

- Hepatotoxicity (see section 4.4)
- Severe Skin Reactions (see section 4.4)
- Diabetes Mellitus/Hyperglycemia (see section 4.4)
- Fat Redistribution (see section 4.4)
- Immune Reconstitution Syndrome (see section 4.4)
- Hemophilia (see section 4.4)

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

### **Clinical Trials Experience**

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

#### Treatment 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. 2.3% of subjects in the darunavir/ritonavir arm discontinued treatment due to ADRs.

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 6 and subsequent text below the table.

**Table 6: Selected Clinical Adverse Drug Reactions to Darunavir/ritonavir 800/100 mg Once Daily\* 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
<b>Gastrointestinal Disorders</b>		
Abdominal pain	6%	6%
Diarrhea	9%	16%
Nausea	4%	4%
Vomiting	2%	4%
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	< 1%	3%
<b>Metabolism and Nutrition Disorders</b>		
Anorexia	2%	< 1%
<b>Nervous System Disorders</b>		
Headache	7%	6%
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	6%	7%

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

\* 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 7.

**Table 7: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects\* (Trial TMC114-C211)**



Laboratory parameter %	Limit	darunavir/ritonavir 800/100 mg once daily + TDF/FTC	lopinavir/ritonavir 800/200 mg per day + TDF/FTC
<b>Biochemistry</b>			
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 \* Grade 4 data not applicable in Division of AIDS grading scale.

#### Treatment-Experienced Adults: TMC114-C214

The safety assessment is based on all safety data from the Phase 3 trial TMC114-C214 comparing darunavir/ritonavir 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in 595 antiretroviral treatment-experienced HIV-1-infected adult subjects. The total mean exposure for subjects in the darunavir/ritonavir 600/100 mg twice daily arm and in the lopinavir/ritonavir 400/100 mg twice daily arm was 80.7 and 76.4 weeks, respectively.

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

ADRs to darunavir/ritonavir 600/100 mg twice daily of at least moderate intensity (greater than or equal to Grade 2) in antiretroviral treatment-experienced HIV-1-infected adult subjects are presented in Table 8 and subsequent text below the table.

**Table 8: Selected Clinical Adverse Drug Reactions to Darunavir/ritonavir 600/100 mg Twice Daily\* of at Least Moderate Intensity (≥ Grade 2) Occurring in ≥ 2% of Antiretroviral Treatment-Experienced HIV-1-Infected Adult Subjects (Trial TMC114-C214)**

<b>System organ class, preferred term, %</b>	<b>darunavir/ritonavir 600/100 mg twice daily + OBR N = 298</b>	<b>lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297</b>
<b>Gastrointestinal Disorders</b>		
Abdominal distension	2%	< 1%
Abdominal pain	6%	3%
Diarrhea	14%	20%
Dyspepsia	2%	1%
Nausea	7%	6%
Vomiting	5%	3%
<b>General Disorders and Administration Site Conditions</b>		
Asthenia	3%	1%
Fatigue	2%	1%
<b>Metabolism and Nutrition Disorders</b>		
Anorexia	2%	2%
Diabetes mellitus	2%	< 1%
<b>Nervous System Disorders</b>		
Headache	3%	3%
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	7%	3%

N=total number of subjects per treatment group; OBR=optimized background regimen

\* Excluding laboratory abnormalities reported as ADRs

#### *Less Common Adverse Reactions*

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

*Gastrointestinal Disorders:* acute pancreatitis, flatulence

*Musculoskeletal and Connective Tissue Disorders:* myalgia

*Psychiatric Disorders:* abnormal dreams

*Skin and Subcutaneous Tissue Disorders:* pruritus, urticaria

#### *Laboratory Abnormalities*

Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir 600/100 mg twice daily are presented in Table 9.

**Table 9: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Experienced HIV-1-Infected Adult Subjects\* (Trial TMC114-C214)**

<b>Laboratory parameter, %</b>	<b>Limit</b>	<b>darunavir/ ritonavir 600/100 mg twice daily + OBR</b>	<b>lopinavir/ ritonavir 400/100 mg twice daily + OBR</b>
<b>Biochemistry</b>			
Alanine Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	7%	5%
Grade 3	> 5.0 to ≤ 10.0 X ULN	2%	2%
Grade 4	> 10.0 X ULN	1%	2%
Aspartate Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	6%	6%
Grade 3	> 5.0 to ≤ 10.0 X ULN	2%	2%
Grade 4	> 10.0 X ULN	< 1%	2%
Alkaline Phosphatase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	< 1%	0%
Grade 3	> 5.0 to ≤ 10.0 X ULN	< 1%	< 1%
Grade 4	> 10.0 X ULN	0%	0%
Hyperbilirubinemia			
Grade 2	> 1.5 to ≤ 2.5 X ULN	< 1%	2%
Grade 3	> 2.5 to ≤ 5.0 X ULN	< 1%	< 1%
Grade 4	> 5.0 X ULN	< 1%	0%
Triglycerides			
Grade 2	5.65-8.48 mmol/L 500-750 mg/dL	10%	11%
Grade 3	8.49-13.56 mmol/L 751-1200 mg/dL	7%	10%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	3%	6%
Total Cholesterol			
Grade 2	6.20-7.77 mmol/L 240-300 mg/dL	25%	23%
Grade 3	> 7.77 mmol/L > 300 mg/dL	10%	14%
Low-Density Lipoprotein Cholesterol			

Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	14%	14%
Grade 3	≥ 4.91 mmol/L ≥ 191 mg/dL	8%	9%
Elevated Glucose Levels			
Grade 2	6.95-13.88 mmol/L 126-250 mg/dL	10%	11%
Grade 3	13.89-27.75 mmol/L 251-500 mg/dL	1%	< 1%
Grade 4	> 27.75 mmol/L > 500 mg/dL	< 1%	0%
Pancreatic Lipase			
Grade 2	> 1.5 to ≤ 3.0 X ULN	3%	4%
Grade 3	> 3.0 to ≤ 5.0 X ULN	2%	< 1%
Grade 4	> 5.0 X ULN	< 1%	0%
Pancreatic Amylase			
Grade 2	> 1.5 to ≤ 2.0 X ULN	6%	7%
Grade 3	> 2.0 to ≤ 5.0 X ULN	7%	3%
Grade 4	> 5.0 X ULN	0%	0%

N=total number of subjects per treatment group; OBR = optimized background regimen  
\* Grade 4 data not applicable in Division of AIDS grading scale

### Serious ADRs

The following serious ADRs of at least moderate intensity (greater than or equal to Grade 2) occurred in the Phase 2b 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.

### 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 section 4.4). 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 3 Phase 2 trials. TMC114-C212, in which 80 antiretroviral treatment-experienced HIV-1-infected pediatric subjects 6 to less than 18 years of age and weighing at least 20 kg were included, TMC114-C228, in which 21 antiretroviral treatment-experienced HIV-1-infected pediatric subjects 3 to less than 6 years of age and weighing at least 10 kg were

included, and 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-C212 and C228 trials evaluated darunavir/ritonavir twice daily dosing and the TMC114-C230 trial evaluated darunavir /ritonavir once daily dosing (see section 5.1).

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

#### *TMC114-C212*

Clinical ADRs to darunavir/ritonavir (all grades, greater than or equal to 3%), were vomiting (13%), diarrhea (11%), abdominal pain (10%), headache (9%), rash (5%), nausea (4%), and fatigue (3%).

Grade 3 or 4 laboratory abnormalities were ALT increased (Grade 3: 3%; Grade 4: 1%), AST increased (Grade 3: 1%), pancreatic amylase increased (Grade 3: 4%, Grade 4: 1%), pancreatic lipase increased (Grade 3: 1%), total cholesterol increased (Grade 3: 1%), and LDL increased (Grade 3: 3%).

#### *TMC114-C228*

Clinical ADRs to darunavir/ritonavir (all grades, greater than or equal to 5%), were diarrhea (24%), vomiting (19%), rash (19%), abdominal pain (5%), and anorexia (5%).

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

#### *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.

### **Postmarketing Experience**

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

Redistribution of body fat has been reported.

Rarely, rhabdomyolysis (associated with co-administration with HMG-CoA reductase inhibitors and darunavir/ritonavir) has been reported.

In addition, toxic epidermal necrolysis, acute generalized exanthematous pustulosis and drug rash with eosinophilia and systemic symptoms have been reported rarely (see section 4.4).

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 local reporting system.

### **4.9. Overdose**

Human experience of acute overdose with darunavir/ritonavir is limited. No specific antidote is available for overdose with darunavir. Treatment of overdose with darunavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitors, ATC code: J05AE10.

#### **Mechanism of Action**

Darunavir is an HIV-1 antiviral drug.

#### **Pharmacodynamics**

##### Cardiac Electrophysiology

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

#### **Microbiology**

##### 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.

##### Antiviral Activity

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 EC<sub>50</sub> 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<sub>50</sub> values ranging from less than 0.1 to 4.3 nM. The EC<sub>50</sub> 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 EC<sub>50</sub> values ranging from 125 nM to 3461 nM.

*Clinical trials of darunavir/ritonavir in treatment-experienced subjects:* In a pooled analysis of the 600/100 mg darunavir/ritonavir twice daily arms of trials TMC114-C213, TMC114-C202, TMC114-C215, and the control arms of etravirine trials TMC125-C206 and TMC125-C216, the amino acid substitutions V32I and I54L or M developed most frequently on darunavir/ritonavir in 41% and 25%, respectively, of the treatment-experienced subjects who experienced virologic failure, either by rebound or by never being suppressed (less than 50 copies/mL). Other substitutions that developed frequently in darunavir/ritonavir virologic failure isolates occurred at amino acid positions V11I, I15V, L33F, I47V, I50V, and L89V. These amino acid substitutions were associated with decreased susceptibility to darunavir; 90% of the virologic failure isolates had a greater than 7-fold decrease in susceptibility to darunavir at failure. The median darunavir phenotype (fold change from reference) of the virologic failure isolates was 4.3-fold at baseline and 85-fold at failure. Amino acid substitutions were also observed in the protease cleavage sites in the Gag polyprotein of some darunavir/ritonavir virologic failure isolates. In trial TMC114-C212 of treatment-experienced pediatric subjects, the amino acid substitutions V32I, I54L and L89M developed most frequently in virologic failures on darunavir/ritonavir.

In the 96-week as-treated analysis of the Phase 3 trial TMC114-C214, the percent of virologic failures (never suppressed, rebounders and discontinued before achieving suppression) was 21% (62/298) in the group of subjects receiving darunavir/ritonavir 600/100 mg twice daily compared to 32% (96/297) of subjects receiving lopinavir/ritonavir 400/100 mg twice daily. Examination of subjects who failed on darunavir/ritonavir 600/100 mg twice daily and had post-baseline genotypes and phenotypes showed that 7 subjects (7/43; 16%) developed PI substitutions on darunavir/ritonavir treatment resulting in decreased susceptibility to darunavir. Six of the 7 had baseline PI resistance-associated substitutions and baseline darunavir phenotypes greater than 7. The most common emerging PI substitutions in these virologic failures were V32I, L33F, M46I or L, I47V, I54L, T74P and L76V. These amino acid substitutions were associated with 59- to 839-fold decreased susceptibility to darunavir at failure. Examination of individual subjects who failed in the comparator arm on lopinavir/ritonavir and had post-baseline genotypes and phenotypes showed that 31 subjects (31/75; 41%) developed substitutions on lopinavir treatment resulting in decreased susceptibility to lopinavir (greater than 10-fold) and the most common substitutions emerging on treatment were L10I or F, M46I or L, I47V or A, I54V and L76V. Of the 31 lopinavir/ritonavir virologic failure subjects, 14 had reduced susceptibility (greater than 10-fold) to lopinavir at baseline.

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:* 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 EC<sub>50</sub> values less than 3 for tipranavir, indicative of limited cross-resistance between darunavir and tipranavir. In trials TMC114-C213, TMC114-C202, and TMC114-C215, 34% (64/187) of subjects in the darunavir/ritonavir arm whose baseline isolates had decreased susceptibility to tipranavir (tipranavir fold change greater than 3) achieved less than 50 copies/mL serum HIV-1 RNA levels at Week 96. Of the viruses isolated from subjects experiencing virologic failure on darunavir/ritonavir 600/100 mg twice daily (greater than 7-fold change), 41% were still susceptible to tipranavir and 10% were susceptible to saquinavir while less than 2% were susceptible to the other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir or nelfinavir).

In trial TMC114-C214, the 7 darunavir/ritonavir virologic failures with reduced susceptibility to darunavir at failure were also resistant to the approved PIs (fos)amprenavir, atazanavir, lopinavir, indinavir, and nelfinavir at failure. Six of these 7 were resistant to saquinavir and 5 were resistant to tipranavir. Four of these virologic failures were already PI-resistant at baseline.

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.

### Baseline Genotype/Phenotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining darunavir susceptibility before initiation of darunavir/ritonavir 600/100 mg twice daily therapy. The effect of baseline genotype and phenotype on virologic response at 96 weeks was analyzed in as-treated analyses using pooled data from the Phase 2b trials (Trials TMC114-C213, TMC114-C202, and TMC114-C215) (n=439). The findings were confirmed with additional genotypic and phenotypic data from the control arms of etravirine trials TMC125-C206 and TMC125-C216 at Week 24 (n=591).

Diminished virologic responses were observed in subjects with 5 or more baseline IAS-defined primary protease inhibitor resistance-associated substitutions (D30N, V32I,

L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, L76V, V82A/F/L/S/T, I84V, N88S, L90M) (see Table 10).

**Table 10: Response to Darunavir/ritonavir 600/100 mg Twice Daily by Baseline Number of IAS-Defined Primary PI Resistance-Associated Substitutions: As-treated Analysis of Trials TMC114-C213, TMC114-C202, and TMC114-C215**

# IAS-defined primary PI substitutions	Proportion of subjects with < 50 copies/mL at Week 96 N=439		
	Overall	<i>de novo</i> ENF	Re-used/ No ENF
All	44% (192/439)	54% (61/112)	40% (131/327)
0 - 4	50% (162/322)	58% (49/85)	48% (113/237)
5	22% (16/74)	47% (9/19)	13% (7/55)
≥ 6	9% (3/32)	17% (1/6)	8% (2/26)

ENF=enfuvirtide

IAS Primary PI Substitutions (2008): D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, L76V, V82A/F/L/S/T, I84V, N88S, L90M

The presence at baseline of two or more of the substitutions V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V was associated with a decreased virologic response to darunavir/ritonavir. In subjects not taking enfuvirtide *de novo*, the proportion of subjects achieving viral load less than 50 plasma HIV-1 RNA copies/mL at 96 weeks was 59%, 29%, and 12% when the baseline genotype had 0-1, 2 and greater than or equal to 3 of these substitutions, respectively.

Baseline darunavir phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Response rates assessed by baseline darunavir phenotype are shown in Table 11. These baseline phenotype groups are based on the select patient populations in the trials TMC114-C213, TMC114-C202, and TMC114-C215, and are not meant to represent definitive clinical susceptibility breakpoints for darunavir/ritonavir. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to darunavir.

**Table 11: Response (HIV-1 RNA < 50 copies/mL at Week 96) to Darunavir/ritonavir 600/100 mg Twice Daily by Baseline Darunavir Phenotype and by Use of Enfuvirtide: As-treated Analysis of Trials TMC114-C213, TMC114-C202, and TMC114-C215**

Baseline DRV phenotype	Proportion of subjects with < 50 copies/mL at Week 96 N=417		
	All	<i>de novo</i> ENF	Re-used/ No ENF
Overall	175/417 (42%)	61/112 (54%)	131/327 (40%)
0 - 7	148/270 (55%)	44/65 (68%)	104/205 (51%)
> 7 -20	16/53 (30%)	7/17 (41%)	9/36 (25%)
> 20	11/94 (12%)	6/23 (26%)	5/71 (7%)

ENF=enfuvirtide

## **Pediatric Use**

Darunavir/ritonavir is not recommended in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age (see sections 4.4, 4.6 and 5.2).

The safety, pharmacokinetic profile, and virologic and immunologic responses of darunavir/ritonavir administered twice daily were evaluated in treatment-experienced HIV-1-infected pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg. These subjects were evaluated in clinical trials TMC114-C212 (80 subjects, 6 to less than 18 years of age) and TMC114-228 (21 subjects, 3 to less than 6 years of age) (see section 4.8, 5.1 and 5.2). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults (see section 4.8). Refer to *section 4.2* for twice-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

In clinical trial TMC114-C230, the safety, pharmacokinetic profile and virologic and immunologic responses of darunavir/ritonavir administered once daily were evaluated in treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age (12 subjects) (see sections 4.8, 5.1 and 5.2). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults (see section 4.8). Once daily dosing recommendations for pediatric patients 3 to less than 12 years of age were derived using population pharmacokinetic modeling and simulation. Although a darunavir/ritonavir once daily dosing pediatric trial was not conducted in children less than 12 years of age, there is sufficient clinical safety data to support the predicted darunavir exposures for the dosing recommendations in this age group (see section 5.2). Please see *section 4.2* for once-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

### Juvenile Animal Data

In a juvenile toxicity study where rats were directly dosed with darunavir (up to 1000 mg/kg), deaths occurred from post-natal day 5 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) 2 times the human plasma exposure levels.

## **Geriatric Use**

Clinical studies of darunavir did not include sufficient numbers of patients aged 65 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 in elderly patients, reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy (see section 5.2).

## **Hepatic Impairment**

No dosage adjustment of darunavir/ritonavir is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of darunavir/ritonavir in subjects with severe hepatic impairment. Therefore, darunavir/ritonavir is not recommended for use in patients with severe hepatic impairment (see sections 4.2 and 5.2).

## **Renal Impairment**

Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected subjects with moderate renal impairment (CrCL between 30-60 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 (see section 5.2).

## CLINICAL STUDIES

### Description of Adult Clinical Trials

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 and 96-week data from a randomized, controlled, open-label Phase 3 trial in antiretroviral treatment-experienced (TMC114-C214) HIV-1-infected adult subjects. In addition, 96-week data are included from 2 randomized, controlled Phase 2b trials, TMC114-C213 and TMC114-C202, in antiretroviral treatment-experienced 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<sup>3</sup> or greater than or equal to 200 cells/mm<sup>3</sup>). 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 12). Table 12 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 12: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C211**

	<b>darunavir/ritonavir 800/100 mg once daily + TDF/FTC N = 343</b>	<b>lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346</b>
<b>Demographic characteristics</b>		
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%
<b>Baseline characteristics</b>		
Mean baseline plasma HIV-1 RNA (log <sub>10</sub> copies/mL)	4.86	4.84
Median baseline CD4+ cell count (cells/mm <sup>3</sup> ) (range, cells/mm <sup>3</sup> )	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/mm <sup>3</sup>	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 13.

**Table 13: Virologic Outcome of Randomized Treatment of Trial TMC114-C211 at 192 Weeks**

	<b>darunavir/ritonavir 800/100 mg once daily + TDF/FTC N = 343</b>	<b>lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346</b>
Virologic success HIV-1 RNA < 50 copies/mL	70%*	61%
Virologic failure†	12%	15%
No virologic data at Week 192 window‡		
Reasons		
Discontinued trial due to adverse event or death§	5%	13%
Discontinued trial for other reasons¶	13%	12%
Missing data during window‡ but on trial	< 1%	0%

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

\* 95% CI: 1.9; 16.1

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

‡ Window 186-198 Weeks.

§ 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.

¶ 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<sup>3</sup> in the darunavir/ritonavir 800/100 mg once daily arm and 263 cells/mm<sup>3</sup> 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 14 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 14: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C229**

	<b>Darunavir/ritonavir 800/100 mg once daily + OBR N = 294</b>	<b>Darunavir/ritonavir 600/100 mg twice daily + OBR N = 296</b>
<b>Demographic characteristics</b>		
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%
<b>Baseline characteristics</b>		
Mean baseline plasma HIV-1 RNA (log <sub>10</sub> copies/mL)	4.19	4.13
Median baseline CD4+ cell count (cells/mm <sup>3</sup> ) (range, cells/mm <sup>3</sup> )	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 <sup>3</sup>	43%	39%
Median darunavir fold change (range)*	0.50 (0.1-1.8)	0.50 (0.1-1.9)
Median number of resistance-associated†:		
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 mutations†:		
0	84%	84%
1	8%	9%
2	5%	4%
≥ 3	3%	2%
Median number of ARVs previously used†:		
NRTIs	3	3
NNRTIs	1	1



PIs (excluding low-dose ritonavir)	1	1
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OBR=optimized background regimen

\* Based on phenotype (Antivirogram®)

† 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

‡ 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 15.

**Table 15: Virologic Outcome of Randomized Treatment of Trial TMC114-C229 at 48 Weeks**

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

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

\* Includes patients who discontinued prior to Week 48 for lack or loss of efficacy, patients who are  $\geq 50$  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  $\geq 50$  copies/mL).

† Window 42-54 Weeks

‡ 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.

§ 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<sup>3</sup> and 112 cells/mm<sup>3</sup> in the darunavir/ritonavir 800/100 mg once daily arm and the darunavir/ritonavir 600/100 mg twice daily arm, respectively).

### TMC114-C214

TMC114-C214 is a randomized, controlled, open-label Phase 3 trial comparing darunavir/ritonavir 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in antiretroviral treatment-experienced, lopinavir/ritonavir-naïve HIV-1-infected adult

subjects. Both arms used an optimized background regimen consisting of at least 2 antiretrovirals (NRTIs with or without NNRTIs).

HIV-1-infected subjects who were eligible for this trial had plasma HIV-1 RNA greater than 1000 copies/mL and 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 400 copies/mL. Analyses included 595 subjects in trial TMC114-C214 who had completed 96 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the darunavir/ritonavir arm and the lopinavir/ritonavir arm (see Table 16). Table 16 compares the demographic and baseline characteristics between subjects in the darunavir/ritonavir 600/100 mg twice daily arm and subjects in the lopinavir/ritonavir 400/100 mg twice daily arm in trial TMC114-C214.

**Table 16: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C214**

	<b>darunavir/ritonavir 600/100 mg twice daily + OBR N = 298</b>	<b>lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297</b>
<b>Demographic characteristics</b>		
Median age (years) (range, years)	40 (18-68)	41 (22-76)
Sex		
Male	77%	81%
Female	23%	19%
Race		
White	54%	57%
Black	18%	17%
Hispanic	15%	15%
Asian	9%	9%
<b>Baseline characteristics</b>		
Mean baseline plasma HIV-1 RNA (log <sub>10</sub> copies/mL)	4.33	4.28
Median baseline CD4+ cell count (cells/mm <sup>3</sup> ) (range, cells/mm <sup>3</sup> )	235 (3-831)	230 (2-1096)
Percentage of patients with baseline viral load ≥ 100,000 copies/mL	19%	17%
Percentage of patients with baseline CD4+ cell count < 200 cells/mm <sup>3</sup>	40%	40%
Median darunavir fold change (range)	0.60 (0.10-37.40)	0.60 (0.1-43.8)
Median lopinavir fold change (range)	0.70 (0.40-74.40)	0.80 (0.30-74.50)
Median number of resistance-associated*:		

PI mutations	4	4
NNRTI mutations	1	1
NRTI mutations	2	2
Percentage of subjects with number of baseline primary protease inhibitor mutations*:		
≤ 1	78%	80%
2	8%	9%
≥ 3	13%	11%
Median number of ARVs previously used†:		
NRTIs	4	4
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	1	1
Percentage of subjects resistant‡ to all available§ PIs at baseline, excluding darunavir	2%	3%

OBR=optimized background regimen

\* Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: Fall 2006. Top HIV Med 2006; 14(3): 125-130

† Only counting ARVs, excluding low-dose ritonavir

‡ Based on phenotype (Antivirogram®)

§ Commercially available PIs at the time of trial enrollment

Week 96 outcomes for subjects on darunavir/ritonavir 600/100 mg twice daily from trial TMC114-C214 are shown in Table 17.

**Table 17: Virologic Outcome of Randomized Treatment of Trial TMC114-C214 at 96 Weeks**

	<b>darunavir/ritonavir 600/100 mg twice daily + OBR N = 298</b>	<b>lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297</b>
Virologic success HIV-1 RNA < 50 copies/ mL	58%	52%
Virologic failure*	26%	33%
No virologic data at Week 96 window†		
Reasons		
Discontinued trial due to adverse event or death‡	7%	8%
Discontinued trial for other reasons§	8%	7%
Missing data during window† but on trial	1%	< 1%

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

\* Includes patients who discontinued prior to Week 96 for lack or loss of efficacy and patients who are ≥ 50 copies in the 96-week window and patients who had a change in their OBR that was not permitted by the protocol.

† Window 90-102 Weeks

‡ 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.

§ 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-C214 at 96 weeks of treatment, the median increase from baseline in CD4+ cell counts was 81 cells/mm<sup>3</sup> in the darunavir/ritonavir 600/100 mg twice daily arm and 93 cells/mm<sup>3</sup> in the lopinavir/ritonavir 400/100 mg twice daily arm.

#### TMC114-C213 and TMC114-C202

TMC114-C213 and TMC114-C202 are randomized, controlled, Phase 2b trials in adult subjects with a high level of PI resistance consisting of 2 parts: an initial partially-blinded, dose-finding part and a second long-term part in which all subjects randomized to darunavir/ritonavir received the recommended dose of 600/100 mg twice daily.

HIV-1-infected subjects who were eligible for these trials had plasma HIV-1 RNA greater than 1000 copies/mL, had prior treatment with PI(s), NNRTI(s) and NRTI(s), had at least one primary PI mutation (D30N, M46I/L, G48V, I50L/V, V82A/F/S/T, I84V, L90M) at screening, and were on a stable PI-containing regimen at screening for at least 8 weeks. Randomization was stratified by the number of PI mutations, screening viral load, and the use of enfuvirtide.

The virologic response rate was evaluated in subjects receiving darunavir/ritonavir plus an OBR versus a control group receiving an investigator-selected PI(s) regimen plus an OBR. Prior to randomization, PI(s) and OBR were selected by the investigator based on genotypic resistance testing and prior ARV history. The OBR consisted of at least 2 NRTIs with or without enfuvirtide. Selected PI(s) in the control arm included: lopinavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%; 98% of control subjects received a ritonavir boosted PI regimen out of which 23% of control subjects used dual-boosted PIs. Approximately 47% of all subjects used enfuvirtide, and 35% of the use was in subjects who were ENF-naïve. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1 log<sub>10</sub> versus baseline.

In the pooled analysis for TMC114-C213 and TMC114-C202, demographics and baseline characteristics were balanced between the darunavir/ritonavir arm and the comparator PI arm (see Table 18). Table 18 compares the demographic and baseline characteristics between subjects in the darunavir/ritonavir 600/100 mg twice daily arm and subjects in the comparator PI arm in the pooled analysis of trials TMC114-C213 and TMC114-C202.

**Table 18: Demographic and Baseline Characteristics of Subjects in the Trials TMC114-C213 and TMC114-C202 (Pooled Analysis)**

	<b>Darunavir/ritonavir 600/100 mg twice daily + OBR N = 131</b>	<b>Comparator PI(s) + OBR N = 124</b>
<b>Demographic characteristics</b>		
Median age (years) (range, years)	43 (27-73)	44 (25-65)
Sex		
Male	89%	88%
Female	11%	12%

Race		
White	81%	73%
Black	10%	15%
Hispanic	7%	8%
<b>Baseline characteristics</b>		
Mean baseline plasma HIV-1 RNA (log <sub>10</sub> copies/mL)	4.61	4.49
Median baseline CD4+ cell count (cells/mm <sup>3</sup> ) (range, cells/mm <sup>3</sup> )	153 (3-776)	163 (3-1274)
Percentage of patients with baseline viral load > 100,000 copies/mL	24%	29%
Percentage of patients with baseline CD4+ cell count < 200 cells/mm <sup>3</sup>	67%	58%
Median darunavir fold change	4.3	3.3
Median number of resistance-associated*:		
PI mutations	12	12
NNRTI mutations	1	1
NRTI mutations	5	5
Percentage of subjects with number of baseline primary protease inhibitor mutations*:		
≤ 1	8%	9%
2	22%	21%
≥ 3	70%	70%
Median number of ARVs previously used†:		
NRTIs	6	6
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	5	5
Percentage of subjects resistant† to all available‡ PIs at baseline, excluding tipranavir and darunavir	63%	61%
Percentage of subjects with prior use of enfuvirtide	20%	17%

OBR=optimized background regimen

\* Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: Fall 2006. Top HIV Med 2006; 14(3): 125-130

† Based on phenotype (Antivirogram®)

‡ Commercially available PIs at the time of trial enrollment

Week 96 outcomes for subjects on the recommended dose darunavir/ritonavir 600/100 mg twice daily from the pooled trials TMC114-C213 and TMC114-C202 are shown in Table 19.

**Table 19: Outcomes of Randomized Treatment through Week 96 of the Trials TMC114-C213 and TMC114-C202 (Pooled Analysis)**

	Randomized trials TMC114-C213 and TMC114-C202	
	Darunavir/ritonavir 600/100 mg twice daily + OBR N=131	Comparator PI(s) + OBR N=124
Virologic responders confirmed at least 1 log <sub>10</sub> HIV-1 RNA below baseline through Week 96 (< 50 copies/mL at Week 96)	57% (39%)	10% (9%)
Virologic failures	29%	80%
Lack of initial response*	8%	53%
Rebounder†	17%	19%
Never suppressed‡	4%	8%
Death or discontinuation due to adverse events	9%	3%
Discontinuation due to other	5%	7%

OBR=optimized background regimen

\* Subjects who did not achieve at least a confirmed 0.5 log<sub>10</sub> HIV-1 RNA drop from baseline at Week 12

† Subjects with an initial response (confirmed 1 log<sub>10</sub> drop in viral load), but without a confirmed 1 log<sub>10</sub> drop in viral load at Week 96

‡ Subjects who never reached a confirmed 1 log<sub>10</sub> drop in viral load before Week 96

In the pooled trials TMC114-C213 and TMC114-C202 through 48 weeks of treatment, the proportion of subjects with HIV-1 RNA less than 400 copies/mL in the arm receiving darunavir/ritonavir 600/100 mg twice daily compared to the comparator PI arm was 55.0% and 14.5%, respectively. In addition, the mean changes in plasma HIV-1 RNA from baseline were -1.69 log<sub>10</sub> copies/mL in the arm receiving darunavir/ritonavir 600/100 mg twice daily and -0.37 log<sub>10</sub> copies/mL for the comparator PI arm. The mean increase from baseline in CD4+ cell counts was higher in the arm receiving darunavir/ritonavir 600/100 mg twice daily (103 cells/mm<sup>3</sup>) than in the comparator PI arm (17 cells/mm<sup>3</sup>).

### Pediatric Patients

The pharmacokinetic profile, safety and antiviral activity of darunavir/ritonavir were evaluated in 3 randomized, open-label, multicenter studies.

#### TMC114-C212

Treatment-experienced pediatric subjects between the ages of 6 and less than 18 years and weighing at least 20 kg were stratified according to their weight (greater than or equal to 20 kg to less than 30 kg, greater than or equal to 30 kg to less than 40 kg,

greater than or equal to 40 kg) and received darunavir tablets with either ritonavir capsules or oral solution plus background therapy consisting of at least two non-protease inhibitor antiretroviral drugs. Eighty patients were randomized and received at least one dose of darunavir/ritonavir. Pediatric subjects who were at risk of discontinuing therapy due to intolerance of ritonavir oral solution (e.g., taste aversion) were allowed to switch to the capsule formulation. Of the 44 pediatric subjects taking ritonavir oral solution, 23 subjects switched to the 100 mg capsule formulation and exceeded the weight-based ritonavir dose without changes in observed safety.

The 80 randomized pediatric subjects had a median age of 14 (range 6 to less than 18 years), and were 71% male, 54% Caucasian, 30% Black, 9% Hispanic and 8% other. The mean baseline plasma HIV-1 RNA was 4.64 log<sub>10</sub> copies/mL, and the median baseline CD4+ cell count was 330 cells/mm<sup>3</sup> (range: 6 to 1505 cells/mm<sup>3</sup>). Overall, 38% of pediatric subjects had baseline plasma HIV-1 RNA ≥ 100,000 copies/mL. Most pediatric subjects (79%) had previous use of at least one NNRTI and 96% of pediatric subjects had previously used at least one PI.

Seventy-seven pediatric subjects (96%) completed the 24-week period. Of the patients who discontinued, one patient discontinued treatment due to an adverse event. An additional 2 patients discontinued for other reasons, one patient due to compliance and another patient due to relocation.

The proportion of pediatric subjects with HIV-1 RNA less than 400 copies/mL and less than 50 copies/mL was 64% and 50%, respectively. The mean increase in CD4+ cell count from baseline was 117 cells/mm<sup>3</sup>.

#### TMC114-C228

Treatment-experienced pediatric subjects between the ages of 3 and less than 6 years and weighing greater than or equal to 10 kg to less than 20 kg received darunavir oral suspension with ritonavir oral solution plus background therapy consisting of at least two active non-protease inhibitor antiretroviral drugs. Twenty-one subjects received at least one dose of darunavir/ritonavir.

The 21 subjects had a median age of 4.4 years (range 3 to less than 6 years), and were 48% male, 57% Black, 29% Caucasian and 14% other. The mean baseline plasma HIV-1 was 4.34 log<sub>10</sub> copies/mL, the median baseline CD4+ cell count was 927 x 10<sup>6</sup> cells/L (range: 209 to 2,429 x 10<sup>6</sup> cells/L) and the median baseline CD4+ percentage was 27.7% (range: 15.6% to 51.1%). Overall, 24% of subjects had a baseline plasma HIV-1 RNA greater than or equal to 100,000 copies/mL. All subjects had used greater than or equal to 2 NRTIs, 62% of subjects had used greater than or equal to 1 NNRTI and 76% had previously used at least one HIV PI.

Twenty subjects (95%) completed the 48 week period. One subject prematurely discontinued treatment due to vomiting assessed as related to ritonavir.

The proportion of subjects with HIV-1 RNA less than 50 copies/mL at Week 48 was 71%. The mean increase in CD4+ percentage from baseline was 4%. The mean change in CD4+ cell count from baseline was 187 x 10<sup>6</sup> cells/L.

#### 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 log<sub>10</sub> copies/mL, and the median baseline CD4+

cell count was 282 cells/mm<sup>3</sup> (range: 204 to 515 cells/mm<sup>3</sup>). Overall, 41.7% of pediatric subjects had baseline plasma HIV-1 RNA  $\geq$  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 x 10<sup>6</sup> cells/L.

## 5.2. Pharmacokinetic properties

### Pharmacokinetics in Adults

#### General

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

The pharmacokinetics of darunavir, co-administered with low dose ritonavir (100 mg), has been evaluated in healthy adult volunteers and in HIV-1-infected subjects. Table 20 displays the population pharmacokinetic estimates of darunavir after oral administration of darunavir/ritonavir 600/100 mg twice daily (based on sparse sampling in 285 patients in trial TMC114-C214, 278 patients in trial TMC114-C229 and 119 patients [integrated data] from trials TMC114-C202 and TMC114-C213) and 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 20: 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) and Darunavir/ritonavir 600/100 mg Twice Daily (Trial TMC114-C214, 48-Week Analysis, Trial TMC114-C229, 48-Week Analysis and Integrated Data from Trials TMC114-C213 and TMC114-C202, Primary 24-Week Analysis)**

Parameter	Darunavir / ritonavir 800/100 mg once daily		Darunavir / ritonavir 600/100 mg twice daily		
	TMC114- C211 N = 335	TMC114- C229 N = 280	T M C 1 1 4 - C214 N = 285	TMC114- C229 N = 278	TMC114-C213 + T M C 1 1 4 - C 2 0 2 (integrated data) N =119
AUC <sub>24h</sub> (ng·h/mL)*					
Mean $\pm$ Standard Deviation	93026 $\pm$ 27050	93334 $\pm$ 28626	116796 $\pm$ 33594	114302 $\pm$ 32681	124698 $\pm$ 32286
Median (Range)	87854 (45000-2 19240)	87788 (45456-23 6920)	111632 (64874-355 360)	109401 (48934-32 3820)	123336 (67714-212980)
C <sub>0h</sub> (ng/mL)					



Mean ± Standard Deviation	2 2 8 2 ± 1168	2 1 6 0 ± 1201	3 4 9 0 ± 1401	3 3 8 6 ± 1372	3578 ± 1151
Median (Range)	2041 (368-7242)	1896 (184-7881)	3307 (1517-13198)	3197 (250-11865)	3539 (1255-7368)

N = number of subjects with data

\*AUC<sub>24h</sub> is calculated as AUC<sub>12h</sub>\*2

### Absorption and Bioavailability

Darunavir, co-administered with 100 mg ritonavir twice daily, was absorbed following oral administration with a T<sub>max</sub> of approximately 2.5-4 hours. The absolute oral bioavailability of a single 600 mg dose of darunavir alone and after co-administration with 100 mg ritonavir twice daily was 37% and 82%, respectively. *In vivo* data suggest that darunavir/ritonavir is an inhibitor of the P-glycoprotein (P-gp) transporters.

### Effects of Food on Oral Absorption

When darunavir tablets were administered with food, the C<sub>max</sub> and AUC of darunavir, co-administered with ritonavir, is approximately 40% higher relative to the fasting state. Within the range of meals studied, darunavir exposure is similar. The total caloric content of the various meals evaluated ranged from 240 Kcal (12 gms fat) to 928 Kcal (56 gms fat).

### *Distribution*

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

### *Metabolism*

*In vitro* experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by CYP enzymes, primarily by CYP3A. A mass balance study in healthy volunteers showed that after a single dose administration of 400 mg <sup>14</sup>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 <sup>14</sup>C-darunavir, co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose of <sup>14</sup>C-darunavir was recovered in the feces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when co-administered with ritonavir. After intravenous administration, the clearance of darunavir, administered alone and co-administered with 100 mg twice daily ritonavir, was 32.8 L/h and 5.9 L/h, respectively.

### Special Populations

#### *Hepatic Impairment*

Darunavir is primarily metabolized by the liver. The steady-state pharmacokinetic parameters of darunavir were similar after multiple dose co-administration of 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 has not been evaluated (see sections 4.2 and 5.1).

#### *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 <sup>14</sup>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 section 5.1).

#### *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 section 5.1).

#### *Pediatric Patients*

##### Darunavir/ritonavir administered twice daily

The pharmacokinetics of darunavir in combination with ritonavir in 93 antiretroviral treatment-experienced HIV-1-infected pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg showed that the administered weight-based dosages resulted in similar darunavir exposure when compared to the darunavir exposure achieved in treatment-experienced adults receiving darunavir/ritonavir 600/100 mg twice daily (see section 4.2).

##### Darunavir/ritonavir administered once daily

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 (see section 4.2).

Based on population pharmacokinetic modeling and simulation, the proposed darunavir/ritonavir once daily dosing regimens for pediatric patients 3 to less than 12 years of age is predicted to result in similar darunavir exposures when compared to the darunavir exposures achieved in treatment-naïve adults receiving darunavir/ritonavir 800/100 mg once daily (see section 4.2).

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

**Table 21: Population Pharmacokinetic Estimates of Darunavir Exposure (Trials TMC114-C230, TMC114-C212 and TMC114-C228) Following Administration of Doses in Table 2**

Parameter	Darunavir / ritonavir once daily	Darunavir/ ritonavir twice daily		
	TMC114-C230 <sup>β</sup> N = 12	TMC114-C212 N = 74	TMC114-C228*	
			10 to less than 15 kg <sup>‡</sup> N = 10	15 to less than 20 kg <sup>§</sup> N = 13
AUC <sub>24h</sub> (ng·h/mL) <sup>†</sup>				
Mean ± Standard Deviation	84390 ± 23587	1 2 6 3 7 7 ± 34356	1 3 7 8 9 6 ± 51420	157760 ± 54080
Median (Range)	86741 (35527-123325)	127340 (67054-230720)	124044 (89688-261090)	132698 (112310 - 294840)
C <sub>0h</sub> (ng/mL)				
Mean ± Standard Deviation	2141 ± 865	3948 ± 1363	4510 ± 2031	4848 ± 2143
Median (Range)	2234 (542-3776)	3888 (1836-7821)	4126 (2456-9361)	3927 (3046 - 10292)

N = number of subjects with data.

\* Subjects may have contributed pharmacokinetic data to both the 10 kg to less than 15 kg weight group and the 15 kg to less than 20 kg weight group.

<sup>†</sup> AUC<sub>24h</sub> is calculated as AUC<sub>12h</sub>\*2.

<sup>‡</sup> Calculated from individual pharmacokinetic parameters estimated for Week 2 and Week 4, based on the Week 48 analysis that evaluated a darunavir dose of 20 mg/kg twice daily with ritonavir 3 mg/kg twice daily.

<sup>§</sup> The 15 kg to less than 20 kg weight group received 380 mg (3.8 mL) darunavir oral suspension twice daily with 48 mg (0.6 mL) ritonavir oral solution twice daily in TMC114-C228. Calculated from individual pharmacokinetic parameters estimated for Week 2 post-dose adjustment visit; Week 24 and Week 48 based on the - Week 48 analysis that evaluated a darunavir dose of 380 mg twice daily.

<sup>β</sup> 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 600/100 mg twice daily and darunavir/ritonavir 800/100 mg once daily as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum (see Table 22, Table 23 and Figure 1).

**Table 22: Pharmacokinetic Results of Total Darunavir after Administration of Darunavir/ritonavir at 600/100 mg Twice Daily as Part of an Antiretroviral Regimen, During the 2<sup>nd</sup> Trimester of Pregnancy, the 3<sup>rd</sup> Trimester of Pregnancy and Postpartum**

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

\* n=10 for AUC<sub>24h</sub>

† excluding C<sub>min</sub> value below LLOQ, n=10 for reference

‡ AUC<sub>24h</sub> is calculated as AUC<sub>12h</sub> \*2.

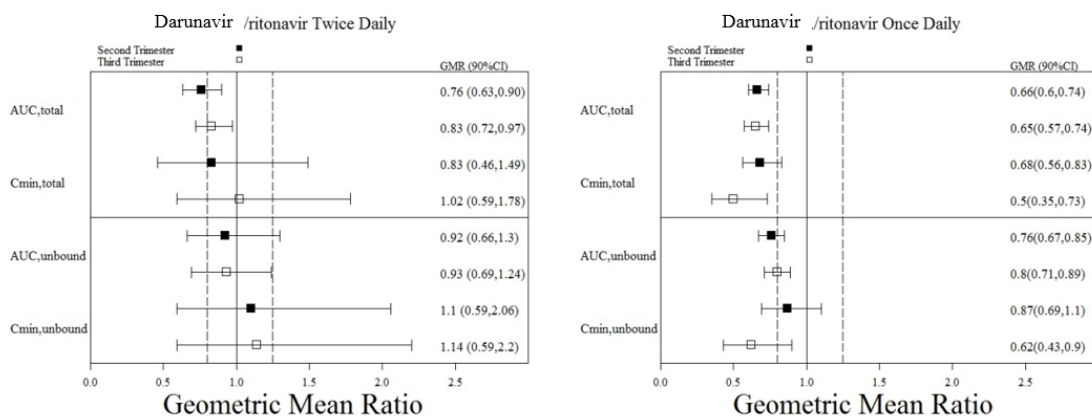
**Table 23: Pharmacokinetic Results of Total Darunavir after Administration of Darunavir/ritonavir at 800/100 mg Once Daily as Part of an Antiretroviral Regimen, During the 2<sup>nd</sup> Trimester of Pregnancy, the 3<sup>rd</sup> Trimester of Pregnancy and Postpartum**

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

\* N=12 for postpartum, N=15 for 2<sup>nd</sup> trimester and N=14 for 3<sup>rd</sup> trimester

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

**Figure 1: Pharmacokinetic Results (Within-Subject Comparison) of Total and Unbound Darunavir After Administration of Darunavir/ritonavir at 600/100 mg Twice Daily or 800/100 mg Once Daily as Part of an Antiretroviral Regimen, During the 2<sup>nd</sup> and 3<sup>rd</sup> 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.

### Drug Interactions

(see sections 4.3, 4.4 and 4.5)

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

Darunavir and ritonavir are metabolized by CYP3A. *In vitro* data indicate that darunavir may be a P-gp substrate. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir and ritonavir and other drugs that inhibit CYP3A or P-gp may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir.

Drug interaction studies were performed with darunavir and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of darunavir on the AUC,  $C_{max}$ , and  $C_{min}$  values are summarized in Table 24 (effect of other drugs on darunavir) and Table 25 (effect of darunavir on other drugs). For information regarding clinical recommendations, see section 4.5.

Several interaction studies have been performed with a dose other than the recommended dose of the co-administered drug or darunavir; however, the results are applicable to the recommended dose of the co-administered drug and/or darunavir.

**Table 24: Drug Interactions: Pharmacokinetic Parameters for Darunavir in the Presence of Co-Administered Drugs**

Co-administered drug	Dose/Schedule		N	PK	LS Mean ratio (90% CI) of <u>darunavir</u> Pharmacokinetic parameters with/without co-administered drug no effect =1.00		
	Co-administered Drug	Darunavir / ritonavir			$C_{max}$	AUC	$C_{min}$
<b>Co-administration with other HIV protease inhibitors</b>							

Atazanavir	300 mg q.d.*	400/100 mg b.i.d.†	13	↔	1.02 (0.96-1.09)	1.03 (0.94-1.12)	1.01 (0.88-1.16)
Indinavir	800 mg b.i.d.	400/100 mg b.i.d.	9	↑	1.11 (0.98-1.26)	1.24 (1.09-1.42)	1.44 (1.13-1.82)
Lopinavir/ ritonavir	400/100 mg b.i.d.	1200/100 mg b.i.d.‡	14	↓	0.79 (0.67-0.92)	0.62 (0.53-0.73)	0.49 (0.39-0.63)
	533/133.3 mg b.i.d.	1200 mg b.i.d.‡	15	↓	0.79 (0.64-0.97)	0.59 (0.50-0.70)	0.45 (0.38-0.52)
Saquinavir hard gel capsule	1000 mg b.i.d.	400/100 mg b.i.d.	14	↓	0.83 (0.75-0.92)	0.74 (0.63-0.86)	0.58 (0.47-0.72)
<b>Co-administration with other HIV antiretrovirals</b>							
Didanosine	400 mg q.d.	600/100 mg b.i.d.	17	↔	0.93 (0.86-1.00)	1.01 (0.95-1.07)	1.07 (0.95-1.21)
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↓	0.85 (0.72-1.00)	0.87 (0.75-1.01)	0.69 (0.54-0.87)
Etravirine	200 mg b.i.d.	600/100 mg b.i.d.	15	↔	1.11 (1.01-1.22)	1.15 (1.05-1.26)	1.02 (0.90-1.17)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.40 <sup>§</sup> (1.14-1.73)	1.24 <sup>§</sup> (0.97-1.57)	1.02 <sup>§</sup> (0.79-1.32)
Rilpivirine	150 mg q.d.	800/100 mg q.d.	15	↔	0.90 (0.81-1.00)	0.89 (0.81-0.99)	0.89 (0.68-1.16)
Tenofovir disoproxil fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.16 (0.94-1.42)	1.21 (0.95-1.54)	1.24 (0.90-1.69)
<b>Co-administration with HCV NS3-4A protease inhibitors</b>							
Simeprevir	50 mg q.d. €	800 mg q.d.	25 <sup>+</sup>	↑	1.04 (0.99-1.10)	1.18 (1.11-1.25)	1.31 (1.13-1.52)
<b>Co-administration with other drugs</b>							
Artemether/ lumefantrine	80/480 mg (6 doses at 0, 8, 24, 36, 48, and 60 hours)	600/100 mg b.i.d.	14	↔	1.00 (0.93-1.07)	0.96 (0.90-1.03)	0.87 (0.77-0.98)
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	↔	1.04 (0.93-1.16)	0.99 (0.90-1.08)	0.85 (0.73-1.00)

Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↔	0.83 (0.72-0.96)	0.87 (0.75-1.01)	1.01 (0.81-1.26)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	14	↑	1.21 (1.04-1.40)	1.42 (1.23-1.65)	1.73 (1.39-2.14)
Omeprazole	20 mg q.d.	400/100 mg b.i.d.	16	↔	1.02 (0.95-1.09)	1.04 (0.96-1.13)	1.08 (0.93-1.25)
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↔	0.97 (0.92-1.02)	1.02 (0.95-1.10)	1.07 (0.96-1.19)
Pitavastatin	4 mg q.d.	800/100 mg q.d.	27	↔	1.06 (1.00-1.12)	1.03 (0.95-1.12)	NA
Ranitidine	150 mg b.i.d.	400/100 mg b.i.d.	16	↔	0.96 (0.89-1.05)	0.95 (0.90-1.01)	0.94 (0.90-0.99)
Rifabutin	150 mg q.o.d.†	600/100 mg b.i.d.	11	↑	1.42 (1.21-1.67)	1.57 (1.28-1.93)	1.75 (1.28-2.37)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↔	1.01 (0.89-1.14)	0.98 (0.84-1.14)	0.94 (0.76-1.16)

N = number of subjects with data

\* q.d. = once daily

† b.i.d. = twice daily

‡ The pharmacokinetic parameters of darunavir in this study were compared with the pharmacokinetic parameters following administration of darunavir/ritonavir 600/100 mg twice daily.

§ Ratio based on between-study comparison.

¶ q.o.d. = every other day

€ The dose of simeprevir in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir compared to 150 mg once daily in the simeprevir alone treatment group.

+ Maximum number of subjects

**Table 25: Drug Interactions: Pharmacokinetic Parameters for Co-Administered Drugs in the Presence of Darunavir/ritonavir**

Co-administered drug	Dose/Schedule		N	PK	LS Mean ratio (90% CI) of <u>co-administered drug pharmacokinetic parameters with/without darunavir</u> no effect =1.00		
	Co-administered drug	Darunavir / ritonavir			C <sub>max</sub>	AUC	C <sub>min</sub>
<b>Co-administration with other HIV protease inhibitors</b>							

Atazanavir	300 mg q.d.* /100 mg ritonavir q.d. when administered alone  300 mg q.d. when administered with darunavir/ritonavir	400/100 mg b.i.d.†	13	↔	0.89 (0.78-1.01)	1.08 (0.94-1.24)	1.52 (0.99-2.34)
Indinavir	800 mg b.i.d. /100 mg ritonavir b.i.d. when administered alone  800 mg b.i.d. when administered with darunavir/ritonavir	400/100 mg b.i.d.	9	↑	1.08 (0.95-1.22)	1.23 (1.06-1.42)	2.25 (1.63-3.10)
Lopinavir / ritonavir	400/100 mg b.i.d.‡  533/133.3 mg b.i.d.‡	1200/100 mg b.i.d.  1200 mg b.i.d.	14  15	↔  ↔	0.98 (0.78-1.22)  1.11 (0.96-1.30)	1.09 (0.86-1.37)  1.09 (0.96-1.24)	1.23 (0.90-1.69)  1.13 (0.90-1.42)
Saquinavir hard gel capsule	1000 mg b.i.d. /100 mg ritonavir b.i.d. when administered alone  1000 mg b.i.d. when administered with darunavir/ritonavir	400/100 mg b.i.d.	12	↔	0.94 (0.78-1.13)	0.94 (0.76-1.17)	0.82 (0.52-1.30)
<b>Co-administration with other HIV antiretrovirals</b>							
Didanosine	400 mg q.d.	600/100 mg b.i.d.	17	↔	0.84 (0.59-1.20)	0.91 (0.75-1.10)	-
Dolutegravir	30 mg q.d.	600/100 mg b.i.d.	15	↓	0.89 (0.83-0.97)	0.78 (0.72-0.85)	0.62 <sup>Ω</sup> (0.56-0.69)



Dolutegravir	50 mg q.d.	600/100 mg b.i.d. with 200 mg b.i.d. etravirine	9	↓	0.88 (0.78-1.00)	0.75 (0.69-0.81)	0.63 <sup>Ω</sup> (0.52-0.76)
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↑	1.15 (0.97-1.35)	1.21 (1.08-1.36)	1.17 (1.01-1.36)
Etravirine	100 mg b.i.d.	600/100 mg b.i.d.	14	↓	0.68 (0.57-0.82)	0.63 (0.54-0.73)	0.51 (0.44-0.61)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.18 (1.02-1.37)	1.27 (1.12-1.44)	1.47 (1.20-1.82)
Rilpivirine	150 mg q.d.	800/100 mg q.d.	14	↑	1.79 (1.56-2.06)	2.30 (1.98-2.67)	2.78 (2.39-3.24)
Tenofovir disoproxil fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.24 (1.08-1.42)	1.22 (1.10-1.35)	1.37 (1.19-1.57)
Maraviroc	150 mg b.i.d.	600/100 mg b.i.d.	12	↑	2.29 (1.46-3.59)	4.05 (2.94-5.59)	8.00 (6.35-10.1)
		600/100 mg b.i.d. with 200 mg b.i.d. etravirine	10	↑	1.77 (1.20-2.60)	3.10 (2.57-3.74)	5.27 (4.51-6.15)
<b>Co-administration with HCV NS3-4A protease inhibitors</b>							
Simeprevir	50 mg q.d. €	800/100 mg q.d.	25+	↑	1.79 (1.55-2.06)	2.59 (2.15-3.11)	4.58 (3.54-5.92)
<b>Co-administration with other drugs</b>							
Atorvastatin	40 mg q.d. when administered alone	300/100 mg b.i.d.	15	↑	0.56 (0.48-0.67)	0.85 (0.76-0.97)	1.81 (1.37-2.40)
	10 mg q.d. when administered with darunavir/ritonavir						
Artemether Dihydroartemisinin	80 mg single dose	600/100 mg b.i.d.	15	↓	0.85 (0.68-1.05)	0.91 (0.78-1.06)	-
			15	↑	1.06 (0.82-1.39)	1.12 (0.96-1.30)	-

Artemether	artemether/ lumefantrine 80/480 mg (6 doses at 0, 8, 24, 36, 48, a n d 6 0 hours)	600/100 mg b.i.d.	15	↓	0.82 (0.61-1. 11)	0.84 (0.69- 1.02)	0.97 (0.90-1. 05)
Dihydroartemisin in			15	↓	0.82 (0.66-1. 01)	0.82 (0.74- 0.91)	1.00 (0.82-1. 22)
Lumefantrine			15	↑	1.65 (1.49-1. 83)	2.75 (2.46- 3.08)	2.26 (1.92-2. 67)
Buprenorphine/ Naloxone	8/2 mg to 16/4 mg q.d.	600/100 mg b.i.d.	17	↔	0.92 <sup>s</sup> (0.79-1. 08)	0.89 <sup>s</sup> (0.78- 1.02)	0.98 <sup>s</sup> (0.82-1. 16)
Norbuprenorphin e			17	↑	1.36 (1.06-1. 74)	1.46 (1.15- 1.85)	1.71 (1.29-2. 27)
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	↑	1.43 (1.34-1. 53)	1.45 (1.35- 1.57)	1.54 (1.41-1. 68)
Carbamazepine epoxide			16	↓	0.46 (0.43-0. 49)	0.46 (0.44- 0.49)	0.48 (0.45-0. 51)
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↑	1.26 (1.03-1. 54)	1.57 (1.35- 1.84)	2.74 (2.30-3. 26)
Dextromethorph an	30 mg	600/100 mg b.i.d.	12	↑	2.27 (1.59-3. 26)	2.70 (1.80- 4.05)	-
Dextrorphan			↓	0.87 (0.77-0. 98)	0.96 (0.90- 1.03)	-	
Digoxin	0.4 mg	600/100 mg b.i.d.	8	↑	1.15 (0.89-1. 48)	1.36 (0.81- 2.27)	-
Ethinyl estradiol (EE)	Ortho-Novum 1/35 (35 µg EE / 1 mg NE)	600/100 mg b.i.d.	11	↓	0.68 (0.61-0. 74)	0.56 (0.50- 0.63)	0.38 (0.27-0. 54)
Norethindrone (NE)			11	↓	0.90 (0.83-0. 97)	0.86 (0.75- 0.98)	0.70 (0.51-0. 97)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	15	↑	2.11 (1.81-2. 44)	3.12 (2.65- 3.68)	9.68 (6.44-1 4.55)
R-Methadone	55-150 mg q.d.	600/100 mg b.i.d.	16	↓	0.76 (0.71-0. 81)	0.84 (0.78- 0.91)	0.85 (0.77-0. 94)

Omeprazole	40 mg single dose	600/100 mg b.i.d.	12	↓	0.66 (0.48-0.90)	0.58 (0.50-0.66)	-
5-hydroxy omeprazole				↓	0.93 (0.71-1.21)	0.84 (0.77-0.92)	-
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↓	0.64 (0.59-0.71)	0.61 (0.56-0.66)	0.63 (0.55-0.73)
Pitavastatin	4 mg q.d.	800/100 mg q.d.	27	↓	0.96 (0.84-1.09)	0.74 (0.69-0.80)	NA
Pravastatin	40 mg single dose	600/100 mg b.i.d.	14	↑	1.63 (0.95-2.82)	1.81 (1.23-2.66)	-
Rifabutin	150 mg q.o.d.† when administered with darunavir/ritonavir	600/100 mg b.i.d.‡	11	↑	0.72 (0.55-0.93)	0.93 (0.80-1.09)	1.64 (1.48-1.81)
25-O-desacetyl-rifabutin	300 mg q.d. when administered alone		11	↑	4.77 (4.04-5.63)	9.81 (8.09-11.9)	27.1 (22.2-33.2)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↓	0.56 (0.49-0.63)	0.51 (0.46-0.58)	0.51 (0.45-0.57)
Sildenafil	100 mg (single dose) administered alone  25 mg (single dose) when administered with darunavir/ritonavir	400/100 mg b.i.d.	16	↑	0.62 (0.55-0.70)	0.97 (0.86-1.09)	-
S-warfarin	10 mg single dose	600/100 mg b.i.d.	12	↓	0.92 (0.86-0.97)	0.79 (0.73-0.85)	-
7-OH-S-warfarin			12	↑	1.42 (1.24-1.63)	1.23 (0.97-1.57)	-

N = number of subjects with data; -= no information available

\* q.d. = once daily

† b.i.d. = twice daily

‡ The pharmacokinetic parameters of lopinavir in this study were compared with the pharmacokinetic parameters following administration of lopinavir/ritonavir 400/100 mg twice daily.

§ ratio is for buprenorphine; mean  $C_{max}$  and  $AUC_{24}$  for naloxone were comparable when buprenorphine/naloxone was administered with or without darunavir/ritonavir

¶ q.o.d. = every other day

# In comparison to rifabutin 300 mg once daily.

Ω Noted as  $C_T$  or  $C_{24}$  in the dolutegravir U.S. prescribing information

+ Maximum number of subjects

€ The dose of simeprevir in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir compared to 150 mg once daily in the simeprevir alone treatment group.

A cocktail study was conducted in 12 healthy volunteers to evaluate the effect of steady state pharmacokinetics of darunavir/ritonavir on the activity of CYP2D6 (using dextromethorphan as probe substrate), CYP2C9 (using warfarin as probe substrate), and CYP2C19 (using omeprazole as probe substrate). The pharmacokinetic results are shown in Table 25.

### 5.3. Preclinical safety data

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

##### Carcinogenesis and Mutagenesis

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).

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

##### Impairment of Fertility

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Silicified Microcrystalline cellulose  
Crospovidone  
Colloidal silicon dioxide  
Magnesium Stearate  
Opadry II Orange 85F530009  
Opadry II Orange 85F530027  
Purified Water

#### **Composition of Opadry II Complete Film Coating System 85F530009 Orange**

Polyvinyl Alcohol part hydrolysed  
Titanium Dioxide  
Macrogol/PEG  
Talc  
FD&C Yellow #6 / Sunset Yellow FCF Aluminium Lake (15% - 18%)

## **Composition of Opadry II Complete Film Coating System 85F530027 Orange**

Polyvinyl Alcohol part hydrolysed

Titanium Dioxide

Macrogol/PEG

Talc

FD&C Yellow #6 / Sunset Yellow FCF Aluminium Lake (38% - 42%)

FD&C Yellow #6 / Sunset Yellow FCF Aluminium Lake (15% - 18%)

### **6.2. Incompatibilities**

Not applicable.

### **6.3. Shelf life**

24 Months

### **6.4. Special precautions for storage**

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]

### **6.5. Nature and contents of container**

400 mg tablets-

Opaque, white, 85cc high density polyethylene (HDPE) plastic bottle containing 60 tablets, fitted with a HDPE non child resistant closure, and foil induction seal.

600 mg tablets-

Opaque, white, 150cc high density polyethylene (HDPE) plastic bottle containing 60 tablets, fitted with an HDPE non child resistant closure, and foil induction seal.

### **6.6. Special precautions for disposal**

No special requirements.

### **6.7. Category of Distribution:**

Prescription Only Medicine.

## **7. MARKETING AUTHORISATION HOLDER**

Cipla Limited.

## **8. MARKETING AUTHORISATION NUMBER (S)**

TAN 22 HM 0334

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

21/09/2022

## **10. DATE OF REVISION OF THE TEXT**

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