



HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use DARUNAVIR TABLETS safely and effectively. See Full Prescribing Information for

DARUNAVIR TABLETS. DARUNAVIR tablets, for oral use

Initial U.S. Approval: 2006 ....INDICATIONS AND IISAGE.... Darunavir tablets are a human immunodeficiency virus (HIV-1) protease inhibitor indicated for the treatment of HIV-1 infection in adult and pediatric patients 3 years of age and older. Darunavir tablets must be co-administered with ritonavir (darunavir tablets/ritonavir) and with other antiretroviral agents. (1)

....DOSAGE AND ADMINISTRATION..... o In treatment-experienced patients, treatment history genotypic and/or phenotypic testing is recommended prior to initiation of therapy with darunavir tablets/ritonavir to assess drug susceptibility of the HIV-1 virus (2.1, 12.4)

Monitor serum liver chemistry tests before and during therapy with darunavir tablets/ritonavir. (2.1, 2.2, 5.2) Treatment-naïve adult patients and treatment-experienced adult patients with no darunavir resistance associated substitutions: 800 mg (one 800 mg tablet) taken with ritonavir 100 mg once daily and with food. (2.3) Treatment-experienced adult patients with at least one darunavir resistance associated substitution: 600 mg (one 600 mg tablet) taken with ritonavir

100 mg twice daily and with food. (2.3) Pregnant patients: 600 mg (one 600 mg tablet) taken with ritonavir 100 mg twice daily and with food. (2.4) Pediatric patients (3 to less than 18 years of age and weighing at least 10 kg): dosage of darunavir tablets and ritonavir is based on body weight and should

not exceed the adult dose. Darunavir tablets should be taken with ritonavir and with food. (2.5) Darunavir tablets/ritonavir is not recommended for use in patients with severe hepatic impairment. (2.6)

 Tablets: 600 mg, and 800 mg (3) ····CONTRAINDICATIONS···

Co-administration of darunavir tablets/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). (4)

----WARNINGS AND PRECAUTIONS-----Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with darunavir/ritonavir. Monitor liver function before and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transactions.

FULL PRESCRIBING INFORMATION: CONTENTS\*

INDICATIONS AND USAGE DOSAGE AND ADMINISTRATION Testing Prior to Initiation of darunavir tablets/ritonavir Monitoring During Treatment with darunavir tablets/ritonavir 2.3 Recommended Dosage in Adult Patients Recommended Dosage During Pregnancy
Recommended Dosage in Pediatric Patients (age 3 to less than 18 years)

2.6 Not Recommended in Patients with Severe Hepatic Impairmen DOSAGE FORMS AND STRENGTHS CONTRAINDICATIONS WARNINGS AND PRECAUTIONS

5.3 Severe Skin Reactions 5.5 Risk of Serious Adverse Reactions due to Drug Interactions 5.6 Diabetes Mellitus/Hyperglycemia

5.8 Immune Reconstitution Syndrome 5.9 Hemophilia 5.10 Not Recommended in Pediatric Patients Below 3 Years of Age

ADVERSE REACTIONS

Treatment-Experienced Adult Patients

6.1 Clinical Trials Experience 6.2 Postmarketing Experience DRUG INTERACTIONS

7.1 Potential for darunavir/ritonavir to Affect Other Drugs
7.2 Potential for Other Drugs to Affect Darunavir
7.3 Established and Other Potentially Significant Drug Interactions

FULL PRESCRIBING INFORMATION INDICATIONS AND USAGE Darunavir tablets, co-administered with ritonavir (darunavir tablets/ritonavir), in combination with other antiretroviral agents, is indicated for the treatment of human

DOSAGE AND ADMINISTRATION 2.1 Testing Prior to Initiation of darunavir tablets/riton In treatment-experienced patients, treatment history, genotypic and/or phenotypic testing is recommended to assess drug susceptibility of the HIV-1 virus [see Microbiology (12.4)]. Refer to Dosage and Administration (2.3), (2.4) and (2.5) for dosing recommendations.

immunodeficiency virus (HIV-1) infection in adult and pediatric patients 3 years of age and older [see Use in Specific Populations (8.4) and Clinical Studies (14)]

Appropriate laboratory testing such as serum liver biochemistries should be conducted prior to initiating therapy with darunavir tablets/ritonavir [see Warnings and 2.2 Monitoring During Treatment with darunavir tablets/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 tablets/ritonavir treatment/see Warnings and Precautions (5,2)]. 2.3 Recommended Dosage in Adult Patients 2.3 necommended bosage in Adult r actions
Darunavir tablets must be co-administered with ritionavir to exert its therapeutic effect. Failure to correctly co-administer darunavir tablets with ritionavir will result in plasma levels of darunavir that will be insufficient to achieve the desired antiviral effect and will alter some drug interactions.

Patients who have difficulty swallowing darunavir tablets can use the 100 mg per mL darunavir oral suspensio Treatment-Naïve Adult Patients ecommended oral dose of darunavir is 800 mg (one 800 mg tablet or 8 mL of the oral suspension) 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. An 8 mL darunavir tablets dose should be taken as two 4 mL administrations with the

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

	Formulation and Recomm	nended Dosing
Baseline Resistance	Darunavir tablets with ritonavir tablets or capsule	Darunavir oral suspension (100 mg/mL) with ritonavir oral solution (80 mg/mL)
With no darunavir resistance associated substitutions <sup>a</sup>	One 800 mg darunavir tablet with one 100 mg ritonavir tablet/capsule, taken once daily with food	8 mL <sup>b</sup> darunavir oral suspension with 1.25 mL ritonavir oral solution, taken once daily with food
With at least one darunavir resistance associated substitutions <sup>a</sup> , or with no baseline resistance information	One 600 mg darunavir tablet with one 100 mg ritonavir tablet/capsule, taken twice daily with food	6 mL darunavir oral suspension with 1.25 mL ritonavir oral solution, taken twice daily with food

<sup>b</sup>An 8 mL darunavir dose should be taken as two 4 mL administrations with the included oral dosing syringe. 2.4 Recommended Dosage During Pregnancy

recommended or all dosage for treatment-experienced adult patients is summarized in Table 1.

The recommended dosage in pregnant patients is darunavir tablets 600 mg taken with ritonavir 100 mg twice daily with food. Darunavir tablets 800 mg taken with ritonavir 100 mg once daily should only be considered in certain pregnant patients who are already on a stable darunavir tablets 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 tablets 600 mg with ritonavir 100 mg may compromise tolerability or compliance. 2.5 Recommended Dosage in Pediatric Patients (age 3 to less than 18 years)

and dosing instruction to minimize risk for medication errors, overdose, and underdose. Prescribers should select the appropriate dose of darunavir tablets/ritonavir for each individual child based on body weight (kg) and should not exceed the Before prescribing darunavir tablets, children weighing greater than or equal to 15 kg should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a tablet, the use of darunavir oral suspension should be The recommended dose of darunavir tablets/ritonavir for pediatric patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see a commendation of the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see a commendation of the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see a commendation of the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see a commendation of the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and weighting at least 10 kg is based on body weight (see a commendation of the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and weighting at least 10 kg is based on body weighting the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and the pediatric patients). The recommendation of the pediatric patients (3 to less than 18 years of age and the pediatric patients). The recommendatiTables 2, 3, 4, and 5) and should not exceed the recommended adult dose. Darunavir tablets should be taken with ritonavir and with for The recommendations for the darunavir tablets/ritonavir dosage regimens were based on pediatric clinical trial data and population pharmacokinetic modeling and simulation /see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]. Dosing Recommendations for Treatment-Naïve Pediatric Patients or Antiretroviral Treatment-Experienced Pediatric Patients with No Darunavir Resistance

lealthcare professionals should pay special attention to accurate dose selection of darunavir tablets, transcription of the medication order, dispensing information

Pediatric Patients Weighing At Least 10 kg but Less than 15 kg The weight-based dose in antiretroviral treatment-naïve pediatric patients or antiretroviral treatment-experienced pediatric patients with no darunavir resistance associated substitutions is darunavir 35 mg/kg once daily with ritonavir 7 mg/kg once daily using the following table: Table 2: Recommended Dose for Pediatric Patients Weighing 10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Darunavir Resistance Associated Substitutions

Body weight (kg)	Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL)
	Dose: once daily with food
Greater than or equal to 10 kg to less than 11 kg	Darunavir 3.6 mL <sup>b</sup> (350 mg) with ritonavir 0.8 mL (64 mg)
Greater than or equal to 11 kg to less than 12 kg	Darunavir 4 mL <sup>b</sup> (385 mg) with ritonavir 0.8 mL (64 mg)
Greater than or equal to 12 kg to less than 13 kg	Darunavir 4.2 mL (420 mg) with ritonavir 1 mL (80 mg)
Greater than or equal to 13 kg to less than 14 kg	Darunavir 4.6 mL <sup>b</sup> (455 mg) with ritonavir 1 mL (80 mg)
Greater than or equal to 14 kg to less than 15 kg	Darunavir 5 mL <sup>b</sup> (490 mg) with ritonavir 1.2 mL (96 mg)

darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V <sup>b</sup> The 350 mg, 385 mg, 455 mg and 490 mg darunavir dose for the specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,

Pediatric Patients Weighing At Least 15 kg Pediatric patients weighing at least 15 kg can be dosed with darunavir oral tablet(s) or suspension using the following table:

Body weight (kg)	Formulation: Darunavir tablet(s) and ritonavir capsules or tablets (100 mg)	Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL)
	Dose: once daily with food	Dose: once daily with food
Greater than or equal to 15 kg to less than 30 kg	Darunavir tablets 600 mg with ritonavir 100 mg	Darunavir 6 mL (600 mg) with ritonavir 1.25 mL (100 mg)
Greater than or equal to 30 kg to less than 40 kg	Darunavir tablets 675 mg with ritonavir 100 mg	Darunavir 6.8 mL <sup>bc</sup> (675 mg) with ritonavir 1.25 m (100 mg)
Greater than or equal to 40 kg	Darunavir tablets 800 mg with ritonavir 100 mg	Darunavir 8 mL <sup>c</sup> (800 mg) with ritonavir 1.25 mL

 $darunavir\,resistance\,associated\,substitutions: V111, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V\,and\,L89V\,and$ The 675 mg dose using darunavir tablets for this weight group is rounded up to 6.8 mL for suspension dosing convenience The 6.8 mL and 8 mL darunavir dose should be taken as two (3.4 mL or 4 mL respectively) administrations with the included oral dosing syringe Dosing Recommendations for Treatment-Experienced Pediatric Patients with At Least One Darunavir Resistance Associated Substitutions

The weight-based dose in antiretroviral treatment-experienced pediatric patients with at least one darunavir resistance associated substitution is darunav

20 mg/kg twice daily with fituliavil 3 mg/kg twice daily using the follow	wing table.
Table 4: Recommended Dose for Pediatric Patients Weighing 10 Resistance Associated Substitution*	) kg to Less Than 15 kg Who are Treatment-Experienced with At Least One Darunavi
	Formulation: Darunavir oral suspension (100 mg/mL) and
Body weight (kg)	ritonavir oral solution (80 mg/mL)
	Dose: twice daily with food
Greater than or equal to 10 kg to less than 11 kg	Darunavir 2 mL (200 mg) with ritonavir 0.4 mL (32 mg)
Greater than or equal to 11 kg to less than 12 kg	Darunavir 2.2 mL (220 mg) with ritonavir 0.4 mL (32 mg)
Greater than or equal to 12 kg to less than 13 kg	Darunavir 2.4 mL (240 mg) with ritonavir 0.5 mL (40 mg)
Greater than or equal to 13 kg to less than 14 kg	Darunavir 2.6 mL (260 mg) with ritonavir 0.5 mL (40 mg)
Greater than or equal to 14 kg to less than 15 kg	Darunayir 2.8 mL (280 mg) with ritonayir 0.6 mL (48 mg)

a darunavir resistance associated substitutions: V11L V32L L33E I47V I50V I54M I54L T74P L76V I84V and L89V Pediatric Patients Weighing At Least 15 kg

Body weight (kg)	Formulation: Darunavir tablet(s) and ritonavir tablets, capsules (100 mg) or oral solution (80 mg/mL)	Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL)
	Dose: twice daily with food	Dose: twice daily with food
Greater than or equal to 15 kg to less than 30 kg	Darunavir tablets 375 mg with ritonavir 0.6 mL (48 mg)	Darunavir 3.8 mL (375 mg) <sup>5</sup> with ritonavir 0.6 mL (48 mg)
Greater than or equal to 30 kg to less than 40 kg	Darunavir tablets 450 mg with ritonavir 0.75 mL (60 mg)	Darunavir 4.6 mL (450 mg) <sup>b</sup> with ritonavir 0.75 mL (60 mg
Greater than or equal to 40 kg	Darunavir tablets 600 mg with ritonavir 100 mg	Darunavir 6 mL (600 mg) with ritonavir 1.25 mL (100 mg)

2.6 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 tablets/ritonavir when co-administered to subjects with severe hepatic impairment; therefore, darunavir tablets/ritonavir is not recommended for use in patients with severe hepatic impairment/see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

The use of darunavir tablets/ritonavir in pediatric patients below 3 years of age is not recommended (see Warnings and Precautions (5.10) and Use in Specific

3 DOSAGE FORMS AND STRENGTHS 600 mg: Yellow, oval shaped, biconvex, film-coated tablets debossed with 'V' on one side and '5' on the other side. 800 mg: Yellow, oval shaped, biconvex, film-coated tablets debossed with 'V' on one side and '7' on the other side.

4 CONTRAINDICATIONS Co-administration of darunavir tablets/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma

Co-administration of administration of administr Alpha 1-adrenoreceptor antagonist: alfuzosin
 Anti-gout: colchicine, in patients with renal and/or hepatic impairment

Antipsychotics: lurasidone, pimozide Cardiac Disorders: dronedarone, ivabradine, ranolazine

Ergot derivatives, e.g. dihydroergotamine, ergotamine, methylergonovine Herbal product: St. John's wort (Hypericum perforatum)

Hepatitis C direct acting antiviral: elbasvir/grazoprevir Lipid modifying agents: lomitapide, lovastatin, simvastatin Opioid Antagonist: naloxegol PDE-5 inhibitor: sildenafil when used for treatment of nulmonary arterial hypertension Sedatives/hypnotics: orally administered midazolam, triazolam

5 WARNINGS AND PRECAUTIONS 5.1 Importance of Co-administration with Ritonavir

Darunavir must be co-administered with ritonavir and food to achieve the desired antiviral effect. Failure to administer darunavir with ritonavir and food may result

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 onship with darunavir/ritonavir therapy has not been established. Appropriate laboratory testing should be conducted prior to initiating therapy with darunavir/ritonavir and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of darunavir/ritonavir treatment. Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea,

jaundice, dark urine, liver tenderness, hepatomegaly) in patients on darunavir/ritonavir should prompt consideration of interruption or discontin 5.3 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. Bash (all grades, regardless of causality) occurred in 10.3% of subjects treated with darunavir/ritonavir (see Adverse Reactions (6)). Bash was mostly mild-tomoderate, 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. Darunavir contains a sulfonamide moiety. Darunavir should be used with caution in patients with a known sulfonamide allergy. In clinical studies with 5.5 Risk of Serious Adverse Reactions due to Drug Interactions Initiation of darunavir/irtonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving darunavir/irtonavir, may increase plasma concentrations of medications metabolized by CYP3A and reduce plasma concentrations of active metabolite(s) formed by CYP3A.

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

narketing cases of liver injury, including some fatalities, have been reported. (5.2) Skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms and acute generalized exanthematous pustulosis, have been reported. Discontinue treatment if severe reaction develops. (5.3) Use with caution in patients with a known sulfonamide allergy. (5.4) Patients may develop new onset diabetes mellitus or hyperglycemia. Initiation or dose adjustments of insulin or oral hypoglycemic agents may be required. (5.6) Patients may develop redistribution/accumulation of body fat or immune reconstitution syndrome. (5.7, 5.8)

nded in pediatric patients below 3 years of age in view of toxicity and mortality observed in juvenile rats dosed with darunavir up to days 23 to 26 of age. (5.10) -----ADVERSE REACTIONS----The most common clinical adverse drug reactions to darunavir/ritonavir (incidence greater than or equal to 5%) of at least moderate intensity (greater than or

equal to Grade 2) were diarrhea, nausea, rash, headache, abdominal pain and vomiting, (6) To report SUSPECTED ADVERSE REACTIONS, contact Annora Pharma Private Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or ....DRUG INTERACTIONS... Co-administration of darunavir/ritonavir with other drugs can alter the concentrations of other drugs and other drugs may alter the concentrations of

 $darunavir. \ The potential\ drug-drug\ interactions\ must\ be\ considered\ prior\ to\ and\ during\ therapy.\ (4,5.5,7,12.3)$ .....USE IN SPECIFIC POPULATIONS..... Pregnancy: Total darunavir exposures were generally lower during pregnancy compared to postpartum period. The reduction in darunavir exposures during pregnancy were greater for once daily dosing compared to the twice daily dosing regimen. (8.1, 12.3)

Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)

Pediatrics: Not recommended for patients less than 3 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

13 NONCLINICAL TOXICOLOGY

CLINICAL STUDIES

14.4 Pediatric Patients

14.1 Description of Adult Clinical Trials

16 HOW SUPPLIED/STORAGE AND HANDLING 17 PATIENT COUNSELING INFORMATION

14.2 Treatment-Naïve Adult Subjects
14.3 Treatment-Experienced Adult Subjects

Sections or subsections omitted from the full prescribing information are not listed.

Patients with hemonhilia may develon increased bleeding events (5.9)

Revised: 01/2025

	7.4	Drugs without Clinically Significant Interactions with Darunavir
8	USEI	N SPECIFIC POPULATIONS
	8.1 8.2 8.3 8.4 8.5 8.6 8.7	Pregnancy Lactation Females and Males of Reproductive Potential Pediatric Use Geriatric Use Hepatic Impairment Renal Impairment
10	OVER	DOSAGE
11	DESC	RIPTION
12	12.1 12.2	Pharmacodynamics Pharmacokinetics
	12.4	Microbiology

See Table 10 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations (see Drug Interactions (7)). onsider the potential for drug interactions prior to and during darunavir/ritonavir therapy; review concomitant medications during darunavir/ritonavir therapy; and monitor for the adverse reactions associated with the concomitant drugs [see Contraindications (4) and Drug Interactions (7)]. 5.6 Diabetes Mellitus/Hyperglycemia
New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIVinfected 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 disconlinued 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

5.7 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.

5.8 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

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with Pls. 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. 5.10 Not Recommended in Pediatric Patients Below 3 Years of Age Darunavir/irtonavir in pediatric patients below 3 years of age is not recommended in view of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age (see Use in Specific Populations (8.1 and 8.4) and Clinical Pharmacology (12.3)].

6 ADVERSE REACTIONS he following adverse reactions are discussed in other sections of labeling: Hepatotoxicity *(see Warnings and Precautions (5.2))* 

Severe Skin Reactions [see Warnings and Precautions (5.3)] Diabetes Mellitus/Hyperglycemia [see Warnings and Precautions (5.6)]

Fat Redistribution/see Warnings and Precautions (5.7)|
Immune Reconstitution Syndrome (see Warnings and Precautions (5.8)) Hemophilia (see Warnings and Precautions (5.9))

adult subjects are presented in Table 6 and subsequent text below the table.

Due to the need for co-administration of darunavir with ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions. 6.1 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. Freatment 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 In a sarry assertion and the sarry transfer of the sarry transfer 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) vere diarrhea, headache, abdominal pain and rash. 2.3% of subjects in the darunavir/ri nued 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

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

Freatment-emergent ADRs of at least moderate intensity (greater than or equal to Grade 2) occurring in less than 2% of antiretroviral treatment-naïve subjects

\*Excluding laboratory abnormalities reported as ADRs

 $N-total \ number \ of \ subjects \ per \ treatment \ group; \ FTC-emtric itabine; \ TDF-tenofovir \ disoproxil \ fumarate$ 

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 Psychiatric Disorders: abnormal dreams

Table 7: Grade 2 to 4 Laboratory Abnormalities Observed in Antiret

Skin and Subcutaneous Tissue Disorders: angioedema, pruritus, Stevens-Johnson Syndrome, urticariaSelected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-naïve adult subjects treated with r/ritonavir 800/100 mg once daily are presented in Table 7.

viral Treatment-Naïve HIV-1-Infected Adult Subjects\* (Trial TMC114-C211)

ritonavir 800/100 mg lopinavir/ritonavir 800/200 mg once daily + TDF/FTC per day + TDF/FTC Alanine Aminotransferase > 2.5 to  $\leq$  5.0 X ULN Grade 2 Grade 3 > 5.0 to  $\leq$  10.0 X ULN <1% 3% Aspartate Amino > 2.5 to  $\leq$  5.0 X ULN 10% Grade 2 Grade 3 > 5.0 to  $\leq$  10.0 X ULN 4% 2% Grade 4 >10.0 X ULN Grade 2 > 2.5 to  $\leq$  5.0 X ULN Grade 3 > 5.0 to  $\leq$  10.0 X ULN <1% Grade 4 >10.0 X ULN 0% Hyperbilirubin Grade 2 > 1.5 to  $\leq 2.5$  X ULN Grade 3 > 2.5 to  $\leq$  5.0 X ULN <1% < 1% >5.0 X ULN Grade 4 5.65 to 8.48 mmol/L Grade 3 8.49 to 13.56 mmol/L 751 to 1200 mg/dL Grade 4 >1200 mg/dL Total Cholesterol 6.20 to 7.77 mmol/L 23% 27% 240 to 300 mg/dL Grade 3 5% > 7.77 mmol/L > 300 mg/dL Low-Density Lipoprotein Choles 14% 12% Grade 2 4.13 to 4.90 mmol/L 160 to 190 mg/dL Grade 3 ≥4.91 mmol/  $\geq$  191 mg/dL

**Elevated Glucose Levels** 6.95 to 13.88 mmol/L 126 to 250 mg/dL 251 to 500 mg/dL Grade 4 > 27.75 mmol/L 0% 0% > 500 mg/dL Pancreatic Lipase Grade 2 > 1.5 to  $\leq$  3.0 X ULN Grade 3 > 3.0 to  $\leq$  5.0 X ULN < 1% 1% Grade 4 >5.0 X ULN < 1% Pancreatic Amylas Grade 2 > 1.5 to  $\leq$  2.0 X ULN

Grade 4 >5.0 X ULN 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.

> 2.0 to  $\leq$  5.0 X ULN

Grade 3

Skin and Subcutaneous Tissue Disorders: pruritus, urticaria

with darunavir/ritonavir 600/100 mg twice daily are presented in Table 9.

Laboratory Abnormalities

Ireatment-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 Iopinavir/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/iritonavir 600/100 mg twice daily were mild in severity. The most common clinical ADRs to darunavir/irtonavir 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/irtonavir 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

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

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

Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated

(The reference regimen for rifabutin was 300 mg once daily.)

rifampin

rifapentine

dasatinib, nilotinib

darunavii

rifabutin

25*-0-*desacetylrifabutir

600/100 mg twice daily Biochemistry Alanine Aminotransferase Grade 2 > 2.5 to  $\leq$  5.0 X ULN > 5.0 to  $\leq$  10.0 X ULN Grade 3 Grade 4

Table 9: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Experienced HIV-1-Infected Adult Subjects' (Trial

Laboratory parameter, %

Darunavir/ritonavir

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 to 8.48 mmol/L 500 to 750 mg/dL	10%	11%
Grade 3	8.49 to 13.56 mmol/L 751 to 1200 mg/dL	7%	10%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	3%	6%
Total Cholesterol		•	
Grade 2	6.20 to 7.77 mmol/L 240 to 300 mg/dL	25%	23%
Grade 3	>7.77 mmol/L >300 mg/dL	10%	14%
Low-Density Lipoprotein Cholester	ol		
Grade 2	4.13 to 4.90 mmol/L 160 to 190 mg/dL	14%	14%
Grade 3	≥ 4.91 mmol/L ≥ 191 mg/dL	8%	9%
Elevated Glucose Levels			
Grade 2	6.95 to 13.88 mmol/L 126 to 250 mg/dL	10%	11%
Grade 3	13.89 to 27.75 mmol/L 251 to 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 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/rito abdominal pain, acute hepatitis, acute pancreatitis, anorexia, asthenia, diabetes mellitus, diarrhea, fatique, headache, hepatic enzyme increased, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, immune reconstitution syndrome, low density lipoprotein increased, nausea, pancreatic enzym increased, rash, Stevens-Johnson Syndrome, and vomiting. Patients Co-Infected with Hepatitis B and/or Hepatitis C Virus

> 2.0 to  $\leq$  5.0 X ULN

N = total number of subjects per treatment group: ORR = optimized background regimes

In subjects co-infected with hepatitis B or C virus receiving darunavir/ritonavir, the incidence of adverse events and clinical chemistry abnormalities was not higher than in subjects receiving darunavir/ritonavir who were not co-infected, except for increased hepatic enzymes [see Warnings and Precautions (5.2)]. 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 treatmentexperienced 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 021 antiretroviral treatment-experienced HIV-1-infected pediatric subjects 6 to less than 6 years of age and weighing at least 20 kg were included, TMC114-C228, in which 021 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 TMC114-22 and the TMC114-C230 trial evaluated darmavirintonavir twice daily dosing and the TMC114-C230 trial evaluated darmavirintonavir twice daily dosing and the TMC114-C230 trial evaluated darmavirintonavir twice daily dosing and the TMC114-C230 trial evaluated darmavirintonavir twice daily dosing and the TMC114-C230 trial evaluated darmavirintona 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 There were no Grade 3 or 4 laboratory abnormalities considered as ADRs in this trial.

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%), ecreased 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 6.2 Postmarketing Experience The following adverse reactions have been identified during post-approval use of darunavir. Because these reactions 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 Metabolism and Nutrition Disorders: Redistribution of body fat

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis (associated with co-administration with HMG-CoA reductase inhibitors and darunavir/ritonavir) Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, acute generalized exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms [see Warnings and Precautions (5.3)] Renal and Urinary Disorders: Crystal nephropathy, crystalluria DRUG INTERACTIONS 7.1 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. Darunavir co-administered with ritonavir with drugs that have active metabolite(s) formed by CYP3A may result in reduced

plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect (see Table 10).

7.2 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 concentration of darunavir and ritonavir (see Table 10). 7.3 Established and Other Potentially Significant Drug Interactions Table 10 provides dosing recommendations as a result of drug interactions with darunavir/ritonavir. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. The table includes examples of potentially significant interactions but is not all inclusive [see Contraindications (4) and Clinical Pharmacology (12.3)], and therefore the label of each

drug that is co-administered with darunavir/ritonavir should be consulted for information related to the route of metabolism, interaction pathways, potential risks,

and specific actions to be taken with regard to co-administration. Table 10: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (see Contraindications (4) for a list of examples of contraindicated drugs) [see Clinical Pharmacology (12.3) for Magnitude of Interaction, Tables 15 and 16] Darunavir Or Concomitant Drug Clinical Comment Drug Name Example: HIV · 1 · Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs) → didanosine after darunavir/ritonavir (which are administered with food). HIV-1-Antiviral Agents: HIV-Proteas Inhibitors (PIs) The appropriate dose of indinavir in combination with darunavir Indinavir (The reference regimen for indinavir ↑ indinavir ritonavir has not been established. lopinavir/ritonavir Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer lopinavir/rit and darunavir, with or without ritonavir. → lopinavir darunavii Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer saquinavir and

Other HIV protease inhibitors, except atazanavir /see Drug	↔ saquinavir	Hence, it is not recommended to co-administer saquinavir and darunavir, with or without ritonavir. As co-administration with darunavir/ritonavir has not been studied, co-administration is not recommended.
Interactions (7.4)]		
HIV-1-Antiviral Agents: CCR5 co-rece		I
maraviroc	↑ maraviroc	When used in combination with darunavir/ritonavir, the dose of maraviroc should be 150 mg twice daily.
Other Agents		,
Alpha 1-adrenoreceptor antagonist:		
alfuzosin	↑ alfuzosin	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.
Antibacterial:		and/or me-timeatening reactions such as hypotension.
Antuacterial: clarithromycin	↔ darunavir ↑ clarithromycin	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:  • For subjects with CLcr of 30 to 60 mL/min, the dose of clarithromycin should be reduced by 50%.  • For subjects with CLcr of < 30 mL/min, the dose of clarithromycin should be reduced by 75%.
Anticoagulants:		
Direct Oral Anticoagulants (DOACs) apixaban	† apixaban	Due to potentially increased bleeding risk, dosing recommendations for co-administration of apixaban with darunavir/intonavir depend on the apixaban dose. Refer to apixaban dosing instructions for co-administrati with P.gp and strong CYP3A inhibitors in apixaban prescribing informat
rivaroxaban	↑ rivaroxaban	Co-administration of darunavir/ritonavir and rivaroxaban is not recommended because it may lead to an increased bleeding risk.
dabigatran etexilate edoxaban	↑ dabigatran ↑ edoxaban	Refer to the dabigatran etexilate or edoxaban prescribing informati for recommendations regarding co-administration. The specific recommendations are based on indication, renal function, and effec of the co-administered P-gp inhibitors on the concentration of dabigatran or edoxaban. Clinical monitoring is recommended when is DDAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with darunav /ritonavir.
Other Anticoagulants warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations are decreased when co-administered with darunavitritionavir. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with darunavitritionavir.
Anticonvulsants: carbamazepine	↔ darunavir ↑ carbamazepine	The dose of either darunavir/ritonavir or carbamazepine does not need to be adjusted when initiating co-administration with darunav ritonavir and carbamazepine. Clinical monitoring of carbamazepine concentrations and its dose titration is recommended to achieve the desired clinical response.
clonazepam	↑ clonazepam	Clinical monitoring of anticonvulsants that are metabolized by CYP3A is recommended.
phenobarbital, phenytoin	↔ darunavir ↓ phenytoin ↓ phenobarbital	Phenytoin and phenobarbital levels should be monitored when co- administering with darunavir/ritonavir.
Antidepressants:		
Selective Serotonin Reuptake Inhibitors (SSRIs): paroxetine, sertraline	↓ paroxetine ↓ sertraline	If either sertraline or paroxetine is initiated in patients receiving darunavir/ritonavir, dose titrating the SSRI based on a clinical assessment of antidepressant response is recommended. Monitor for antidepressant response in patients on a stable dose of sertraline or paroxetine who start treatment with darunavir/ritonavir.
<u>Tricyclic Antidepressants (TCAs):</u> amitriptyline, desipramine,		
amurptymie, desipramine, imipramine, nortriptyline	↑ amitriptyline ↑ desipramine ↑ imipramine ↑ nortriptyline	Use a lower dose of the tricyclic antidepressants and trazodone due to potential increased adverse events such as nausea, dizziness, hypotension and syncope.
Other:		
trazodone	↑ trazodone	
Antifungals:		
itraconazole, isavuconazole, ketoconazole, posaconazole voriconazole	↑ darunavir ↑ itraconazole ↑ isavuconazole ↑ ketoconazole ↔ posaconazole ↓ voriconazole	Monitor for increased darunavir/irtonavir and/or antifungal adverse events with concomitant use of these antifungals. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg with monitoring for increased antifungal adverse events.  Voriconazole is not recommended for patients receiving darunavir //irtonavir unless an assessment comparing predicted benefit to risk ratio justifies the use of voriconazole.
Anti-gout: colchicine	↑ colchicine	Co-administration is contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or
		life-threatening reactions.  For patients without renal or hepatic impairment:  • Treatment of gout-flares –co-administration of colchicine inpatients on darunavir/irionavir; 0.6 mg (1 tablet) × 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days.  • Prophylaxis of gout-flares –co-administration of colchicine inpatients on darunavir/irionavir:  If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day, the regimen should be adjusted to 0.3 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.  • Treatment of familial Mediterranean fever –co-administration of colchicine in patients on darunavir/irionavir:  maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimalarial: artemether/lumefantrine	↓ artemether     ↓ dihydroartemisinin     ↑ lumefantrine     ↔ darunavir	The combination of darunavir/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.

Co-administration is contraindicated due to potential for loss of

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.

Co-administration of darunavir/ritonavir with rifapentine is not

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.

therapeutic effect and development of resistance

Drug Name vinblastine, vincristine	Darunavir Or Concomitant Drug	Clinical Comment  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/irtonavir is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consideration should be given to initiating a revised regimen that does not include a CYP3A or P-gp inhibitor.
Antipsychotics: lurasidone	↑ lurasidone	Co-administration is contraindicated due to potential for serious
pimozide	↑ pimozide	and/or life-threatening reactions.  Co-administration is contraindicated due to potential for serious
quetiapine	↑ quetiapine	and/or life-threatening reactions such as cardiac arrhythmias.  Initiation of darunavir with ritonavir in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in
		quetiapine exposures. If co-administration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for
		quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring.
		Initiation of quetiapine in patients taking darunavir with ritonavir: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
e.g. perphenazine, risperidone, thioridazine	† antipsychotics	A decrease in the dose of antipsychotics that are metabolized by CYP3A or CYP2D6 may be needed when co-administered with
β-Blockers:		darunavir/ritonavir.
e.g. carvedilol, metoprolol, timolol	↑ beta-blockers	Clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with darunavir/ritonavir and a lower dose of the beta blocker should be considered.
Calcium Channel Blockers: amlodipine, diltiazem, felodipine,	↑ calcium channel blockers	Clinical monitoring of patients is recommended.
nicardipine, nifedipine, verapamil  Cardiac Disorders:		
ranolazine, ivabradine 	↑ ranolazine  ↑ ivabradine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
dronedarone Other antiarrhythmics	↑ dronedarone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
e.g. amiodarone, bepridil, disopyramide, flecainide, lidocaine	↑ antiarrhythmics	Therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with darunavir/ritonavi
(systemic), mexiletine, propafenone, quinidine		
digoxin	↑ digoxin	The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Corticosteroids: dexamethasone (systemic)	↓ darunavir	Co-administration of darunavir/ritonavir with systemic dexamethaso
		or other systemic corticosteroids that induce CYP3A may result in lo of therapeutic effect and development of resistance to darunav Consider alternative corticosteroids.
Corticosteroids primarily metabolized by CYP3A:	↑ corticosteroids	Co-administration with corticosteroids (all routes of administration which exposures are significantly increased by strong CYP3A inhibi
e.g. betamethasone		can increase the risk for Cushing's syndrome and adrenal suppression  Alternative corticosteroids including beclomethasone, prednisone,
budesonide ciclesonide fluticasone		prednisolone (for which PK and/or PD are less affected by strong CY inhibitors relative to other steroids) should be considered, particul
methylprednisolone mometasone		for long term use.
triamcinolone Endothelin receptor antagonist:		
bosentan	↑ bosentan	Co-administration of bosentan in patients on darunavir/ritonavir: In patients who have been receiving darunavir/ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every
		other day based upon individual tolerability.  Co-administration of darunavir/ritonavir in patients on bosentan:
		Discontinue use of bosentan at least 36 hours prior to initiation of darunavir/ritonavir. After at least 10 days following the
Enne de de		initiation of darunavir/ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
Ergot derivatives: e.g. dihydroergotamine, ergotamine,	↑ ergot derivatives	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity
methylergonovine		and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Hepatitis C virus (HCV):  Direct-Acting Antivirals:	Adl	
elbasvir/grazoprevir	↑elbasvir/grazoprevir	Co-administration is contraindicated due to potential for the increased risk of alanine transaminase (ALT) elevations.
glecaprevir/pibrentasvir	↑ glecaprevir ↑ pibrentasvir	Co-administration of darunavir/ritonavir with glecaprevir/pibrentasvir is not recommended.
Herbal product: St. John's wort (Hypericum	↓ darunavir	Co-administration is contraindicated due to potential for reduced
perforatum)		plasma concentrations of darunavir, which may result in loss of therapeutic effect and development of resistance.
Hormonal contraceptives:		Effective alternative (non-hormonal) contraceptive method or a barrier method of contraception is recommended <i>(see Use in</i>
ethinyl estradiol,	↓ ethinyl estradiol	Specific Populations (8.3)].  For co-administration with drospirenone, clinical monitoring is
norethindrone, drospirenone	↓ norethindrone	recommended due to the potential for hyperkalemia.
	drospirenone: effects unknown	No data are available to make recommendations on co-administrat with other hormonal contraceptives.
Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus	† immunosuppressants	Therapeutic concentration monitoring of the immunosuppressive agent is recommended when co-administered with darunavir/
Immunosuppressant/neoplastic:		ritonavir.
everolimus		Co-administration of everolimus and darunavir/ritonavir is not recommended.
irinotecan		Discontinue darunavir/ritonavir at least 1 week prior to starting irinotecan therapy. Do not administer darunavir/ritonavir with irinotecan unless there are no therapeutic alternatives.
Inhaled beta agonist: salmeterol	↑ salmeterol	rinotecan unless there are no therapeutic alternatives.  Co-administration of salmeterol and darunavir/ritonavir is not
		recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Lipid Modifying Agents: HMG·CoA reductase inhibitors:		- Francisco and sinus taurifudiula.
HMG-COA reductase inhibitors: lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis.
atorvastatin, pravastatin, rosuvastatin	HMG-CoA reductase     inhibitors	Co-administration of darunavir/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
Other lipid modifying agents:		events. Do not exceed atorvastatin 20 mg/day.
lomitapide	↑ lomitapide	Co-administration is contraindicated due to potential for markedly increased transaminases.
Narcotic analgesics metabolized by CYP3A: e.g. fentanyl, oxycodone	↑ fentanyl	Caroful manitoring of the caronic off
o.g. remanyi, uxyeudone	↑ tentanyl	Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A- metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended
tramadol	↑ tramadol	with co-administration.  A dose decrease may be needed for tramadol with concomitant use.
Narcotic analgesics/treatment of opioid dependence:		
buprenorphine, buprenorphine/naloxone	<ul> <li>→ buprenorphine, naloxone</li> <li>↑ norbuprenorphine</li> <li>(metabolite)</li> </ul>	No dose adjustment for buprenorphine or buprenorphine/naloxone is required with concurrent administration of darunavir/ritonavir.
methadone		Clinical monitoring is recommended if darunavir/ritonavir and buprenorphine or buprenorphine/naloxone are co-administered.
methadone	↓ methadone	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
Opioid Antagonist		maintenance therapy may need to be adjusted in some patients.
naloxegol	↑ naloxegol	Co-administration of darunavir/ritonavir and naloxegol is contraindicated due to potential for precipitating opioid withdrawal symptoms.
PDE-5 inhibitors: e.g. avanafil, sildenafil, tadalafil,	↑ PDE-5 inhibitors (only the	Co-administration with darunavir/ritonavir may result in an
vardenafil	use of sildenafil at doses used for treatment of erectile	increase in PDE-5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances and priapism.
	dysfunction has been studied with darunavir/ritonavir)	Use of PDE-5 inhibitors for pulmonary arterial hypertension
		(PAH):  Co-administration with sildenafil used for PAH is contraindicated
		due to potential for sildenafil associated adverse reactions (which include visual disturbances, hypotension, prolonged erection, and syncope).
		The following dose adjustments are recommended for use of
		tadalafil with darunavir/ritonavir:  Co-administration of tadalafil in patients on darunavir/ritonavi In patients receiving darunavir/ritonavir for at least one week,
		start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.
		Co-administration of darunavir/ritonavir in patients on tadalafil:
		Avoid use of tadalafil during the initiation of darunavir/ ritonavir. Stop tadalafil at least 24 hours prior to starting darunavir/ritonavir. After at least one week following the
		initiation of darunavir/ritonavir, resume tadalafil at 20 mg
		once daily. Increase to 40 mg once daily based upon individual
		once daily. Increase to 40 mg once daily based upon individual tolerability.  Use of PDE-5 inhibitors for erectile dysfunction:
		tolerability.

solifenacin solifenacin not exceed a solifenacin dose of 5 mg once daily. 7.4 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. 8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Pregnancy Exposure Registry

Platelet aggregation inhibitor

prasugrel

Proton pump inhibitor

Sedatives/hypnotics:

metabolized by CYP3A

e.g. buspirone, diazepam, estazolam, zolpidem

parenterally administered

↓ clopidogrel active

→ prasugrel active

triazolam

sedatives/hypnotics

Co-administration of darunavir/ritonavir and ticagrelor is not

Co-administration of darunavir/ritonavir and clonidogral is not

recommended due to potential reduction of the antiplatelet

No dose adjustment is needed when prasugrel is co-administered

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

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

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

Co-administration of parenteral midazolam should be done in a

setting which ensures close clinical monitoring and appropriate

medical management in case of respiratory depression and/or

prolonged sedation. Dosage reduction for midazolam should be

considered, especially if more than a single dose of midazolam is

When fesoterodine is co-administered with darunavir/ritonavir, do

When solifenacin is co-administered with darunavir/ritonavir, do

monitoring for adverse events.

activity of clopidogrel.

Risk Summary Prospective pregnancy data from the APR are not sufficient to adequately assess the risk of birth defects or miscarriage. Available limited data from the APR show no statistically significant difference in the overall risk of major birth defects for darunavir compared with the background  $rate for major birth \ defects \ of \ 2.7\% \ in \ a \ U.S. \ reference \ population \ of \ the \ Metropolitan \ Atlanta \ Congenital \ Defects \ Program \ (MACDP) \ / see \ Data).$ 

There is a prognancy exposure registry that monitors pregnancy outcomes in women exposed to darunavir during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) 1-800-258-4263.

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 to 20%. The background risk of major birth defects and miscarriage for the indicated population is unknown as  $\frac{1}{2}$  and  $\frac{1}{2}$  is 15 to 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 **Clinical Considerations** 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 Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

Darunavir/iritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 36 pregnant women during the second and third trimesters, and postpartum. Eighteen subjects were enrolled in each BID and OD treatment arms. Twenty-nine subjects completed the trial through the postpartum period (6 to 12 weeks after delivery) and 7 subjects discontinued before trial completion, 5 subjects in the BID arm and The pharmacokinetic data demonstrate that exposure to darunavir and ritonavir as part of an antiretroviral regimen was lower during pregnancy compared with postpartum (6 to 12 weeks). Exposure reductions during pregnancy were greater for the once daily regimen as compared to the twice daily regimen [see Clinical Virologic response was preserved. In the BID arm, the proportion of subjects with HIV-1 RNA < 50 copies/mL were 39% (7/18) at baseline, 61% (11/18) through ne third trimester visit, and 61% (11/18) through the 6 to 12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA

≥ 50 copies/mL for 11% (2/18) of subjects and were missing for 5 subjects (1 subject discontinued prematurely due to virologic failure). In the QD arm, the proportion of subjects with HIV-1 RNA < 50 copies/mL were 61% (11/18) at baseline, 83% (15/18) through the third trimester visit, and 78% (14/18) through the 6 to 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 Tablets	
Read this Patient Information before you start taking darunavir tablets and each time you.  There may be new information. This information does not take the place of talking to your provider about your medical condition or your treatment.	ime you get a refill. to your healthcare
<ul> <li>Also read the Patient Information leaflet for ritonavir.</li> <li>What is the most important information I should know about darunavir tablets?</li> <li>Ask your healthcare provider or pharmacist about medicines that should no with darunavir tablets. For more information, see "Who should not take tablets?" and "What should I tell my healthcare provider before taking</li> </ul>	olets? ould not be taken t take darunavir taking darunavir
<ul> <li>Darunavir tablets may cause liver problems. Some people taking darunavir tablets in combination with ritonavir have developed liver problems, which may be life-threatening. Your healthcare provider should do blood tests before and during your darunavir tablets and ritonavir combination treatment. If you have chronic hepatitis B or C infection, your healthcare provider should check your blood tests more often because you have an increased chance of developing liver problems. Tell your healthcare provider if you have any of the below signs and symptoms of liver problems.</li> </ul>	rrunavir tablets in threatening. Your blets and ritonavir nealthcare provider ance of developing s and symptoms of s
o dark (tea colored) urine o vomiting o yellowing of your skin or o pain or tenderness on whites of your eyes your right side below your ribs o pale colored stools o loss of appetite (bowel movements) o nausea o tiredness	
arunavir tablets may cause severe or life-threatening ometimes these skin reactions and skin rashes can become seve spital. Tell your healthcare provider right away if you develop ablets and ritonavir combination treatment and tell your healthcave any skin changes with symptoms below:  Oblisters or skin lesions	skin reactions or rash. se and require treatment in a a rash. Stop taking darunavir are provider right away if you
O tiredness O mouth sores or ulcers O muscle or joint pain O red or inflamed eyes, like "pink eye" (conjunctivitis) Rash occurred more often in people taking darunavir tablets and raltegravir together than with either drug separately, but was generally mild. See "What are the possible side effects of darunavir tablets?" for more information about side	) ner than with either rmation about side
What are darunavir tablets?  What are darunavir tablets?  Darunavir tablets are a prescription HIV-1 (Human Immunodeficiency Virus-type 1) medicine us with ritonavir and other antiretroviral medicines to treat HIV-1 infection in adults and children years of age and older. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).	e 1) medicine used ults and children 3 ancy Syndrome).
<ul> <li>When used with other antiretroviral medicines to treat HIV-1 infection, darunavir tablets may he reduce the amount of HIV-1 in your blood. This is called "viral load".</li> <li>increase the number of CD4 + (T) cells in your blood that help fight off other infections.</li> <li>Reducing the amount of HIV-1 and increasing the CD4 + (T) cells in your blood may improve immune system. This may reduce your risk of death or getting infections that can happen when immune system.</li> </ul>	ablets may help: ections. may improve your
Darunavir tablets does not cure HIV-1 infection or AIDS. You must keep taking HIV-1 to control HIV-1 infection and decrease HIV-related illnesses.	ng HIV-1 medicines
<ul> <li>Avoid doing things that can spread HIV-1 infection to others:</li> <li>Do not share or re-use needles or other injection equipment.</li> <li>Do not share personal items that can have blood or body fluids on them, like toothbrushes</li> </ul>	toothbrushes and
<ul> <li>razor blades.</li> <li>Do not have any kind of sex without protection. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or in the chance of sexual contact with semen, vaginal secretions, or in the chance of sexual contact with semen.</li> </ul>	by using a latex or ginal secretions, or
bloou.  Ask your healthcare provider if you have any questions on how to prevent pas people.	prevent passing HIV to other
Who should not take darunavir tablets?  Do not take darunavir tablets with any medicine that contains:	
<ul> <li>alfuzosin</li> <li>colchicine, if you have liver or kidney problems</li> <li>dronedarone</li> </ul>	
O dinydroergotamine O ergotamine tartrate O methylergonovine	
naloxegol pimozide	
ranolazine rifampin sildenafil. when used for the treatment of pulmonary arterial hypertension (P	AH)
n wort ( <i>Hypericum perforatum</i> )	:
triazolam erious problems can happen if you or your child take any of these iblets.This is not a complete list of medicines. Therefore, tell your he	medicines with darunavir althcare provider about all
What should I tell my healthcare provider before taking darunavir tablets?  Before taking darunavir tablets, tell your healthcare provider if you:  have liver problems, including hepatitis B or hepatitis C	
are allergic to sulfa medicines have high blood sugar (diabetes)	
<ul> <li>nave nemopmina</li> <li>have any other medical conditions</li> <li>are pregnant or plan to become pregnant. Tell your healthcare provider if you</li> </ul>	u become pregnant
while taking darunavir tablets.  O <b>Pregnancy Registry</b> : There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in	take antiretroviral ormation about the ou can take part in
<ul> <li>this registry.</li> <li>are breastfeeding or plan to breastfeed. Do not breastfeed if you take darunavir tablets.</li> <li>Vou should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to yo</li> <li>It is not known if darunavir can pass into your breast milk.</li> </ul>	r tablets. IV-1 to your baby.
o Talk to your healthcare provider about the best way to feed your baby.	

	Artwork information				
Customer	Camber	Market	USA		
Dimensions (mm)	480 x 900 mm	Non Printing Colors	Die cut		
Pharma Code No.	Front-345 & Back-346				
Printing Colours	Black				
Others: Pharma code based on fold	position and Orientatio	on are tentative, will be	e changed		

Darunavir/ritonavir was well tolerated during pregnancy and postpartum. There were no new clinically relevant safety findings compared with the known safety Among the 31 infants with HIV test results available data, born to the 31 HIV-infected pregnant women who completed trial through delivery or postpartum period. all 31 infants had test results that were negative for HIV-1 at the time of delivery and/or through 16 weeks postpartum. All 31 infants received anti prophylactic treatment containing zidovudine. Based on prospective reports to the APR of over 980 exposures to darunavir- containing regimens during pregnancy resulting in live births (including over 660 exposed in the first trimester and over 320 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.6.% (95% CI; 2.3% to 5.3.%) with first trimester exposure to darunavir-containing regimens and 2.5% (95% Cl: 1.1% to 4.8%) with second/third trimester exposure to darun

Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice (doses up to 1000 mg/kg from gestation day (GD) 6 to 15 with darunavir alone) and rats (doses up to 1000 mg/kg from GD 7 to 19 in the presence or absence of ritonavir) as well as in rabbits (doses up to 1000 mg/kg/day from GD 8 to 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. 8.2 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 Use in Specific Populations (8.4)].

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.

8.3 Females and Males of Reproductive Potential Use of darunavir may reduce the efficacy of combined hormonal contraceptives and the progestin only pill. Advise patients to use an effective alternative (nonhormonal) contraceptive method or add a barrier method of contraception. For co-administration with drospirenone, clinical monitoring is recommended due to the

potential for hyperkalemia [see Drug Interactions (7.3)]. 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  $20\,mg/kg\,to\,1000\,mg/kg)\,up\,to\,days\,23\,to\,26\,of\,age/see\,\textit{Warnings and Precautions}\,(5.10), \textit{Use in Specific Populations}\,(8.1)\,and\,\textit{Clinical Pharmacology}\,(12.3)/.$ The safety, pharmacokinetic profile, and virologic and immunologic responses of darunavir/irtonavir administered twice daily were evaluated in treatment-experienced HIV-1-infected pediatric subjects 3 to less than 18 years of age and weighting at least 10 kg. These subjects were evaluated in clinical trials TMC114-C212 (80 subjects, 6 to less than 18 years of age) and TMC114-228 (21 subjects, 3 to less than 6 years of age) [see Adverse Reactions (6.1), Clinical plogy (12.3) and Clinical Studies (14.4)]. Frequency, type, and severity of adverse drug reactions in pediatric subjec in adults [see Adverse Reactions (6.1)]. Refer to Dosage and Administration (2.5) 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-naive. HIV-1 infected pediatric subjects 12 to less than 18 years of age [12 subjects] /see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.4). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults /see Adverse Reactions (6.1). 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 Clinical Pharmacology (12,3)). Please see ation (2.5) 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 level

to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) 2 times the human plasma 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 decrepancy of 8.6 Hepatic Impairment

ment of darunavir/ritonavir is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are

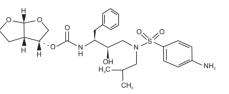
ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2

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 Dosage and Administration (2.6) and Clinical Pharmacology (12.3)). Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected subjects with moderate renal impairment (CrCL between 30 to 60 mL/min, n = 20). No pharmacokinetic data are available in HIV-1-infected patients with severe renal impairment or end stage renal disease; however, because the renal clearance of darunavir is limited, a decrease in 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 Clinical 10 OVERDOSAGE Human experience of acute overdose with darunavir/ritonavir is limited. No specific antidote is available for overdose with darunavir. Treatment of overdose with

darunavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance. 11 DESCRIPTION odeficiency virus (HIV-1) protease

Darunavir, in the form of darunavir amorphous, has the following chemical name: [(1S,2R-3-[[(4-Amino-pheny|]sulfonyl)]/2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]-furan-3-yl ester. Its molecular formula is C<sub>2</sub>,H<sub>2</sub>,N<sub>2</sub>O,S and its molecular weight is 547.67. Darunavir amorphous has the following structural formula:



Darunavir amorphous is an off-white to pale brown colored powder, freely soluble in chloroform and in dichloromethan Darunavir 600 mg tablets are available as yellow, oval shaped, biconvex, film-coated tablets debossed with 'V' on one side and '5' on the other side. Each 600 mg Darunavir 800 mg tablets are available as yellow, oval shaped, biconvex, film-coated tablets debossed with 'V' on one side and '7' on the other side. Each 800 mg tablet contains darunavir amorphous equivalent 800 mg of darunavir. Each tablet also contains the inactive ingredients colloidal silicon dioxide, crospovidone, magnesium stearate, silicified microcrystalline cellulose. The film coating contains iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide All dosages for darunavir are expressed in terms of the free form of darunavir 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action Darunavir is an HIV-1 antiviral drug /see Microbiology (12.4)]. 12.2 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.

Pharmacokinetics in Adults 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. fore, 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 11 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 11: 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)

	800/100 mg		600/100 mg twice daily								
Parameter	TMC114-C211 N=335	TMC114-C229 N=280	TMC114-C214 N=285	TMC114-C229 N=278	TMC114-C213 + TMC114-C202 (integrated data) N=119						
AUC24h (ng.h/mL) <sup>a</sup>											
Mean ± Standard Deviation	93026 ± 27050	93334 ± 28626	116796 ± 33594	114302 ± 32681	124698 ± 32286						
Median (Range)	87854 (45000 to 219240)	87788 (45456 to 236920)	111632 (64874 to 355360)	109401 (48934 to 323820)	123336 (67714 to 212980)						
Con (ng/mL)											
Mean ± Standard Deviation	2282 ± 1168	2160 ± 1201	3490 ± 1401	3386 ± 1372	3578 ± 1151						
Median (Range)	2041 (368 to 7242)	1896 (184 to 7881)	3307 (1517 to 13198)	3197 (250 to 11865)	3539 (1255 to 7368)						
I = number of subjects v											

Absorption and Bioavailability Darunavir, co-administered with 100 mg ritonavir twice daily, was absorbed following oral administration with a T<sub>m</sub>, of approximately 2.5 to 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  $\label{eq:data-suggest} data \ suggest \ that \ darunavir/riton avir is \ an inhibitor \ of \ the \ P-glycoprotein \ (P-gp) \ transporters.$ 

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

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 "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. A mass balance study in healthy volunteers showed that after single dose administration of 400 mg "C-darunavir, co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose of "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 Dosag and Administration (2.6) and Use in Specific Populations (8.6)].

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 coinfection status had no apparent effect on the exposure of darunavir

Results from a mass balance study with "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 to 60 mL/min, n=20). There are no pharmacokinetic data available in HIV-1-infected patients with severe renal impairment or end stage renal disease [see Use in Specific Populations (8.7)] Population pharmacokinetic analysis showed higher mean darunavir exposure in HIV-1-infected females compared to males. This difference is not clinically

Population pharmacokinetic analysis of darunavir in HIV-1-infected subjects indicated that race had no apparent effect on the exposure to darunavir Geriatric Patients Population pharmacokinetic analysis in HIV-1-infected subjects showed that darunavir pharmacokinetics are not considerably different in the age range (18 to

75 years) evaluated in HIV-1-infected subjects (n = 12, age greater than or equal to 65) [see Use in Specific Populations (8.5)].

Pediatric Patients

Pregnancy and Postpartum

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/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/irtonavir 800/100 mg once daily resulted in similar darunavir exposures when compared to the darunavir exposure achieved in treatment-naïve adults receiving darunavir/irtonavir 800/100 mg once daily [see Dosage and Administration (2.5]]. 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 Dosage and Administration (2.5)/. The population pharmacokinetic parameters in pediatric subjects with darunavir/ritonavir administered once or twice daily are summarized in the table below: Table 12: Population Pharmacokinetic Estimates of Darunavir Exposure (Trials TMC114-C230, TMC114-C212 and TMC114-C228) Following Administration of Doses in Tables 2 and 3

Darunavir/ritonavir Darunavir/ritonavi once daily twice daily

			TMC11	4-C228°
Parameter	TMC114-C230 <sup>a</sup> N=12	TMC114-C212 N=74	10 to less than 15 kg <sup>b</sup> N=10	15 to less than 20 kg <sup>d</sup> N=13
AUC <sub>24h</sub> (ng·h/mL) <sup>e</sup>				
Mean ± Standard Deviation	84390 ± 23587	126377 ± 34356	137896 ± 51420	157760 ± 54080
Median (Range)	86741 (35527 to 123325)	127340 (67054 to 230720)	124044 (89688 to 261090)	132698 (112310 to 294840)
Coh (ng/mL)				
Mean ± Standard Deviation	2141 ± 865	3948 ± 1363	4510 ± 2031	4848 ± 2143
Median (Range)	2234 (542 to 3776)	3888 (1836 to 7821)	4126 (2456 to 9361)	3927 (3046 to 10292)
HV-1 infected subjects from 12	ation pharmacokinetic paramet ? to < 18 years of age – Week-4	48 Analyses.	administration of DRV/rtv at 800/1	

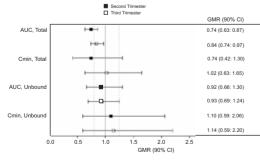
Calculated from individual pharmacokinetic parameters estimated for Week 2 and Week 4, based on the Week 48 analysis that evaluated a darunavir dose of  $20\,mg/kg$  twice daily with ritonavir  $3\,mg/kg$  twice daily. ts may have contributed pharmacokinetic data to both the 10 kg to less than 15 kg weight group and the 15 kg to less than 20 kg weight group. <sup>4</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. \* AUC<sub>24b</sub> is calculated as AUC<sub>12b</sub>\*2.

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 ntiretroviral regimen was generally lower during pregnancy compared with postpartum (see Table 13, Table 14 and Figure 1). Table 13: Pharmacokinetic Results of Total Darunavir After Administration of darunavir/ritonavir at 600/100 mg Twice Daily as Part of an

Pharmacokinetics of total darunavir (mean ± standard deviation)	2 <sup>nd</sup> Trimester of pregnancy (n=12) <sup>a</sup>	3 <sup>rd</sup> Trimester of pregnancy (n = 12)	Postpartum (6 to 12 Weeks) (n=12)
C <sub>max</sub> , ng/mL	4668 ± 1097	5328 ± 1631	6659 ± 2364
AUC <sub>24h</sub> , ng·h/mL <sup>b</sup>	78740 ± 19194	91760 ± 34720	113780 ± 52680
C <sub>min</sub> , ng/mL	1922 ± 825	2661 ± 1269	2851 ± 2216

Pharmacokinetics of total	2nd Trimester of pregnancy	3rd Trimester of pregnancy	Postpartum
darunavir	(n=17)	(n=15)	(6 to 12 Weeks)
(mean ± standard deviation)			(n = 16)
C <sub>max</sub> , ng/mL	4964 ± 1505	5132 ± 1198	7310 ± 1704
AUC24h , ng·h/mL	62289 ± 16234	61112 ± 13790	92116 ± 29241
C <sub>min,</sub> ng/mL	1248 ± 542	1075 ± 594	1473 ± 1141
Due to an increase in the unbound	fraction of darunavir during pregnancy com	pared to postpartum, unbound darunav	ir exposures were less reduced durin
reanancy as compared to postpartu	m. Exposure reductions during pregnancy we	re greater for the once daily regimen as co	omnared to the twice daily regimen (see

tinetic Results (Within-Subject Comparison) of Total and Unbound Darunavir After Administration of darunavir/rit 600/100 mg Twice Daily or 800/100 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd and 3nd Trimester of Pregnanc



		Dan inavir/	ritonavir Once	Daily	
		and Trimester		Duny	
		ond Trimester 1 Trimester			
	L Inite	1 Irimester			GMR (90% CI)
AUC, Total	H=-(				0.69 (0.61: 0.79)
	1-0-0				0.68 (0.59: 0.78)
Cmin, Total	H=-1				0.70 (0.57: 0.85)
	<b>⊢e</b> —⊢				0.50 (0.35: 0.72)
AUC, Unbound	P <del>+ ■</del>				0.79 (0.70: 0.90)
	н				0.82 (0.73: 0.91)
Cmin, Unbound	H=H				0.88 (0.70: 1.11)
L	<b>⊢•</b> ⊢1				0.61 (0.43: 0.88)
0.0	0.5 1.0	1.5	2.0	2.5	
		GN	IR (90% CI)		

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. /See also Contraindications (4), Warnings and Precautions (5.5) and Drug Interactions (7).]

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 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 common common drugs and some drugs common drugs likely to be co-administered and some drugs common drugs likely to be co-administered and some drugs common drugs likely to be co-administered and some drugs likely to interactions. The effects of co-administration of darunavir on the AUC,  $C_{\infty}$  and  $C_{\infty}$  values are summarized in Table 15 (effect of other drugs on darunavir) and Table 16 (effect of darunavir on other drugs). For information regarding clinical recommendations, see *Drug Interactions (7)*. 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 15: Drug Interactions: Pharmacokinetic Parameters for Darunavir in the Presence of Co-Administered Drugs

Co-administered		chedule				CI) of <u>darunavir</u> Pharma t co-administered drug n	
drug	Co-administered Drug	Darunavir/ ritonavir	N	PK	C <sub>max</sub>	AUC	Cmin
Co-administration w	ith other HIV protease i	nhibitors					
Atazanavir	300 mg q.d.°	400/100 mg b.i.d. <sup>b</sup>	13	$\leftrightarrow$	1.02 (0.96 to 1.09)	1.03 (0.94 to 1.12)	1.01 (0.88 to 1.1
Indinavir	800 mg b.i.d.	400/100 mg b.i.d.	9	1	1.11 (0.98 to 1.26)	1.24 (1.09 to 1.42)	1.44 (1.13 to 1.8
Lopinavir/ritonavir	400/100 mg b.i.d.	1200/100 mg b.i.d. <sup>c</sup>	14	1	0.79 (0.67 to 0.92)	0.62 (0.53 to 0.73)	0.49 (0.39 to 0.6
	533/133.3 mg b.i.d.	1200 mg b.i.d. <sup>c</sup>	15	<b>↓</b>	0.79 (0.64 to 0.97)	0.59 (0.50 to 0.70)	0.45 (0.38 to 0.5
Saquinavir hard gel capsule	1000 mg b.i.d.	400/100 mg b.i.d.	14	1	0.83 (0.75 to 0.92)	0.74 (0.63 to 0.86)	0.58 (0.47 to 0.7
Co-administration w	vith other HIV antiretrov	irals					
Didanosine	400 mg q.d.	600/100 mg b.i.d.	17	$\leftrightarrow$	0.93 (0.86 to 1.00)	1.01 (0.95 to 1.07)	1.07 (0.95 to 1.2
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	1	0.85 (0.72 to 1.00)	0.87 (0.75 to 1.01)	0.69 (0.54 to 0.8
Etravirine	200 mg b.i.d.	600/100 mg b.i.d.	15	$\leftrightarrow$	1.11 (1.01 to 1.22)	1.15 (1.05 to 1.26)	1.02 (0.90 to 1.1
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	1	1.40 <sup>d</sup> (1.14 to 1.73)	1.24 <sup>d</sup> (0.97 to 1.57)	1.02 <sup>d</sup> (0.79 to 1.3
Rilpivirine	150 mg q.d.	800/100 mg q.d.	15	$\leftrightarrow$	0.90 (0.81 to 1.00)	0.89 (0.81 to 0.99)	0.89 (0.68 to 1.1
Tenofovir disoproxil fumarate	300 mg q.d.	300/100 mg b.i.d.	12	1	1.16 (0.94 to 1.42)	1.21 (0.95 to 1.54)	1.24 (0.90 to 1.6
Co-administration w	rith other drugs						
Artemether/ lumefantrine	80/480 mg (6 doses at 0, 8, 24, 36, 48, and 60 hours)	600/100 mg b.i.d.	14	$\leftrightarrow$	1.00 (0.93 to 1.07)	0.96 (0.90 to 1.03)	0.87 (0.77 to 0.9
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	$\leftrightarrow$	1.04 (0.93 to 1.16)	0.99 (0.90 to 1.08)	0.85 (0.73 to 1.0
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	$\leftrightarrow$	0.83 (0.72 to 0.96)	0.87 (0.75 to 1.01)	1.01 (0.81 to 1.2
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	14	1	1.21 (1.04 to 1.40)	1.42 (1.23 to 1.65)	1.73 (1.39 to 2.1
Omeprazole	20 mg q.d.	400/100 mg b.i.d.	16	$\leftrightarrow$	1.02 (0.95 to 1.09)	1.04 (0.96 to 1.13)	1.08 (0.93 to 1.2
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	$\leftrightarrow$	0.97 (0.92 to 1.02)	1.02 (0.95 to 1.10)	1.07 (0.96 to 1.1
Pitavastatin	4 mg q.d.	800/100 mg q.d.	27	$\leftrightarrow$	1.06 (1.00 to 1.12)	1.03 (0.95 to 1.12)	NA
Ranitidine	150 mg b.i.d.	400/100 mg b.i.d.	16	$\leftrightarrow$	0.96 (0.89 to 1.05)	0.95 (0.90 to 1.01)	0.94 (0.90 to 0.9
Rifabutin	150 mg q.o.d. <sup>e</sup>	600/100 mg b.i.d.	11	1	1.42 (1.21 to 1.67)	1.57 (1.28 to 1.93)	1.75 (1.28 to 2.3
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	$\leftrightarrow$	1.01 (0.89 to 1.14)	0.98 (0.84 to 1.14)	0.94 (0.76 to 1.1

N = number of subjects with data aq.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.

					LS Mean rati	o (90% CI) of <u>co-ad</u>	ministered drug
	Dose/S	chedule				no effect = 1.00	
Co-administered drug	Co-administered drug	Darunavir/ ritonavir	N	PK	Cmax	AUC	Cmin
Co-administration wit Atazanavir	h other HIV protease inhib 300 mg q.d.* /100 mg	400/100 mg b.i.d. <sup>b</sup>	13	$\leftrightarrow$	0.89	1.08	1.52
	ritonavir q.d. when administered alone	400) 100 mg s.n.a.			(0.78 to 1.01)	(0.94 to 1.24)	(0.99 to 2.34
	300 mg q.d. when						
	administered with darunavir/ritonavir						
Indinavir	800 mg b.i.d. /100 mg	400/100 mg b.i.d.	9	1	1.08	1.23	2.25
	ritonavir b.i.d. when administered alone				(0.95 to 1.22)	(1.06 to 1.42)	(1.63 to 3.10
	800 mg b.i.d. when administered with						
	darunavir/ritonavir			L			
Lopinavir/ritonavir	400/100 mg b.i.d. <sup>c</sup>	1200/100 mg b.i.d.	14	↔	0.98 (0.78 to 1.22)	1.09 (0.86 to 1.37)	1.23 (0.90 to 1.69
	533/133.3 mg b.i.d. <sup>c</sup>	1200 mg b.i.d.	15	$\leftrightarrow$	1.11 (0.96 to 1.30)	1.09 (0.96 to 1.24)	1.13 (0.90 to 1.42
Saquinavir hard gel	1000 mg b.i.d. /100 mg	400/100 mg b.i.d.	12	$\leftrightarrow$	0.94	0.94	0.82
capsule	ritonavir b.i.d. when administered alone				(0.78 to 1.13)	(0.76 to 1.17)	(0.52 to 1.30
	1000 mg b.i.d. when						
	administered with darunavir/ritonavir						
Co-administration wit	h other HIV antiretrovirals	600/100 mg b.i.d.	17	$\leftrightarrow$	0.84	0.91	1
	400 mg q.d.				(0.59 to 1.20)	(0.75 to 1.10)	
Dolutegravir	30 mg q.d	600/100 mg b.i.d.	15	1	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 <sup>d</sup> (0.56 to 0.69
Dolutegravir	50 mg q.d.	600/100 mg b.i.d. with 200 mg	9	1	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 <sup>d</sup> (0.52 to 0.76
Ff		b.i.d. etravirine					
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	1	1.15 (0.97 to 1.35)	1.21 (1.08 to 1.36)	1.17 (1.01 to 1.36
Etravirine	100 mg b.i.d.	600/100 mg b.i.d.	14	1	0.68 (0.57 to 0.82)	0.63 (0.54 to 0.73)	0.51 (0.44 to 0.61
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	1	1.18	1.27	1.47
Rilpivirine	150 mg q.d.	800/100 mg q.d.	14	1	(1.02 to 1.37) 1.79	(1.12 to 1.44) 2.30	(1.20 to 1.82 2.78
Tenofovir disoproxil	300 mg q.d.	300/100 mg b.i.d.	12	1	(1.56 to 2.06) 1.24	(1.98 to 2.67) 1.22	(2.39 to 3.24
fumarate Maraviroc	150 mg b.i.d.	600/100 mg b.i.d.	12	1	(1.08 to 1.42) 2.29	(1.10 to 1.35) 4.05	(1.19 to 1.57 8.00
Maraviruc	150 mg a.i.a.				(1.46 to 3.59)	(2.94 to 5.59)	(6.35 to 10.1
		600/100 mg b.i.d. with 200 mg b.i.d.	10	1	1.77 (1.20 to 2.60)	3.10 (2.57 to 3.74)	5.27 (4.51 to 6.15
Co-administration wit	h other druge	etravirine					
Atorvastatin	40 mg q.d. when	300/100 mg b.i.d.	15	1	0.56	0.85	1.81
	administered alone 10 mg q.d. when				(0.48 to 0.67)	(0.76 to 0.97)	(1.37 to 2.40
	administered with						
Artemether	darunavir/ritonavir 80 mg	600/100 mg b.i.d.	15	<b>1</b>	0.85	0.91	
Dihydroartemisinin	single dose		15	<b>↑</b>	(0.68 to 1.05) 1.06	(0.78 to 1.06)	
				1	(0.82 to 1.39)	(0.96 to 1.30)	·
Artemether	artemether/lumefantrine 80/480 mg	600/100 mg b.i.d.	15	1	0.82 (0.61 to 1.11)	0.84 (0.69 to 1.02)	0.97 (0.90 to 1.05
Dihydroartemisinin	(6 doses at 0, 8, 24, 36, 48, and 60 hours)		15	1	0.82 (0.66 to 1.01)	0.82 (0.74 to 0.91)	1.00 (0.82 to 1.22
Lumefantrine			15	1	1.65	2.75	2.26
Buprenorphine/	8/2 mg to 16/4 mg q.d.	600/100 mg b.i.d.	17	↔	(1.49 to 1.83) 0.92°	(2.46 to 3.08) 0.89°	(1.92 to 2.67 0.98°
Naloxone					(0.79 to 1.08)	(0.78 to 1.02)	(0.82 to 1.16
Norbuprenorphine			17	1	1.36 (1.06 to 1.74)	1.46 (1.15 to 1.85)	1.71 (1.29 to 2.27
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	1	1.43 (1.34 to 1.53)	1.45 (1.35 to 1.57)	1.54 (1.41 to 1.68
Carbamazepine			16	1	0.46	0.46 (0.44 to 0.49)	0.48
epoxide Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	1	(0.43 to 0.49) 1.26	1.57	(0.45 to 0.51 2.74
Dabigatran etexilate	150 mg	800/100 mg single	14	1	(1.03 to 1.54) 1.64	(1.35 to 1.84) 1.72	(2.30 to 3.26
oungation otoxinate	100	dose			(1.21 to 2.23)	(1.33 to 2.23)	
		800/100 mg q.d.'	13	1	1.22 (0.89 to 1.67)	1.18 (0.90 to 1.53)	
Dextromethorphan	30 mg	600/100 mg b.i.d.	12	1	2.27 (1.59 to 3.26)	2.70 (1.80 to 4.05)	
Dextrorphan				1	0.87	0.96	
Digoxin	0.4 mg	600/100 mg b.i.d.	8	1	(0.77 to 0.98) 1.15	(0.90 to 1.03) 1.36	
Ethinyl estradiol (EE)	Ortho-Novum 1/35	600/100 mg b.i.d.	11	1	(0.89 to 1.48) 0.68	(0.81 to 2.27) 0.56	0.38
	(35 mcg EE /1 mg NE)	ooo, too ing u.i.u.			(0.61 to 0.74)	(0.50 to 0.63)	(0.27 to 0.54
Norethindrone (NE)			11	1	0.90 (0.83 to 0.97)	0.86 (0.75 to 0.98)	0.70 (0.51 to 0.97
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	15	1	2.11 (1.81 to 2.44)	3.12 (2.65 to 3.68)	9.68 (6.44 to 14.5)
R-Methadone	55 to 150 mg q.d.	600/100 mg b.i.d.	16	1	0.76	0.84	0.85
Omeprazole	40 mg single dose	600/100 mg b.i.d.	12	1	(0.71 to 0.81) 0.66	(0.78 to 0.91) 0.58	(0.77 to 0.94
	-				(0.48 to 0.90)	(0.50 to 0.66)	
5-hydroxy omeprazole				Ţ	0.93 (0.71 to 1.21)	0.84 (0.77 to 0.92)	
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	Ţ	0.64 (0.59 to 0.71)	0.61 (0.56 to 0.66)	0.63 (0.55 to 0.73
Pitavastatin	4 mg q.d.	800/100 mg q.d.	27	1	0.96 (0.84 to 1.09)	0.74 (0.69 to 0.80)	NA NA
Pravastatin	40 mg single dose	600/100 mg b.i.d.	14	1	1.63	1.81	
Rifabutin	150 mg q.o.d. <sup>g</sup> when	600/100 mg b.i.d. <sup>h</sup>	11	1	(0.95 to 2.82) 0.72	(1.23 to 2.66) 0.93	1.64
-	administered with darunavir/ritonavir			Ι΄.	(0.55 to 0.93)	(0.80 to 1.09)	(1.48 to 1.81
	300 mg q.d. when						
25- <i>O</i> -desacetyl-	administered alone		11	1	4.77	9.81	27.1
rifabutin Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	· ↓	(4.04 to 5.63) 0.56	(8.09 to 11.9) 0.51	(22.2 to 33.2 0.51
					(0.49 to 0.63)	(0.46 to 0.58)	(0.45 to 0.57
Sildenafil	100 mg (single dose)	400/100 mg b.i.d.	16	1	0.62 (0.55 to 0.70)	0.97 (0.86 to 1.09)	
	administered alone 25 mg (single dose)						
	when administered						
	with darunavir/ ritonavir	ı		1	I	I	I
S-warfarin	10 mg single dose	600/100 mg b.i.d.	12	↓	0.92	0.79	

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

The pharmacokinetic parameters of lopinavir in this study were compared with the pharmacokinetic parameters following administration of lopinavir/ritonavi Noted as C.or C24 in the dolutegravir U.S. prescribing information Ratio is for buprenorphine; mean C<sub>max</sub> and AUC<sub>24</sub> for naloxone were comparable when buprenorphine/naloxone was administered with or without

800/100 mg g.d. for 14 days before co-administered with dabigatran etexilate. In comparison to rifabutin 300 mg once daily.

12.4 Microbiology

b.i.d. = twice daily

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 Antiviral Activity

Darunavir skhibits 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  $EC_{so}$  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 0 primary isolates with EC<sub>uv</sub>values ranging from less than 0.1 to 4.3 nM. The EC<sub>uv</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 Testion to the control of the contro

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, K550, H690, 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 L10E V11L L13V L15V G16E L23L V32L L33E S37N M46L L47V L50V E53L L63P A71V G73S L76V V82L 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 on 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 V321 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 failur ranner, entire by Teomon on by these demandance was been a complexime. One abusing the abusing the properties of the second of t 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/irtonavir virologic failure isolates. In trial TMC114-C212 of treatment-experienced pediatric subjects, the amino acid substitutions V321, I54L and L89M developed most frequently in virologic failures on darunavir/irtonavir.

In the 96-week as treated analysis of the Phase 3 trial TMC114-C214, the percent of virologic failures (never suppressed, rebounders and discontinued befor 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 activities and phenotypes showed that 7 subjects 17/43; 16%) developed PI substitutions on darunavir/intonavir treatment resulting in decreased susceptibility 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 V321, L33F, M46l or L, I47V, I54L, T74P and L76V. These amin pacid 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

genotypes and pinentrypes snowed into 3 subjects (3173, 4-14) developed substitutions on inquart realment resulting in decreased susceptibility (greater than 10-fold) and the most common substitutions emerging on treatment were L101 or F, M461 or L, I47V or A, I54V and L76V. Of the 31 lopinavir/ri 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 800/100 mg twice daily. Examination of isolates from subjects who failed on darunavir/ironavir 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-folia 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

nnavir in treatment-naïve subjects: In the 192-week as-treated analysis censoring those who discontinued before Week 4 of the Phas 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 he 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 comparato 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 M1841

substitution and/or resistance to emtricitabine, which was included in the fixed background regimen, was identified in 4 virologic failures from the

oss-resistance among Pls 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 Pls remain Darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir in cell culture. However, six of nine darmarin resistant viruses selected in cell culture from P1-resistant viruses selected in cell culture from 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 In trial TMC114-C214, the 7 darunavir/ritonavir virologic failures with reduced suscentibility to darunavir at failure were also resistant to the approved PIs

In that I MC 14-C214, the 7 deruitavirintonavi viriougic randes with reduced susceptionity to datinavir at failure were also testistant to the approved it (foslamprenavir, atazanavir, fopinavir, indiavir, and nelfinavir at failure. Six of these 7 were resistant to saquinavir and 5 were resistant to tipranavir. Four of thes virologic failures were already PI-resistant at baseline.

CCR5 co-receptor antagonists, or integrase inhibitors is unlikely because the viral targets are different.

Cross-resistance between darunavir and nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, fusion inhibitors,

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 V32) 1335 MARIJ 147AV CARV ISDI V ISAJ M 176V V82A FILIST 184V N88S 190M (see Table 17)

# IAS-defined primary PI substitutions	Proportion o	f subjects with < 50 copies/mL at N=439	Week 96
	Overall	de novo ENF	Re-used/No ENI
All	44% (192/439)	54% (61/112)	40% (131/327)
0 to 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)

The presence at baseline of two or more of the substitutions V111, V321, 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 to 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 18. 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 18: 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 Proportion of subjects with < 50 copies/mL at Week 96 N = 417de novo ENF 175/417 (42%) 61/112 (54%) 131/327 (40%) 148/270 (55% 0 to 7 44/65 (68%) 104/205 (51%) >7 to 20 16/53 (30%) 7/17 (41%) 9/36 (25%) >20

13.1 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 acrinomas 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 reserve mutation (Ames), chromosomal aberration in human

Impairment of Fertility No effects on fertility or early embryonic development were observed with darunavir in rats. 14 CLINICAL STUDIES

lymphocytes and in vivo micronucleus test in mice.

14.1 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. 14.2 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/mn 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 19). Table 19 compares the demographic and baseline characteristics between subjects in the darunavir/ritonavir 800/100 mg once daily arm and subjects in the lopinavir/ritonavir

	Darunavir/ritonavir 800/100 mg once daily + TDF/FTC N=343	lopinavir/ritonavir 800/200 mg per day + TDF/FTC N=346
Demographic characteristics		
Median age (years) (range, years)	34 (18 to 70)	33 (19 to 68)
Sex		
Male	70%	70%
Female	30%	30%
Race		
White	40%	45%
Black	23%	21%
Hispanic	23%	22%
Asian	13%	11%
Baseline characteristics		•
Mean baseline plasma HIV-1 RNA (log10 copies/mL)	4.86	4.84
Median baseline CD4+ cell count (cells/mm³) (range, cells/mm³)	228 (4 to 750)	218 (2 to 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%

ercentage of patients with baseline CD4+ cell count < 200 cells/mm³	41%	43%
= emtricitabine; TDF = tenofovir disoproxil fumarate ek 192 outcomes for subjects on darunavir/ritonavir 80	0/100 mg once daily from trial TMC114-C211 are sh	own in Table 20.
le 20: Virologic Outcome of Randomized Treatmer	nt of Trial TMC114-C211 at 192 Weeks	
	Darunavir/ritonavir 800/100 mg once daily + TDF/FTC N=343	lopinavir/ritonavir 800/200 mg per day + TDF/FTC N=346
/irologic success HIV-1 RNA < 50 copies/mL	70%°	61%
'irologic failure <sup>b</sup>	12%	15%
lo virologic data at Week 192 window <sup>c</sup>		
Reasons		
Discontinued trial due to adverse event or death <sup>d</sup>	5%	13%
Discontinued trial for other reasons®	13%	12%
Missing data during window <sup>c</sup> but on trial	< 1%	0%
total number of subjects with data; FTC – emtricitabin % Cl: 1.9; 16.1 ludes patients who discontinued prior to Week 192 for	lack or loss of efficacy and patients who are ≥ 50 co	opies in the 192-week window and patients
		opies in the 192-week window and patien

a change in their background regimen that was not permitted by the protocol. Window 186 to 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

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/mm³ in the darunavir/ritonavir 800/100 mg once daily arm and 263 cells/mm³ 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. 14.3 Treatment-Experienced Adult Subjects 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. V111, V321, L33F, 147V, 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

ble 21: Demographic and Baseline Characteristics of Subjects in Trial	1 W G 1 14-6223	
	Darunavir/ritonavir 800/100 mg once daily + OBR N=294	Darunavir/ritonavir 600/100 mg twice daily + OBR N=296
Demographic characteristics		
Median age (years) (range, years)	40 (18 to 70)	40 (18 to 77)
Sex		
Male	61%	67%
Female	39%	33%
Race		
White	35%	37%
Black	28%	24%
Hispanic	16%	20%
Asian	16%	14%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA (log <sub>10</sub> copies/mL)	4.19	4.13
Median baseline CD4+ cell count (cells/mm³) (range, cells/mm³)	219 (24 to 1306)	236 (44 to 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) <sup>a</sup>	0.50 (0.1 to 1.8)	0.50 (0.1 to 1.9)
Median number of resistance-associated <sup>b</sup> :		
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 <sup>b</sup> :		
0	84%	84%
1	8%	9%
2	5%	4%
≥3	3%	2%
Median number of ARVs previously used <sup>c</sup> :		
NRTIs	3	3
NNRTIs	1	1
Pls (excluding low-dose ritonavir)	1	1

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 to 145. Only counting ARVs, excluding low-dose ritonavir.

	Darunavir/ritonavir 800/100 mg once daily + OBR N=294	Darunavir/ritonavir 600/100 m twice daily + OBR N=296
Virologic success HIV-1 RNA < 50 copies/mL	69%	69%
Virologic failure*	26%	23%
No virologic data at Week 48 window <sup>5</sup>		
Reasons		
Discontinued trial due to adverse event or death <sup>c</sup>	3%	4%
Discontinued trial for other reasons <sup>d</sup>	2%	3%
Missing data during window but on trial	0%	< 1%

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 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 to 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/mm² and 112 cells/mm² in the darunavir/ritonav 800/100 mg once daily arm and the darunavir/ritonavir 600/100 mg twice daily arm, respectively).

TMC114-C214 is a randomized, controlled, open-label Phase 3 trial comparing darunavir/ritonavir 600/100 mg twice daily yersus loginavir/ritonavir 400/100 mg

twice daily in antitertoviral reatment-expensed, including open and the twice daily in antitertoviral reatment-expensed, logical packaground regiment consisting of at least 2 antitertovirals (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 Demographics and baseline characteristics were balanced between the darunavir/ritonavir arm and the lopinavir/ritonavir arm (see Table 23). Table 23 compares

595 subjects in trial TMC114-C214 who had completed 96 weeks of treatment or discontinued earlier. the demographic and baseline characteristics between subjects in the darunavir/ritonavir 600/100 mg twice daily arm in trial TMC114-C214. Table 23: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C214

	N=230	N=237
Demographic characteristics		
Median age (years) (range, years)	40 (18 to 68)	41 (22 to 76)
Sex		
Male	77%	81%
Female	23%	19%
Race		
White	54%	57%
Black	18%	17%
Hispanic	15%	15%
Asian	9%	9%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA (log <sub>10</sub> copies/mL)	4.33	4.28
Median baseline CD4+ cell count (cells/mm³) (range, cells/mm³)	235 (3 to 831)	230 (2 to 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 to 37.40)	0.60 (0.1 to 43.8
Median lopinavir fold change (range)	0.70 (0.40 to 74.40)	0.80 (0.30 to 74.
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 <sup>a</sup> :		
≤1	78%	80%
2	8%	9%
≥3	13%	11%
Median number of ARVs previously used <sup>b</sup> :		
NRTIs	4	4
NNRTIS	1	1
Pls (excluding low-dose ritonavir)	1	1
Percentage of subjects resistant to all available Pls at baseline.		
excluding darunavir	2%	3%

\*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 24. Table 24: Virologic Outcome of Randomized Treatment of Trial TMC114-C214 at 96 Weeks

	Darunavir/ritonavir 600/100 mg twice daily + OBR N=298	lopinavir/ritonavir 400/100 mg twice daily + OBR N=297
Virologic success HIV-1 RNA < 50 copies/mL	58%	52%
Virologic failure <sup>a</sup>	26%	33%
No virologic data at Week 96 window <sup>b</sup>		
Reasons		
Discontinued trial due to adverse event or death <sup>c</sup>	7%	8%
Discontinued trial for other reasons <sup>d</sup>	8%	7%
Missing data during window <sup>b</sup> but on trial	1%	< 1%
= total number of subjects with data; OBR = optimized backgr ncludes patients who discontinued prior to Week 96 for lack of the product of the product of th		in the 96-week window and patients who I

Window 90 to 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.

<sup>4</sup> 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/mm³ in the darunavir/ritonavir 600/100 mg twice daily arm and 93 cells/mm3 in the lopinavir/ritonavir 400/100 mg twice daily arm. TMC114-C213 and TMC114-C202 MC114-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 recom 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 25). Table 25 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 25: Demographic and Baseline Characteristics of Subjects in the Trials TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Darunavir/ritonavir 600/100 mg twice daily + OBR N=131	Comparator PI(s) + OBR N=124
Demographic characteristics		
Median age (years) (range, years)	43 (27 to 73)	44 (25 to 65)
Sex		
Male	89%	88%
Female	11%	12%
Race		
White	81%	73%
Black	10%	15%
Hispanic	7%	8%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA (log <sub>10</sub> copies/mL)	4.61	4.49
Median baseline CD4+ cell count (cells/mm³) (range, cells/mm³)	153 (3 to 776)	163 (3 to 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 <sup>a</sup> :		
≤1	8%	9%
2	22%	21%
≥3	70%	70%
Median number of ARVs previously used <sup>b</sup> :		
NRTIs	6	6
NNRTIs	1	1
Pls (excluding low-dose ritonavir)	5	5
Percentage of subjects resistant <sup>8</sup> to all available <sup>6</sup> PIs at baseline, excluding tipranavir and darunavir	63%	61%
Percentage of subjects with prior use of enfuvirtide	20%	17%

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 to 130 <sup>b</sup> Based on phenotype (Antivirogram<sup>®</sup>).
<sup>c</sup> 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 Table 26: 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 10 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 <sup>a</sup>	8%	53%	
Rebounder <sup>b</sup>	17%	19%	
Never suppressed <sup>c</sup>	4%	8%	
Death or discontinuation due to adverse events	9%	3%	
Discontinuation due to other reasons	5%	7%	
Discontinuation due to other reasons BR = optimized background regimen	5%	7%	

Subjects who did not achieve at least a confirmed 0.5 log in HIV-1 RNA drop from baseline at Week 12. Subjects with an initial response (confirmed 1 log<sub>30</sub> drop in viral load), but without a confirmed 1 log<sub>30</sub> drop in viral load at Week 96. Subjects who never reached a confirmed 1 log<sub>30</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/iritonavir 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>). 14.4 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/mm³ (range: 6 to 1505 cells/mm³). 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 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 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 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 × 10<sup>6</sup> cells/L (range: 209 to 2,429 × 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

change in CD4+ cell count from baseline was 187 × 10°cells/L. 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-process of the state of t 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 The 12 randomized petaltits subjects had a freeding age of 14-7 years (angle 12-0 of 17-3 years), and were 33-3 m fines, 30-3 m Galdasian and 41-7 m Data. The mean baseline plasma HIV-1 RNA was 4.72  $\log_n$  copies/mL. 41.7% of pediatric subjects had baseline plasma HIV-1 RNA  $\geq 100,000$  copies/mL.

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 increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase in CD4+ percentage from baseline was 4%. The mean increase from baseline was 4%. The mean increa

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+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7%, respectively. The mean increase in CD4+100 copies/mL was 83.0% and 91.7% and 91.7%cell count from baseline was 221 × 10<sup>6</sup> cells/L. 16 HOW SUPPLIED/STORAGE AND HANDLING Darunavir 600 mg tablets are available as yellow, oval shaped, biconvex, film-coated tablets debossed with 'V' on one side and '5' on the other side. Each 600 mg Darunavir 600 mg tablets are avanaune as yenour, som anger tablet contains darunavir amorphous equivalent 600 mg of darunavir.

NDC 31722-088-60

Darunavir 800 mg tablets are available as yellow, oval shaped, biconvex, film-coated tablets debossed with 'V' on one side and '7' on the other side. Each 800 mg

tablet contains darunavir amorphous equivalent 800 mg of darunavir NDC 31722-089-30 Bottles of 30 Store at 20°C to 25°C (68°F to 77°F); with excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instruction for Use).

Instructions for Use Advise patients to take darunavir tablets and ritonavir with food every day on a regular dosing schedule, as missed doses can result in development of resistance. Darunavir tablets must always be used with ritonavir in combination with other antiretrovial drugs. Advise patients not to alter the dose of either darunavir tablets or ritonavir, discontinue ritonavir, or discontinue therapy with darunavir tablets without consulting their physician/see Dosage and Administration (2)/. Inform patients that drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with darunavir tablets co-administered with 100 mg of ritonavir. Advise patients about the signs and symptoms of liver problems (See Warnings and Precautions (5.2)). Severe Skin Reactions

Inform patients that skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, drug rash with eosinophilia and systemic symptoms, and

toxic epidermal necrolysis, have been reported with darunavir tablets co-administered with 100 mg of ritonavir. Advise patients to discontinue darunavir tablets/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 (see Warnings and Precautions (5,3)). **Drug Interactions** Darunavir tablets/ritonavir may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort /see Contraindications (4), Warnings and Precautions (5.4, 5.5) and Drug Interactions (7)). Instruct patients receiving combined hormonal contraception or the progestin only pill to use an effective alternative (non-hormonal) contraceptive method or add a barrier method during therapy with darunavir tablets/ritonavir because hormonal levels may decrease (see Drug Interactions (7.3) and Use in Specific Populations (8.3)). Fat Redistribution Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including darunavir tablets/ritonavir, and that the cause and long-term health effects of these conditions are not known at this time/see Warnings and Precautions (5.7). Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and

Pregnancy Registry Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to darunavir tablets [see Use in Specific Populations (8.1)]. Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk [see Use in Specific Populations (8.2)].



CAMBER

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By: Annora Pharma Pvt. Ltd Sangareddy - 502313, Telaı This Patient Inforn

Manufactured for: Camber Pharmaceuticals, Piscataway, NJ 08854 AMBER®

dioxide, g contains

agnesium stearate, silicified polyethylene glycol, polyvinyl

Keep darunavir tablets at room temperature 77°F (25°C).

Keep darunavir tablets and all medicines out of the reach of childre

General information about the safe and effective use of darunavir t

Medicines are sometimes prescribed for purposes other than those lists leaflet. Do not use darunavir tablets for a condition for which it was n darunavir tablets to other people even if they have the same condition you This leaflet summarizes the most important information about darunavir more information, talk to your healthcare provider. You can ask you pharmacist for information about darunavir tablets that is written for heal For more information, call 1-866-495-1995.

What aratho: se listed in a Patient Information was not prescribed. Do not give on you have. It may harm them. runavir tablets. If you would like ask your healthcare provider or or health professionals.

Tell your healthcare pro These are not all of the p Call your doctor for me 1-800-FDA-1088.

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Take darunavir tablets and ritonavir with food.

If you have difficulty swallowing darunavir tablets, darunavir oral suspension is also available. Your healthcare provider will help decide whether darunavir tablets or oral suspension is right for you.

If you child is taking darunavir tablets, your child's healthcare provider will decide the right dose based on your child's weight. Your child's healthcare provider will tell you how much darunavir (tablets or oral suspension) and how much ritonavir (capsules, tablets or solution) your child should take. Your child should take your child should be given with the supplied oral dosing syrings. Shake the suspension well before each use. See the "Instructions for Use" that come with darunavir oral suspension for information about the right way to prepare and take a dose.

It is important that you do not miss or skip doses of darunavir tablets during treatment.

If you take too much darunavir, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of darunavir tablets?

Darunavir tablets may cause serious side effects, including:

See "What is the most important information I should know about darunavir tablets can get worse. Tell your healthcare provider if you notice an increase in thirst or urinate often while taking darunavir tablets. Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term healthcare provider if you notice an increase in thirst or urinate often while taking darunavir body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term healtheffects of these conditions are not known.

Changes in your immune system (immune Reconstitution Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. It ell your habitare provider right away if you start having new symptoms after starting your HIV-1 medic

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