℞ DARUNAVIR
DANAVIR 400/600
400 mg and 600 mg
Film-Coated Tablet
Antiviral (Protease Inhibitor)

℞

DARUNAVIR

DANAVIR 400/600

400 mg and 600 mg Film-Coated Tablet

Antiviral (Protease Inhibitor)

FORMULATION

DANAVIR 400

Each Film-Coated Tablets contains:

Darunavir ....400 mg

DANAVIR 600

Each Film coated tablets contains:

Darunavir ....600 mg

DRUG DESCRIPTION

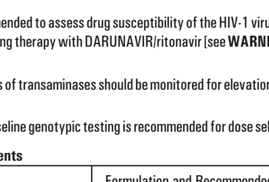
Darunavir Tablets 400 mg:

Orange, oval shaped, bevel edged, biconvex, film-coated tablets de-bossed with "H" on one side and "189" on the other side.

Darunavir Tablets 600 mg:

Orange, oval shaped, biconvex, film-coated tablets de-bossed with "J" on one side and "7" on the other side.

Darunavir is described chemically as I) [(1S,2R-3-[[(4-Amino-phenyl)sulfonyl](2 methylpropyl)amino]- 2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]-furan-3-yl ester ii) (1S,2R,3'R,3'aS,6'aR)-[3'-hexahydrofuro[2,3-b]-furanyl-[3-(4- aminobenzenesulfonyl)isobutylamino]-1-benzyl-2-hydroxy propyl]carbamate The molecular formula is $C_{27}H_{37}N_3O_7S$ and the molecular weight is 547.67. The chemical structure of Darunavir is:



Darunavir is a An off white to pale brown colour powder and a pKa of 11.43 It is Freely soluble in Chloroform and in Dichloromethane.

Darunavir contain the following inactive ingredients: Silicified microcrystalline cellulose(prosolv HD 90), Colloidal silicon dioxide (Aerosil 200), Crospovidone (polyplasdone XL-10), Magnesium stearate, Opadry II Orange 85F530007, Purified Water.

THERAPEUTIC INDICATIONS

DARUNAVIR®, co-administered with ritonavir (DARUNAVIR/ritonavir), in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adult and pediatric patients 3 years of age and older [see Use In Specific Populations and Clinical Studies].

POSOLOGY AND METHOD OF ADMINISTRATION

Testing Prior To Initiation Of DARUNAVIR/ritonavir

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

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

Monitoring During Treatment With DARUNAVIR/ritonavir

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

Treatment-Experienced Adult Patients

The recommended oral dosage for treatment-experienced adult patients is summarized in Table 1.Baseline genotypic testing is recommended for dose selection. However, when genotypic testing is not feasible, DARUNAVIR 600 mg taken with ritonavir 100 mg twice daily is recommended.

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

Baseline Resistance	Formulation and Recommended Dosing
	DARUNAVIR tablets with ritonavir tablets or capsule
With no darunavir resistance associated substitutions*	One 800 mg DARUNAVIR tablet with one 100 mg ritonavir tablet/capsule, taken once daily with food
With at least one darunavir resistance associated substitutions*, or with no baseline resistance information	One 600 mg DARUNAVIR tablet with one 100 mg ritonavir tablet/capsule, taken twice daily with food

* V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V
† An 8 mL darunavir dose should be taken as two 4 mL administrations with the included oral dosing syringe

Recommended Dosage During Pregnancy

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

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

Recommended Dosage In Pediatric Patients (age 3 to less than 18 years)

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

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

Before prescribing DARUNAVIR, children weighing greater than or equal to 15 kg should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a tablet, the use of DARUNAVIR oral suspension should be considered.

The recommended dose of DARUNAVIR/ritonavir for pediatric patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see Tables 2, 3, 4, and 5) and should not exceed the recommended adult dose. DARUNAVIR should be taken with ritonavir and with food.

The recommendations for the DARUNAVIR/ritonavir dosage regimens were based on pediatric clinical trial data and population pharmacokinetic modeling and simulation [see Use In Specific Populations and CLINICAL PHARMACOLOGY].**Dosing Recommendations**

For Treatment-Naïve Pediatric Patients Or Antiretroviral Treatment-Experienced Pediatric Patients With No Darunavir Resistance Associated Substitutions

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)
Greater than or equal to 10 kg to less than 11 kg
Greater than or equal to 11 kg to less than 12 kg
Greater than or equal to 12 kg to less than 13 kg
Greater than or equal to 13 kg to less than 14 kg
Greater than or equal to 14 kg to less than 15 kg

* darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V
† 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, 4 mL, 4.6 mL and 5 mL, respectively.

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:

Table 3: Recommended Dose for Pediatric Patients Weighing At Least 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Darunavir Resistance Associated Substitutions*

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

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

Pediatric Patients Weighing At Least 10 kg But Less Than 15 kg

The weight-based dose in antiretroviral treatment-experienced pediatric patients with at least one darunavir resistance associated substitution is DARUNAVIR 20 mg/kg twice daily with ritonavir 3 mg/kg twice daily using the following table:

Table 4: Recommended Dose for Pediatric Patients Weighing 10 kg to Less Than 15 kg Who are Treatment-Experienced with At Least One Darunavir Resistance Associated Substitution*

Body weight (kg)
Greater than or equal to 10 kg to less than 11 kg
Greater than or equal to 11 kg to less than 12 kg
Greater than or equal to 12 kg to less than 13 kg
Greater than or equal to 13 kg to less than 14 kg
Greater than or equal to 14 kg to less than 15 kg

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

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:

Table 5: Recommended Dose for Pediatric Patients Weighing At Least 15 kg Who are Treatment-Experienced with At Least One Darunavir Resistance Associated Substitution*

Body weight (kg)	Formulation: DARUNAVIR tablet(s) and ritonavir tablets, capsules (100 mg) or oral solution (80 mg/mL)
	Dose: twice daily with food
Greater than or equal to 15 kg to less than 30 kg	DARUNAVIR 375 mg with ritonavir 0.6 mL (48 mg)
Greater than or equal to 30 kg to less than 40 kg	DARUNAVIR 450 mg with ritonavir 0.75 mL (60 mg)
Greater than or equal to 40 kg	DARUNAVIR 600 mg with ritonavir 100 mg

* darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V
† The 375 mg and 450 mg dose using darunavir tablets for this weight group is rounded up to 3.8 mL and 4.6 mL for suspension dosing convenience.

The use of DARUNAVIR/ritonavir in pediatric patients below 3 years of age is not recommended [see **WARNINGS AND** PRECAUTIONS and Use In Specific Populations].

Not Recommended In Patients With Severe Hepatic Impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment. No data are available regarding the use of DARUNAVIR/ritonavir when co-administered to subjects with severe hepatic impairment; therefore, DARUNAVIR/ritonavir is not recommended for use in patients with severe hepatic impairment [see Use In Specific Populations and CLINICAL PHARMACOLOGY].

WARNINGS AND PRECAUTIONS

WARNINGS

Included as part of the **"PRECAUTIONS"** Section

PRECAUTIONS

Importance of Co-administration With Ritonavir

DARUNAVIR must be co-administered with ritonavir and food to achieve the desired antiviral effect. Failure to administer DARUNAVIR with ritonavir and food may result in a loss of efficacy of darunavir. Please refer to ritonavir prescribing information for additional information on precautionary measures.

Hepatotoxicity

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

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

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

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

Severe Skin Reactions

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

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

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

Sulfa Allergy

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

Risk of Serious Adverse Reactions Due To Drug Interactions

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

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

See Table 10 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations [see DRUG INTERACTIONS]. Consider the potential for drug interactions prior to and during DARUNAVIR/ritonavir therapy; review concomitant medications during DARUNAVIR/ritonavir therapy; and monitor for the adverse reactions associated with the concomitant drugs [see CONTRAINDICATIONS and DRUG INTERACTIONS].

Diabetes Mellitus/Hyperglycemia

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

Fat Redistribution

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

Immune Reconstitution Syndrome

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

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

Hemophilia

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

Not Recommended In Pediatric Patients Below 3 Years Of Age

DARUNAVIR/ritonavir in pediatric patients below 3 years of age is not recommended in view of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age [see **Use In Specific Populations** and CLINICAL PHARMACOLOGY].

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 and ritonavir with food every day on a regular dosing schedule, as missed doses can result in development of resistance. DARUNAVIR must always be used with ritonavir in combination with other antiretroviral drugs. Advise patients not to alter the dose of either DARUNAVIR or ritonavir, discontinue ritonavir, or discontinue therapy with DARUNAVIR without consulting their physician [see DOSAGE AND ADMINISTRATION].

Hepatotoxicity

Inform patients that drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with DARUNAVIR co-administered with 100 mg of ritonavir. Advise patients about the signs and symptoms of liver problems [see **WARNINGS AND PRECAUTIONS**].

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 co-administered with 100 mg of ritonavir. Advise patients to 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 [see **WARNINGS AND PRECAUTIONS**].

Drug Interactions

DARUNAVIR/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, **WARNINGS AND PRECAUTIONS** and DRUG INTERACTIONS].

Contraception

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/ritonavir because hormonal levels may decrease [see DRUG INTERACTIONS and **Use In Specific Populations**].

Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including DARUNAVIR/ritonavir, and that the cause and long-term health effects of these conditions are not known at this time [see **WARNINGS AND PRECAUTIONS**].

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started [see **WARNINGS AND PRECAUTIONS**].

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to DARUNAVIR [see **Use In Specific Populations**].

Lactation

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**].

Use In Specific Populations

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy 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.

Risk Summary

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

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

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

Clinical Considerations

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

DARUNAVIR 800 mg taken with ritonavir 100 mg once daily should only be considered in certain pregnant patients who are already on a stable DARUNAVIR 800 mg with ritonavir 100 mg once daily regimen prior to pregnancy, are virologically suppressed (HIV-1 RNA less than 50 copies per mL), and in whom a change to twice daily DARUNAVIR 600 mg with ritonavir 100 mg may compromise tolerability or compliance [see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY].

Data

Human Data

DARUNAVIR/ritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 36 pregnant women during the second and third trimesters, and postpartum. Eighteen subjects were enrolled in each BID and QD treatment arms. Twenty-nine subjects completed the trial through the postpartum period (6-12 weeks after delivery) and 7 subjects discontinued before trial completion, 5 subjects in the BID arm and 2 subjects in the QD arm.

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

Virologic response was preserved. In the BID arm, the proportion of subjects with HIV-1 RNA < 50 copies/mL were 39% (7/18) at baseline, 61% (11/18) through the third trimester visit, and 61% (11/18) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥ 50 copies/mL for 11% (2/18) of subjects and were missing for 5 subjects (1 subject discontinued prematurely due to virologic failure). In the QD arm, the proportion of subjects with HIV-1 RNA < 50 copies/mL were 61% (11/18) at baseline, 83% (15/18) through the third trimester visit, and 78% (14/18) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥ 50 copies/mL for none of the subjects and were missing for 3 subjects (1 subject discontinued prematurely due to virologic failure).

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

Among the 31 infants with HIV test results available data, born to the 31 HIV-infected pregnant women who completed trial through delivery or postpartum period, all 31 infants had test results that were negative for HIV-1 at the time of delivery and/or through 16 weeks postpartum. All 31 infants received antiretroviral prophylactic treatment containing zidovudine.

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

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

Animal Data

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

Lactation

Risk Summary

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

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

Data

Animal Data

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

Females And Males Of Reproductive Potential

Contraception

Use of DARUNAVIR may reduce the efficacy of combined hormonal contraceptives and the progestin only pill. Advise patients to use an effective alternative (non-hormonal) contraceptive method or add a barrier method of contraception. For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia [see DRUG INTERACTIONS].

Pediatric Use

DARUNAVIR/ritonavir is not recommended in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age [see **WARNINGS AND PRECAUTIONS**, **Use In Specific Populations** and CLINICAL PHARMACOLOGY].

The safety, pharmacokinetic profile, and virologic and immunologic responses of DARUNAVIR/ritonavir administered twice daily were evaluated in treatment-experienced HIV-1infected 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, CLINICAL PHARMACOLOGY and Clinical Studies]. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults [see ADVERSE REACTIONS]. Refer to DOSAGE AND ADMINISTRATION for twice-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

In clinical trial TMC114-C230, the safety, pharmacokinetic profile and virologic and immunologic responses of DARUNAVIR/ritonavir administered once daily were evaluated in treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age (12 subjects) [see ADVERSE REACTIONS, CLINICAL PHARMACOLOGY and Clinical Studies]. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults [see ADVERSE REACTIONS]. 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]. Please see DOSAGE AND ADMINISTRATION for once-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

Juvenile Animal Data

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

Geriatric Use

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

Hepatic Impairment

No dosage adjustment of DARUNAVIR/ritonavir is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of DARUNAVIR/ritonavir in subjects with severe hepatic impairment. Therefore, DARUNAVIR/ritonavir is not recommended for use in patients with severe hepatic impairment [see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY].

Renal Impairment

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

PREGNANCY AND LACTATION

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy 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.

Risk Summary

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

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

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

Clinical Considerations

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

DARUNAVIR 800 mg taken with ritonavir 100 mg once daily should only be considered in certain pregnant patients who are already on a stable DARUNAVIR 800 mg with ritonavir 100 mg once daily regimen prior to pregnancy, are virologically suppressed (HIV-1 RNA less than 50 copies per mL), and in whom a change to twice daily DARUNAVIR 600 mg with ritonavir 100 mg may compromise tolerability or compliance [see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY].

Data

Human Data

DARUNAVIR/ritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 36 pregnant women during the second and third trimesters, and postpartum. Eighteen subjects were enrolled in each BID and QD treatment arms. Twenty-nine subjects completed the trial through the postpartum period (6-12 weeks after delivery) and 7 subjects discontinued before trial completion, 5 subjects in the BID arm and 2 subjects in the QD arm.

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

Virologic response was preserved. In the BID arm, the proportion of subjects with HIV-1 RNA < 50 copies/mL were 39% (7/18) at baseline, 61% (11/18) through the third trimester visit, and 61% (11/18) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥ 50 copies/mL for 11% (2/18) of subjects and were missing for 5 subjects (1 subject discontinued prematurely due to virologic failure). In the QD arm, the proportion of subjects with HIV-1 RNA < 50 copies/mL were 61% (11/18) at baseline, 83% (15/18) through the third trimester visit, and 78% (14/18) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥ 50 copies/mL for none of the subjects and were missing for 3 subjects (1 subject discontinued prematurely due to virologic failure).

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

Among the 31 infants with HIV test results available data, born to the 31 HIV-infected pregnant women who completed trial through delivery or postpartum period, all 31 infants had test results that were negative for HIV-1 at the time of delivery and/or through 16 weeks postpartum. All 31 infants received antiretroviral prophylactic treatment containing zidovudine.

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

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

Animal Data

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

Lactation

Risk Summary

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

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

Data

Animal Data

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

Females And Males of Reproductive Potential

Contraception

Use of DARUNAVIR may reduce the efficacy of combined hormonal contraceptives and the progestin only pill. Advise patients to use an effective alternative (non-hormonal) contraceptive method or add a barrier method of contraception. For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia [see **DRUG INTERACTIONS**].

Pediatric Use

DARUNAVIR/ritonavir is not recommended in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age [see **WARNINGS AND PRECAUTIONS, Use In Specific Populations** and CLINICAL PHARMACOLOGY].

The safety, pharmacokinetic profile, and virologic and immunologic responses of DARUNAVIR/ritonavir administered twice daily were evaluated in treatment-experienced HIV-1infected 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, CLINICAL PHARMACOLOGY** and Clinical Studies]. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults [see **ADVERSE REACTIONS**]. Refer to **DOSAGE AND ADMINISTRATION** for twice-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

In clinical trial TMC114-C230, the safety, pharmacokinetic profile and virologic and immunologic responses of DARUNAVIR/ritonavir administered once daily were evaluated in treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age (12 subjects) [see **ADVERSE REACTIONS, CLINICAL PHARMACOLOGY** and Clinical Studies]. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults [see **ADVERSE REACTIONS**]. 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**]. Please see **DOSAGE AND ADMINISTRATION** for once-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

Juvenile Animal Data

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

Geriatric Use

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

Hepatic Impairment

No dosage adjustment of DARUNAVIR/ritonavir is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of DARUNAVIR/ritonavir in subjects with severe hepatic impairment. Therefore, DARUNAVIR/ritonavir is not recommended for use in patients with severe hepatic impairment [see **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY**].

Renal Impairment

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

SIDE EFFECTS

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

- Hepatotoxicity [see **WARNINGS AND** PRECAUTIONS]
- Severe Skin Reactions [see **WARNINGS AND** PRECAUTIONS]
- Diabetes Mellitus/Hyperglycemia [see **WARNINGS AND** PRECAUTIONS]
- Fat Redistribution [see **WARNINGS AND** PRECAUTIONS]
- Immune Reconstitution Syndrome [see **WARNINGS AND** PRECAUTIONS]
- Hemophilia [see **WARNINGS AND** PRECAUTIONS]

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

Clinical Trials Experience

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

Treatment Naïve-Adults: TMC114-C211

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

The majority of the adverse drug reactions (ADRs) reported during treatment with DARUNAVIR/ritonavir 800/100 mg once daily were mild in severity. The most common clinical ADRs to DARUNAVIR/ritonavir 800/100 mg once daily (greater than or equal to 5%) of at least moderate intensity (greater than or equal to Grade 2) were diarrhea, headache, abdominal pain and rash. 2.3% of subjects in the DARUNAVIR/ritonavir arm discontinued treatment due to ADRs.

ADRs to DARUNAVIR/ritonavir 800/100 mg once daily of at least moderate intensity (greater than or equal to Grade 2) in antiretroviral treatment-naive HIV-1-infected adult subjects are presented in Table 6 and subsequent text below the table.

Table 6: Selected Clinical Adverse Drug Reactions to DARUNAVIR/ritonavir 800/100 mg Once Daily* of at Least Moderate Intensity (≥ Grade 2) Occurring in ≥ 2% of Antiretroviral Treatment-Naive HIV-1-Infected Adult Subjects (Trial TMC114-C211)

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

N = total number of subjects per treatment group; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate
* Excluding laboratory abnormalities reported as ADRs.

Less Common Adverse Reactions

Treatment-emergent ADRs of at least moderate intensity (greater than or equal to Grade 2) occurring in less than 2% of antiretroviral treatment-naive subjects receiving DARUNAVIR/ritonavir 800/100 mg once daily are listed below by body system:

Gastrointestinal Disorders: acute pancreatitis, dyspepsia, flatulence
General Disorders and Administration Site Conditions: asthenia
Hepatobiliary Disorders: acute hepatitis (e.g., acute hepatitis, cytolytic hepatitis, hepatotoxicity)
Immune System Disorders: (drug) hypersensitivity, immune reconstitution syndrome
Metabolism and Nutrition Disorders: diabetes mellitus
Musculoskeletal and Connective Tissue Disorders: myalgia, osteonecrosis
Psychiatric Disorders: abnormal dreams
Skin and Subcutaneous Tissue Disorders: angioedema, pruritus, Stevens-Johnson Syndrome, urticaria

Laboratory Abnormalities

Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-naive adult subjects treated with DARUNAVIR/ritonavir 800/100 mg once daily are presented in Table 7.

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

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

N = total number of subjects per treatment group; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate
* Grade 4 data not applicable in Division of AIDS grading scale.

Treatment-Experienced Adults: TMC114-C214

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

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

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

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

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

N = total number of subjects per treatment group; OBR = optimized background regimen
* Excluding laboratory abnormalities reported as ADRs

Less Common Adverse Reactions

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

Gastrointestinal Disorders: acute pancreatitis, flatulence
Musculoskeletal and Connective Tissue Disorders: myalgia
Psychiatric Disorders: abnormal dreams
Skin and Subcutaneous Tissue Disorders: pruritus, urticaria

Laboratory Abnormalities

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

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

Laboratory parameter, %	Laboratory parameter, %	DARUNAVIR/ritonavir 600/100 mg twice daily + OBR	Lopinavir/ritonavir 400/100 mg twice daily + OBR
Biochemistry			
Alanine Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	7%	5%
Grade 3	> 5.0 to ≤ 10.0 X ULN	2%	2%
Grade 4	> 10.0 X ULN	1%	2%
Aspartate Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	6%	6%
Grade 3	> 5.0 to ≤ 10.0 X ULN	2%	2%
Grade 4	> 10.0 X ULN	< 1%	1%
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 1	5.65-8.48 mmol/L 500-750 mg/dL	10%	11%
Grade 2	8.49-13.56 mmol/L 751-1200 mg/dL	7%	10%
Grade 3	> 13.56 mmol/L > 1200 mg/dL	3%	6%
Total Cholesterol			
Grade 2	6.20-7.77 mmol/L 240-300 mg/dL	25%	23%
Grade 3	> 7.77 mmol/L > 300 mg/dL	10%	14%
Low-Density Lipoprotein Cholesterol			
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	14%	14%
Grade 3	≥ 4.91 mmol/L ≥ 191 mg/dL	8%	9%
Elevated Glucose Levels			
Grade 2	6.95-13.88 mmol/L 126-250 mg/dL	10%	11%
Grade 3	13.89-27.75 mmol/L 251-500 mg/dL	1%	< 1%
Grade 4	> 27.75 mmol/L > 500 mg/dL	< 1%	0%
Pancreatic Lipase			
Grade 2	> 1.5 to ≤ 3.0 X ULN	3%	4%
Grade 3	> 3.0 to ≤ 5.0 X ULN	2%	< 1%
Grade 4	> 5.0 X ULN	< 1%	0%
Pancreatic Amylase			
Grade 2	> 1.5 to ≤ 2.0 X ULN	6%	7%
Grade 3	> 2.0 to ≤ 5.0 X ULN	7%	3%
Grade 4	> 5.0 X ULN	0%	0%

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

Serious ADRs

The following serious ADRs of at least moderate intensity (greater than or equal to Grade 2) occurred in the Phase 2b and Phase 3 trials with DARUNAVIR/ritonavir: abdominal pain, acute hepatitis, acute pancreatitis, anorexia, asthenia, diabetes mellitus, diarrhea, fatigue, headache, hepatic enzyme increased, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, immune reconstitution syndrome, low density lipoprotein increased, nausea, pancreatic enzyme increased, rash, Stevens-Johnson Syndrome, and vomiting.

Patients Co-Infected With Hepatitis B And/Or Hepatitis C Virus

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

Clinical Trials Experience: Pediatric Patients

DARUNAVIR/ritonavir has been studied in combination with other antiretroviral agents in 3 Phase 2 trials. TMC114-C212, in which 80 antiretroviral treatment-experienced HIV-1infected pediatric subjects 6 to less than 18 years of age and weighing at least 20 kg were included, TMC114-C228, in which 21 antiretroviral treatment-experienced HIV-1-infected pediatric subjects 3 to less than 6 years of age and weighing at least 10 kg were included, and TMC114-C230 in which 12 antiretroviral treatment-naive HIV-1 infected pediatric patients aged from 12 to less than 18 years and weighing at least 40 kg were included. The TMC114-C212 and C228 trials evaluated DARUNAVIR/ritonavir twice daily dosing and the TMC114-C230 trial evaluated DARUNAVIR/ritonavir once daily dosing [see Use In Specific Populations and Clinical Studies].

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

TMC114-C212

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

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

TMC114-C228

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

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

TMC114-C230

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

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

Postmarketing Experience

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

Redistribution of body fat has been reported.

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

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

OVERDOSE

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

PHARMACOLOGICAL PROPERTIES

CLINICAL PHARMACOLOGY

Mechanism of Action

Darunavir is an HIV-1 antiviral drug [see **Microbiology**].

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

Pharmacokinetics In Adults

General

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

The pharmacokinetics of darunavir, co-administered with low dose ritonavir (100 mg), has been evaluated in healthy adult volunteers and in HIV-1-infected subjects. Table 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)

Parameter	DARUNAVIR / ritonavir 800/100 mg once daily		DARUNAVIR / ritonavir 600/100 mg twice daily		
	TMC114-C211 N = 335	TMC114-C229 N = 280	TMC114-C229 N = 285	TMC114-C229 N = 278	TMC114-C213 + TMC114-C202 (integrated data) N = 119
AUC24h (ngh/mL)*					
Mean ± Standard Deviation	93026 ± 27050	93334 ± 28626	116796 ± 33594	114302 ± 32681	124698 ± 32286
Median (Range)	87854 (45000-219240)	87788 (45456-236920)	111632 (64874-355360)	109401 (48934-323820)	123336 (67714-212980)
C0h (ng/mL)					
Mean ± Standard Deviation	2282 ± 1168	2160 ± 1201	3490 ± 1401	3386 ± 1372	3578 ± 1151
Median (Range)	2041 (368-7242)	1896 (184-7881)	3307 (1517-13198)	3197 (250-11865)	3578 ± 1151

N = number of subjects with data
* AUC24h is calculated as AUC12h*2.

Absorption And Bioavailability

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

Effects of Food On Oral Absorption

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

Distribution

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

Metabolism

In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by CYP enzymes, primarily by CYP3A. A mass balance study in healthy volunteers showed that after a single dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg ritonavir, the majority of the radioactivity in the plasma was due to darunavir. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 90% less than the activity of darunavir against wild-type HIV-1.

Elimination

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

Special Populations

Hepatic Impairment

Darunavir is primarily metabolized by the liver. The steady-state pharmacokinetic parameters of darunavir were similar after multiple dose co-administration of 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 **DOSAGE AND ADMINISTRATION** and **Use In Specific Populations**].

Hepatitis B Or Hepatitis C Virus Co-infection

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

Renal Impairment

Results from a mass balance study with ^{14}C-DARUNAVIR/ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine as unchanged drug. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis.

Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-1-infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n = 20). There are no pharmacokinetic data available in HIV-1-infected patients with severe renal impairment or end stage renal disease [see **Use In Specific Populations**].

Gender

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

Race

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

Geriatric Patients

Population pharmacokinetic analysis in HIV-1-infected subjects showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV-1-infected subjects (n = 12, age greater than or equal to 65) [see Use In Specific Populations].

Pediatric Patients

DARUNAVIR/Ritonavir Administered Twice Daily

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

DARUNAVIR/Ritonavir Administered Once Daily

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

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-naive adults receiving DARUNAVIR/ritonavir 800/100 mg once daily [see DOSAGE AND ADMINISTRATION].

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*Pregnancy And Postpartum*

The exposure to total darunavir and ritonavir after intake of DARUNAVIR/ritonavir 600/100 mg twice daily and DARUNAVIR/ritonavir 800/100 mg once daily as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum (see Table 13, Table 14 and Figure 1).

Parameter	DARUNAVIR/ritonavir once daily	DARUNAVIR/ritonavir twice daily		
	TMC114-C230β N = 12	TMC114-C212 N = 74	TMC114-C228*	
			10 to less than 15 kg‡ N = 10	15 to less than 20 kg§ N = 13
AUC24h (ngh/mL)*				
Mean ± Standard Deviation	84390 ± 23587	126377 ± 34356	137896 ± 51420	157760 ± 54080
Median (Range)	86741 (35527-123325)	127340 (67054-230720)	124044 (89688-261090)	132698 (112310-294840)
C0h (ng/mL)				
Mean ± Standard Deviation	2141 ± 865	3948 ± 1363	4510 ± 2031	4848 ± 2143
Median (Range)	2234 (542-3776)	3888 (1836-7821)	4126 (2456-9361)	3927 (3046-10292)

N = number of subjects with data.
* Subjects may have contributed pharmacokinetic data to both the 10 kg to less than 15 kg weight group and the 15 kg to less than 20 kg weight group.
† AUC24h is calculated as AUC12h*2.
‡ 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.
§ 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.
β Summary statistics for population pharmacokinetic parameter estimates for DRV after administration of DRV/rtv at 800/100 mg once daily in treatment-naive HIV-1 infected subjects from 12 to < 18 years of age – Week-48 Analyses.

Size: 500 x 950 mm
Colour: Black

Table 13: Pharmacokinetic Results of Total Darunavir After Administration of DARUNAVIR/ritonavir at 600/100 mg Twice Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

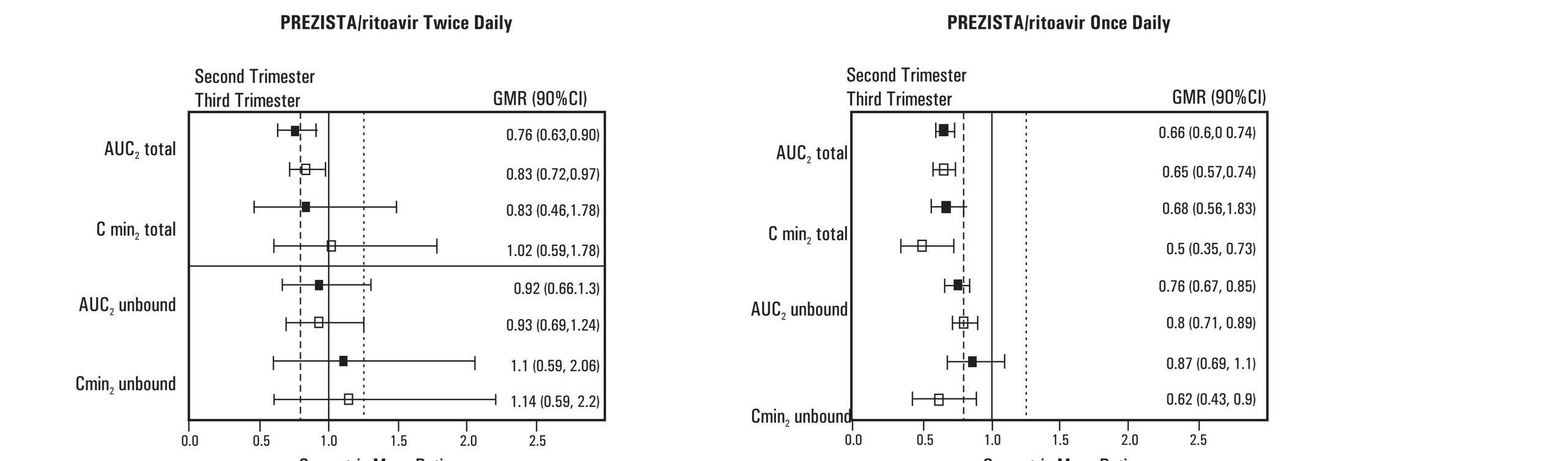
Pharmacokinetics of total darunavir (mean ± standard deviation)	2nd Trimester of pregnancy (n=12)*	3rd Trimester of pregnancy (n=12)	Postpartum (6-12 Weeks) (n=12)
Cmax, ng/mL	4668 ± 1097	5328 ± 1631	6659 ± 2364
AUC24h, ngh/mL‡	78740 ± 19194	91760 ±34720	113780 ± 52680
Cmin, ng/mL	1922 ± 825	2661±1269	2851 ± 2216

Table 14: Pharmacokinetic Results of Total Darunavir After Administration of DARUNAVIR/ritonavir at 800/100 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

Pharmacokinetics of total darunavir (mean ± standard deviation)	2nd Trimester of pregnancy (n=17)	3rd Trimester of pregnancy (n=15)	Postpartum (6-12 Weeks) (n=16)
Cmax, ng/mL	4668 ± 1097	5328 ± 1631	7310 ± 1704
AUC24h, ngh/mL‡	78740 ± 19194	91760 ±34720	92116 ± 29241
Cmin, ng/mL	1922 ± 825	2661±1269	1473 ±1141

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

Figure 1: Pharmacokinetic Results (Within-Subject Comparison) of Total and Unbound Darunavir After Administration of DARUNAVIR/ritonavir at 600/100 mg Twice Daily or 800/100 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd and 3rd Trimester of Pregnancy Compared to Postpartum



Drug Interactions

[See also **CONTRAINDICATIONS,** WARNINGS AND **PRECAUTIONS** and **DRUG INTERACTIONS**]

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

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

Drug interaction studies were performed with darunavir and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of darunavir on the AUC, Cmax, and Cmin 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.**

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 drug	Dose/Schedule		N	PK	LS Mean ratio (90% CI) of darunavir Pharmacokinetic parameters with/without co-administered drug no effect =1.00		
	Co-administere d Drug	Darunavir/ ritonavir			Cmax	AUC	Cmin
Co-administration with other HIV protease inhibitors							
Atazanavir	300 mg q.d.*	400/100 mg b.i.d. †	13	↔	1.02 (0.96-1.09)	1.03 (0.94-1.12)	1.01 (0.88-1.16)
Indinavir	800 mg b.i.d.	400/100 mg b.i.d.	9	↑	1.11 (0.98-1.26)	1.24 (1.09-1.42)	1.44 (1.13-1.82)
Lopinavir/ritonavir	400/100 mg b.i.d.	1200/100 mg b.i.d.‡	14	↓	0.79 (0.67-0.92)	0.62 (0.53-0.73)	0.49 (0.39-0.63)
	533/133.3 mg b.i.d.	1200 mg b.i.d.‡	15	↓	0.79 (0.64-0.97)	0.59 (0.50-0.70)	0.45 (0.38-0.52)
Saquinavir hard gel capsule	1000 mg b.i.d.	400/100 mg b.i.d.	14	↓	0.83 (0.75-0.92)	0.74 (0.63-0.86)	0.58 (0.47-0.72)
Co-administration with other HIV antiretrovirals							
Didanosine	400 mg q.d.	600/100 mg b.i.d.	17	↔	0.93 (0.86-1.00)	1.01 (0.95-1.07)	1.07 (0.95-1.21)
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↓	0.85 (0.72-1.00)	0.87 (0.75-1.01)	0.69 (0.54-0.87)
Etravirine	200 mg b.i.d.	600/100 mg b.i.d.	15	↔	1.11 (1.01-1.22)	1.15 (1.05-1.26)	1.02 (0.90-1.17)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.40 § (1.14-1.73)	1.24 § (0.97-1.57)	1.02 § (0.79-1.32)
Rilpivirine	150 mg q.d.	800/100 mg q.d.	15	↔	0.90 (0.81-1.00)	0.89 (0.81-0.99)	0.89 (0.68-1.16)
Tenofovir disoproxil fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.16 (0.94-1.42)	1.21 (0.95-1.54)	1.24 (0.90-1.69)
Co-administration with HCV NS3-4A protease inhibitors							
Simeprevir	50 mg q.d. €	800 mg q.d.	25+	↑	1.04 (0.99-1.10)	1.18 (1.11-1.25)	1.31 (1.13-1.52)
Co-administration with other drugs							
Artemether/lumefantrine	80/480 mg (6 doses at 0, 8,24, 36, 48, and60 hours)	600/100 mg b.i.d.	14	↔	1.00 (0.93-1.07)	0.96 (0.90-1.03)	0.87 (0.77-0.98)
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	↔	1.04 (0.93-1.16)	0.99 (0.90-1.08)	0.85 (0.73-1.00)
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↔	0.83 (0.72-0.96)	0.87 (0.75-1.01)	1.01 (0.81-1.26)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	14	↑	1.21 (1.04-1.40)	1.42 (1.23-1.65)	1.73 (1.39-2.14)
Omeprazole	20 mg q.d.	400/100 mg b.i.d.	16	↔	1.02 (0.95-1.09)	1.04 (0.96-1.13)	1.08 (0.93-1.25)
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↔	0.97 (0.92-1.02)	1.02 (0.95-1.10)	1.07 (0.96-1.19)
Pitavastatin	4 mg q.d.	800/100 mg q.d.	27	↔	1.06 (1.00-1.12)	1.03 (0.95-1.12)	NA
Ranitidine	150 mg b.i.d.	400/100 mg b.i.d.	16	↔	0.96 (0.89-1.05)	0.95 (0.90-1.01)	0.94 (0.90-0.99)
Rifabutin	150 mg q.o.d.¶	600/100 mg b.i.d.	11	↑	1.42 (1.21-1.67)	1.57 (1.28-1.93)	1.75 (1.28-2.37)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↔	1.01 (0.89-1.14)	0.98 (0.84-1.14)	0.94 (0.76-1.16)

N = number of subjects with data
* q.d. = once daily
† b.i.d. = twice daily
‡ The pharmacokinetic parameters of darunavir in this study were compared with the pharmacokinetic parameters following administration of DARUNAVIR/ritonavir 600/100 mg twice daily.
§ Ratio based on between-study comparison.
¶ q.o.d. = every other day
€ The dose of simeprevir in this interaction study was 50 mg when co-administered in combination with DARUNAVIR/ritonavir compared to 150 mg once daily in the simeprevir alone treatment group.
+ Maximum number of subjects

Table 16: Drug Interactions: Pharmacokinetic Parameters for Co-Administered Drugs in the Presence of DARUNAVIR/ritonavir

Co-administered drug	Dose/Schedule		N	PK	LS Mean ratio (90% CI) of darunavir Pharmacokinetic parameters with/without co-administered drug no effect =1.00		
	Co-administere d Drug	Darunavir/ ritonavir			Cmax	AUC	Cmin
Co-administration with other HIV protease inhibitors							
Atazanavir	300 mg q.d.* /100 mg ritonavir q.d. when administered alone 300 mg q.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d. †	13	↔	0.89 (0.78-1.01)	1.08 (0.94-1.24)	1.52 (0.99-2.34)
Indinavir	800 mg b.i.d. /100 mg ritonavir b.i.d. when administered alone 800 mg b.i.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d.	9	↑	1.08 (0.95-1.22)	1.23 (1.06-1.42)	2.25 (1.63-3.10)
Lopinavir/ritonavir	400/100 mg b.i.d.‡	1200/100 mg b.i.d.	14	↔	0.98 (0.78-1.22)	1.09 (0.86-1.37)	1.23 (0.90-1.69)
	533/133.3 mg b.i.d.‡	1200 mg b.i.d.	15	↔	1.11 (0.96-1.30)	1.09 (0.86-1.37)	1.13 (0.90-1.42)
Saquinavir hard gel capsule	1000 mg b.i.d. / 100 mg ritonavir b.i.d. when administered alone1000 mg b.i.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d	12	↔	0.94 (0.78-1.13)	0.94 (0.76-1.17)	0.82 (0.52-1.30)
Co-administration with other HIV antiretrovirals							
Didanosine	400 mg q.d.	600/100 mg b.i.d.	17	↔	0.84 (0.59-1.20)	0.91 (0.75-1.10)	-
Dolutegravir	30 mg q.d	600/100 mg b.i.d.	15	↓	0.89 (0.83-0.97)	0.78 (0.72-0.85)	0.62n (0.56-0.69)
Dolutegravir	50 mg q.d.	600/100 mg b.i.d. with 200 mg b.i.d. etravirine	9	↓	0.88 (0.78-1.00)	0.75 (0.69-0.81)	0.63 n (0.52-0.76)
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↑	1.15 (0.97-1.35)	1.21 (1.08-1.36)	1.17 (1.01-1.36)
Etravirine	100 mg b.i.d.	600/100 mg b.i.d.	14	↓	0.68 (0.57-0.82)	0.63 (0.54-0.73)	0.51 (0.44-0.61)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.18 (1.02-1.37)	1.27 (1.12-1.44)	1.47 (1.20-1.82)
Rilpivirine	150 mg q.d.	800/100 mg q.d.	14	↑	1.79 (1.56-2.06)	2.30 (1.98-2.67)	2.78 (2.39-3.24)
Tenofovir disoproxil fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.24 (1.08-1.42)	1.22 (1.10-1.35)	1.37 (1.19-1.57)
Maraviroc	150 mg b.i.d.	600/100 mg b.i.d.	12	↑	2.29 (1.46-3.59)	4.05 (2.94-5.59)	8.00 (6.35-10.1)
		600/100 mg b.i.d. with 200 mg b.i.d. etravirine	10	↑	1.77 (1.20-2.60)	3.10 (2.57-3.74)	5.27 (4.51-6.15)
Co-administration with HCV NS3-4A protease inhibitors							
Simeprevir	50 mg q.d. €	800/100 mg q.d.	25+	↑	1.79 (1.55-2.06)	2.59 (2.15-3.11)	4.58 (3.54-5.92)
Co-administration with other drugs							
Atorvastatin	40 mg q.d. when administered alone 10 mg q.d. when administered with darunavir/ritonavir	300/100 mg b.i.d.	15	↑	0.56 (0.48-0.67)	0.85 (0.76-0.97)	1.81 (1.37-2.40)
Artemether	80 mg single dose	600/100 mg b.i.d.	15	↓	0.85 (0.68-1.05)	0.91 (0.78-1.06)	-
Dihydroartemisinin			15	↑	1.06 (0.82-1.39)	1.12 (0.96-1.30)	-
Artemether	artemether/ lumefantrine	600/100 mg b.i.d.	15	↓	0.82 (0.61-1.11)	0.84 (0.69-1.02)	0.97 (0.90-1.05)
Dihydroartemisinin	80/480 mg (6 doses at 0, 8, 24,		15	↑	0.82 (0.66-1.01)	0.82 (0.74-0.91)	1.00 (0.82-1.22)
Lumefantrine	36, 48, and 60 hours)		15	↔	1.65 (1.49-1.83)	2.75 (2.46-3.08)	2.26 (1.92-2.67)
Buprenorphine/ Naloxone	8/2 mg to 16/4 mg q.d.	600/100 mg b.i.d.	17	↔	0.92 § (0.79-1.08)	0.89 § (0.78-1.02)	0.98 § (0.82-1.16)
Norbuprenorphine			17	↑	1.36 (1.06-1.74)	1.46 (1.15-1.85)	1.71 (1.29-2.27)
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	↑	1.43 (1.34-1.53)	1.45 (1.35-1.57)	1.54 (1.41-1.68)
Carbamazepine epoxide			16	↓	0.46 (0.43-0.49)	0.46 (0.44-0.49)	0.48 (0.45-0.51)
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↑	1.26 (1.03-1.54)	1.57 (1.35-1.84)	2.74 (2.30-3.26)
Dextromethorphan	30 mg	600/100 mg b.i.d.	12	↑	2.27 (1.59-3.26)	2.70 (1.80-4.05)	-
Dextrorphan				↓	0.87 (0.77-0.98)	0.96 (0.90-1.03)	-
Digoxin	0.4 mg	600/100 mg b.i.d.	8	↑	1.15 (0.89-1.48)	1.36 (0.81-2.27)	-
Ethinyl estradiol (EE) Norethindrone (NE)	Ortho-Novum 1/35 (35 μg EE /1 mg NE)	600/100 mg b.i.d.	11	↓	0.68 (0.61-0.74)	0.56 (0.50-0.63)	0.38 (0.27-0.54)
			11	↓	0.90 (0.83-0.97)	0.86 (0.75-0.98)	0.70 (0.51-0.97)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	15	↑	2.11 (1.81-2.44)	3.12 (2.65-3.68)	9.68 (6.44- 14.55)
R-Methadone	55-150 mg q.d.	600/100 mg b.i.d.	16	↓	0.76 (0.71-0.81)	0.84 (0.78-0.91)	0.85 (0.77-0.94)
Omeprazole	40 mg single dose	600/100 mg b.i.d.	12	↓	0.66 (0.48-0.90)	0.58 (0.50-0.66)	-
5-hydroxy omeprazole				↓	0.93 (0.71-1.21)	0.84 (0.77-0.92)	-
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↓	0.64 (0.59-0.71)	0.61 (0.56-0.66)	0.63 (0.55-0.73)
Pitavastatin	4 mg q.d.	800/100 mg q.d.	27	↓	0.96 (0.84-1.09)	0.74 (0.69-0.80)	NA
Pravastatin	40 mg single dose	600/100 mg b.i.d.	14	↑	1.63 (0.95-2.82)	1.81 (1.23-2.66)	-
Rifabutin	150 mg q.o.d. ¶ when administered with DARUNAVIR/ ritonavir	600/100 mg b.i.d. #	11	↑	0.72 (0.55-0.93)	0.93 (0.80-1.09)	1.64 (1.48-1.81)
25-O-desacetyl- rifabutin	300 mg q.d. when administered alone		11	↑	4.77 (4.04-5.63)	9.81 (8.09-11.9)	27.1 (22.2-33.2)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↓	0.56 (0.49-0.63)	0.51 (0.46-0.58)	0.51 (0.45-0.57)
Sildenafil	100 mg (single dose) administered alone 25 mg (single dose)when administered with darunavir/ ritonavir	400/100 mg b.i.d.	16	↑	0.62 (0.55-0.70)	0.97 (0.86-1.09)	
S-warfarin	10 mg single dose	600/100 mg b.i.d.	12	↓	0.92 (0.86-0.97)	0.79 (0.73-0.85)	-
7-OH-S-warfarin			12	↑	1.42 (1.24-1.63)	1.23 (0.97-1.57)	-

N = number of subjects with data;- = no information available
* q.d. = once daily
† b.i.d. = twice daily
‡ The pharmacokinetic parameters of lopinavir in this study were compared with the pharmacokinetic parameters following administration of lopinavir/ritonavir 400/100 mg twice daily.
§ratio is for buprenorphine; mean Cmax and AUC24 for naloxone were comparable when buprenorphine/naloxone was administered with or without DARUNAVIR/ritonavir
¶ q.o.d. = every other day
\# In comparison to rifabutin 300 mg once daily.
Ω Noted as C or C24 in the dolutegravir U.S. prescribing information
+ Maximum number of subjects
€ The dose of simeprevir in this interaction study was 50 mg when co-administered in combination with DARUNAVIR/ritonavir compared to 150 mg once daily in the simeprevir alone treatment group. A cocktail study was conducted in 12 healthy volunteers to evaluate the effect of steady state pharmacokinetics of DARUNAVIR/ritonavir on the activity of CYP2D6 (using dextromethorphan as probe substrate), CYP2C9 (using warfarin as probe substrate), and CYP2C19 (using omeprazole as probe substrate). The pharmacokinetic results are shown in Table 16.

Microbiology

Mechanism Of Action

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

Antiviral Activity

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

Resistance

Cell Culture

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

Clinical Trials Of DARUNAVIR/Ritonavir In Treatment-Experienced Subjects

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

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

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

Clinical Trials Of DARUNAVIR/Ritonavir In Treatment-Naive Subjects

In the 192-week as-treated analysis censoring those who discontinued before Week 4 of the Phase 3 trial TMC114-C211, the percentage of virologic failures (never suppressed, rebounders and discontinued before achieving suppression) was 22% (64/288) in the group of subjects receiving DARUNAVIR/ritonavir 800/100 mg once daily compared to 29% (76/263) of subjects receiving lopinavir/ritonavir 800/200 mg per day. In the DARUNAVIR/ritonavir arm, emergent PI resistance-associated substitutions were identified in 11 of the virologic failures with post-baseline genotypic data (n=43). However, none of the darunavir virologic failures had a decrease in darunavir susceptibility (greater than 7-fold change) at failure. In the comparator lopinavir/ritonavir arm, emergent PI resistance-associated substitutions were identified in 17 of the virologic failures with post-baseline genotypic data (n=53), but none of the lopinavir/ritonavir virologic failures had decreased susceptibility to lopinavir (greater than 10fold change) at failure. The reverse transcriptase M184V substitution and/or resistance to emtricitabine, which was included in the fixed background regimen, was identified in 4 virologic failures from the DARUNAVIR/ritonavir arm and 7 virologic failures in the lopinavir/ritonavir arm.

Cross-Resistance

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

Darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir in cell culture. However, six of nine darunavir-resistant viruses selected in cell culture from PI-resistant viruses showed a fold change in EC50 values less than 3 for tipranavir, indicative of limited cross-resistance between darunavir and tipranavir. In trials TMC114-C213, TMC114-C202, and TMC114-C215, 34% (64/187) of subjects in the DARUNAVIR/ritonavir arm whose baseline isolates had decreased susceptibility to tipranavir (tipranavir fold change greater than 3) achieved less than 50 copies/mL serum HIV-1 RNA levels at Week 96. Of the viruses isolated from subjects experiencing virologic failure on DARUNAVIR/ritonavir 600/100 mg twice daily (greater than 7-fold change), 41% were still susceptible to tipranavir and 10% were susceptible to saquinavir while less than 2% were susceptible to the other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir or nelfinavir).

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

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

Baseline Genotype/Phenotype And Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining darunavir susceptibility before initiation of DARUNAVIR/ritonavir 600/100 mg twice daily therapy. The effect of baseline genotype and phenotype on virologic response at 96 weeks was analyzed in as-treated analyses using pooled data from the Phase 2b trials (Trials TMC114-C213, TMC114C202, and TMC114-C215) (n=439). The findings were confirmed with additional genotypic and phenotypic data from the control arms of etravirine trials TMC125-C206 and TMC125-C216 at Week 24 (n=591).

Diminished virologic responses were observed in subjects with 5 or more baseline IAS-defined primary protease inhibitor resistance-associated substitutions (D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, L76V, V82A/F/L/S/T, I84V, N88S, L90M) (see Table 17).

Table 17: Response to DARUNAVIR/ritonavir 600/100 mg Twice Daily by Baseline Number of IAS-Defined Primary PI Resistance-Associated Substitutions: As-treated Analysis of Trials TMC114-C213, TMC114-C202, and TMC114-C215

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

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

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

Baseline darunavir phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Response rates assessed by baseline darunavir phenotype are shown in Table 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 pretreatment 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

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

Clinical Studies

Description Of Adult Clinical Trials

The evidence of efficacy of DARUNAVIR/ritonavir is based on the analyses of 192-week data from a randomized, controlled open-label Phase 3 trial in treatment-naive (TMC114-C211) HIV-1infected 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, TMC114C213 and TMC114-C202, in antiretroviral treatment-experienced HIV-1-infected adult subjects.

Treatment-Naive 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-naive HIV-1infected 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/mm³ or greater than or equal to 200 cells/mm³). 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 800/200 mg per day arm in trial TMC114-C211.

Table 19: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C211

	DARUNAVIR/ritonavir 800/100 mg once daily + TDF/FTC N=343	Lopinavir/ritonavir 800/200 mg per day + TDF/FTC N=346
Demographic characteristics		
Median age (years) (range, years)	34 (18-70)	33 (19-68)
Sex		
Male	70%	70%
Female	30%	30%
Race		
White	40%	45%
Black	23%	21%
Hispanic	23%	22%
Asian	13%	11%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA (log_{10} copies/mL)	4.86	4.84
Median baseline CD4+ cell count (cells/mm³) (range, cells/mm³)	228 (4-750)	218 (2-714)
Percentage of patients with baseline viral load ≥100,000 copies/mL	34%	35%
Percentage of patients with baseline CD4+ cell count <200 cells/mm³	41%	43%

Week 192 outcomes for subjects on DARUNAVIR/ritonavir 800/100 mg once daily from trial TMC114-C211 are shown in Table 20.

Table 20: Virologic Outcome of Randomized Treatment of Trial TMC114-C211 at 192 Weeks

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

N = total number of subjects with data; FTC=emtricitabine; TDF=tenofovir disoproxil fumarate
* 95% CI: 1.9; 16.1
† Includes patients who discontinued prior to Week 192 for lack or loss of efficacy and patients who are ≥50 copies in the 192-week window and patients who had a change in their background regimen that was not permitted by the protocol.
‡ Window 186-198 Weeks.
§ Includes patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
¶ Other includes: withdrew consent, loss to follow-up, etc., if the viral load at the time of discontinuation was <50 copies/mL

In trial TMC114-C211 at 192 weeks of treatment, the median increase from baseline in CD4+ cell counts was 258 cells/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.

Treatment-Experienced Adult Subjects

TMC114-C229

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

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

Table 21 compares the demographic and baseline characteristics between subjects in the DARUNAVIR/ritonavir 800/100 mg once daily arm and subjects in the DARUNAVIR/ritonavir 600/100 mg twice daily arm in trial TMC114-C229. No imbalances between the 2 arms were noted.

Table 21: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C229

	DARUNAVIR/ritonavir 800/100 mg once daily + OBR N=294	DARUNAVIR/ritonavir 600/100 mg twice daily + OBR N=296
Demographic characteristics		
Median age (years) (range, years)	40 (18-70)	40 (18-77)
Sex		
Male	61%	67%
Female	39%	33%
Race		
White	35%	37%
Black	28%	24%
Hispanic	16%	20%
Asian	16%	14%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA (log10 copies/mL)	4.19	4.13
Median baseline CD4+ cell count (cells/mm³) (range, cells/mm³)	219 (24-1306)	236 (44-864)
Percentage of patients with baseline viral load ≥100,000 copies/mL	13%	11%
Percentage of patients with baseline CD4+ cell count <200 cells/mm³	43%	39%
Median darunavir fold change (range)*	0.50 (0.1-1.8)	0.50 (0.1-1.9)
Median number of resistance-associated†		
PI mutations	3	4
NNRTI mutations	2	1
NRTI mutations	1	1
Percentage of subjects susceptible to all available PIs at baseline	88%	86%
Percentage of subjects with number of baseline primary protease inhibitor mutations†:		
0	84%	84%
1	8%	9%
2	5%	4%
≥3	3%	2%
Median number of ARVs previously used‡:		
NRTIs	3	3
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	1	1

OBR=optimized background regimen
* Based on phenotype (Antivirogram®)
† Johnson VA, Brun-Vézinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: December 2008. Top HIV Med 2008; 16(5): 138-145
‡ Only counting ARVs, excluding low-dose ritonavir

Week 48 outcomes for subjects on DARUNAVIR/ritonavir 800/100 mg once daily from trial TMC114-C229 are shown in Table 22.

Table 22: Virologic Outcome of Randomized Treatment of Trial TMC114-C229 at 48 Weeks

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

N = total number of subjects with data; OBR=optimized background regimen
* Includes patients who discontinued prior to Week 48 for lack or loss of efficacy, patients who are ≥50 copies in the 48-week window, patients who had a change in their background regimen that was not permitted in the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of trial medication) and patients who discontinued for reasons other than AEs/death and lack or loss of efficacy (provided their last available viral load was detectable (HIV RNA ≥50 copies/mL).
† Window 42-54 Weeks
‡ Patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
§ Other includes: withdrew consent, loss to follow-up, etc., if the viral load at the time of discontinuation was <50 copies/mL.

The mean increase from baseline in CD4+ cell counts was comparable for both treatment arms (108 cells/mm³ and 112 cells/mm³ in the DARUNAVIR/ritonavir 800/100 mg once daily arm and the DARUNAVIR/ritonavir 600/100 mg twice daily arm, respectively).

TMC114-C214

TMC114-C214 is a randomized, controlled, open-label Phase 3 trial comparing DARUNAVIR/ritonavir 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in antiretroviral treatment-experienced, lopinavir/ritonavir-naive HIV-1-infected adult subjects. Both arms used an optimized background regimen consisting of at least 2 antiretrovirals (NRTIs with or without NNRTIs).

HIV-1-infected subjects who were eligible for this trial had plasma HIV-1 RNA greater than 1000 copies/mL and were on a highly active antiretroviral therapy regimen (HAART) for at least 12 weeks. Virologic response was defined as a confirmed plasma HIV-1 RNA viral load less than 400 copies/mL. Analyses included 595 subjects in trial TMC114-C214 who had completed 96 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the DARUNAVIR/ritonavir arm and the lopinavir/ritonavir arm (see Table 23). Table 23 compares the demographic and baseline characteristics between subjects in the DARUNAVIR/ritonavir 600/100 mg twice daily arm and subjects in the lopinavir/ritonavir 400/100 mg twice daily arm in trial TMC114-C214.

Table 23: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C214

	DARUNAVIR/ritonavir 600/100 mg twice daily + OBR N=298	Lopinavir/ritonavir 400/100 mg twice daily + OBR N=297
Demographic characteristics		
Median age (years) (range, years)	40 (18-68)	41 (22-76)
Sex		
Male	77%	81%
Female	23%	19%
Race		
White	54%	57%
Black	18%	17%
Hispanic	15%	15%
Asian	9%	9%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA (log_{10} copies/mL)	4.33	4.28
Median baseline CD4+ cell count (cells/mm³) (range, cells/mm³)	235 (3-831)	230 (2-1096)
Percentage of patients with baseline viral load ≥100,000 copies/mL	19%	17%
Percentage of patients with baseline CD4+ cell count <200 cells/mm³	40%	40%
Median darunavir fold change (range)	0.60 (0.10-37.40)	0.60 (0.1-43.8)
Median lopinavir fold change (range)	0.70 (0.40-74.40)	0.80 (0.30-74.50)
Median number of resistance-associated*:		
PI mutations	4	4
NNRTI mutations	1	1
NRTI mutations	2	2
Percentage of subjects with number of baseline primary protease inhibitor mutations*:		
≤1	78%	80%
2	8%	9%
≥3	13%	11%
Median number of ARVs previously used†:		
NRTIs	4	4
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	1	1
Percentage of subjects resistant‡ to all available§ PIs at baseline, excluding darunavir	2%	3%

OBR=optimized background regimen
* Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: Fall 2006. Top HIV Med 2006; 14(3): 125130
† Only counting ARVs, excluding low-dose ritonavir
‡ Based on phenotype (Antivirogram®)
§ Commercially available PIs at the time of trial enrollment

Week 96 outcomes for subjects on DARUNAVIR/ritonavir 600/100 mg twice daily from trial TMC114-C214 are shown in Table 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*	26%	33%
No virologic data at Week 96 window†		
Reasons	7%	8%
Discontinued trial due to adverse event or death‡	8%	7%
Discontinued trial for other reasons§	1%	<1%
Missing data during window† but on trial		

N = total number of subjects with data; OBR=optimized background regimen
* Includes patients who discontinued prior to Week 96 for lack or loss of efficacy and patients who are ≥50 copies in the 96-week window and patients who had a change in their OBR that was not permitted by the protocol.
† Window 90-102 Weeks
‡ Includes patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
§ Other includes: withdrew consent, loss to follow-up, etc., if the viral load at the time of discontinuation was <50 copies/mL.

In trial TMC114-C214 at 96 weeks of treatment, the median increase from baseline in CD4+ cell counts was 81 cells/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

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

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

The virologic response rate was evaluated in subjects receiving DARUNAVIR/ritonavir plus an OBR versus a control group receiving an investigator-selected PI(s) regimen plus an OBR. Prior to randomization, PI(s) and OBR were selected by the investigator based on genotypic resistance testing and prior ARV history. The OBR consisted of at least 2 NRTIs with or without enfuvirtide. Selected PI(s) in the control arm included: lopinavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%; 98% of control subjects received a ritonavir boosted PI regimen out of which 23% of control subjects used dual-boosted PIs. Approximately 47% of all subjects used enfuvirtide, and 35% of the use was in subjects who were ENF-naive. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1 log_{10} 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 (27-73)	44 (25-65)
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_{10} copies/mL)	4.61	4.49
Median baseline CD4+ cell count (cells/mm³) (range, cells/mm³)	153 (3-776)	163 (3-1274)
Percentage of patients with baseline viral load >100,000 copies/mL	24%	29%
Percentage of patients with baseline CD4+ cell count <200 cells/mm³	67%	58%
Median darunavir fold change	4.3	3.3
Median number of resistance-associated*:		
PI mutations	12	12
NNRTI mutations	1	1
NRTI mutations	5	5
Percentage of subjects with number of baseline primary protease inhibitor mutations*:		
≤1	8%	9%
2≥	22%	21%
3	70%	70%
Median number of ARVs previously used†:		
NRTIs	6	6
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	5	5
Percentage of subjects resistant† to all available‡ PIs at baseline, excluding tipranavir and darunavir	63%	61%
Percentage of subjects with prior use of enfuvirtide	20%	17%

OBR=optimized background regimen
* Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: Fall 2006. Top HIV Med 2006; 14(3): 125-130
† Based on phenotype (Antivirogram®)
‡ Commercially available PIs at the time of trial enrollment

Week 96 outcomes for subjects on the recommended dose DARUNAVIR/ritonavir 600/100 mg twice daily from the pooled trials TMC114-C213 and TMC114-C202 are shown in Table 26.

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 log10 HIV-1 RNA below baseline through Week 96 (<50 copies/mL at Week 96)	57% (39%)	10% (9%)
Virologic failures	29%	80%
Lack of initial response*	8%	53%
Rebounder†	17%	19%
Never suppressed‡	4%	8%
Death or discontinuation due to adverse events	9%	3%
Discontinuation due to other reasons	5%	7%

OBR=optimized background regimen
* Subjects who did not achieve at least a confirmed 0.5 log10 HIV-1 RNA drop from baseline at Week 12
† Subjects with an initial response (confirmed 1 log10 drop in viral load), but without a confirmed 1 log10 drop in viral load at Week 96
‡ Subjects who never reached a confirmed 1 log10 drop in viral load before Week 96

In the pooled trials TMC114-C213 and TMC114-C202 through 48 weeks of treatment, the proportion of subjects with HIV-1 RNA less than 400 copies/mL in the arm receiving DARUNAVIR/ritonavir 600/100 mg twice daily compared to the comparator PI arm was 55.0% and 14.5%, respectively. In addition, the mean changes in plasma HIV-1 RNA from baseline were – 1.69 log_{10} copies/mL in the arm receiving DARUNAVIR/ritonavir 600/100 mg twice daily and – 0.37 log_{10} 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/mm³) than in the comparator PI arm (17 cells/mm³).

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.

[illegible]

TMC114-C228

[illegible]

TMC114-C230

[illegible]

Availability

PACK: HDPE Bottle Box of 60's

STORAGE CONDITION

Store at temperatures not exceeding 30°C.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Please seek medical attention immediately at the first sign of any adverse drug reaction.

Manufactured by:
HETERO LABS LIMITED
Unit III, 22-110, I.D.A., Jeedimetla,
Hyderabad - 500 055, Telangana,
INDIA.

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Registration Number:
Darunavir 400 mg: [illegible]
Darunavir 600 mg: [illegible]

Date of First Authorization: August 2022
Date of Revision of Package Insert: 12/2022