Baseline characteristics of the subjects included in the TMC114-C215/C208 analysis were comparable to those subjects in Studies TMC114-C213 and TMC114-C202.

The TMC114-C215/C208 24-week efficacy analysis supported the viral load reduction and CD4+ cell count increases observed in the Studies TMC114-C213 and TMC114-C202. Of the 246 subjects at Week 24, 65% had a virologic response defined as a decrease of at least 1.0 $\log_{10}$ in plasma viral load versus baseline and 40% of the subjects reached less than 50 HIV-1 RNA copies/mL. The mean increase in CD4+ cell count versus baseline was 80 cells/mm^3 at Week 20. At Week 24, 57% of the subjects reached less than 400 HIV-1 RNA copies/mL, and the mean changes in plasma HIV-1 RNA from baseline were -1.65 $\log_{10}$ copies/mL.

CONTRAINDICATIONS

PREZISTA is contraindicated in patients with known hypersensitivity to any of the ingredients of the product.

Co-administration of PREZISTA/rtv is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These drugs are listed in Table 9 (also see PRECAUTIONS, *Drug Interactions*, Table 10).

Table 9: Drugs That Are Contraindicated With PREZISTA/rtv

Drug Class	Drugs Within Class That Are Contraindicated With PREZISTA/rtv
Antihistamines	Astemizole, Terfenadine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
GI Motility Agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, Triazolam

Due to the need for co-administration of PREZISTA with 100 mg of ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

WARNINGS

ALERT: Find out about medicines that should not be taken with PREZISTA/rtv. This statement is included on the product's bottle label.

General

PREZISTA (darunavir) must be co-administered with ritonavir and food to exert its therapeutic effect (see DOSAGE and ADMINISTRATION). Failure to correctly administer PREZISTA with ritonavir and food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired antiviral effect.

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

Skin Rash
During the clinical development program, severe skin rash, including erythema multiforme and Stevens-Johnson Syndrome, has been reported. In some cases, fever and elevations of transaminases have also been reported. In clinical trials (n=924), rash (all grades, regardless of causality) occurred in 7% of subjects treated with PREZISTA; the discontinuation rate due to rash was 0.3%. Rashes were generally mild-to-moderate, self-limited maculopapular skin eruptions. Treatment with PREZISTA should be discontinued if severe rash develops.

Sulfa Allergy
Darunavir contains a sulfonamide moiety. PREZISTA (darunavir) should be used with caution in patients with a known sulfonamide allergy.

Drug Interactions
PREZISTA and ritonavir are both inhibitors of CYP3A. Co-administration of PREZISTA/rtv with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see sections CONTRAINDICATIONS and PRECAUTIONS, *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 therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between protease inhibitor therapy and these events have not been established.

PRECAUTIONS

Patients with co-existing conditions
Hepatic Impairment: Darunavir is primarily metabolized by the liver, hence, caution should be exercised when PREZISTA/rtv is given to patients with hepatic impairment, because increased plasma concentrations are expected in patients with hepatic impairment. There are no data regarding the use of PREZISTA/rtv when co-administered to patients with varying degrees of hepatic impairment; therefore, specific dosage recommendations cannot be made. PREZISTA/rtv should be used with caution in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults*, *Special Populations*, *Hepatic Impairment* and DOSAGE AND ADMINISTRATION).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, can have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening of liver disease in such patients, interruption or discontinuation of treatment must be considered.

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). There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease; however,

since 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, *Pharmacokinetics in Adults*, *Special Populations*, *Renal Impairment* and DOSAGE AND ADMINISTRATION).

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

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
During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jeroveci* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment.

Resistance/Cross-Resistance
Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in PREZISTA/rtv treated patients, it is unknown what effect therapy with PREZISTA will have on the activity of subsequently administered protease inhibitors.

Information for Patients
A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with PREZISTA.** A Patient Package Insert for PREZISTA is available for patient information.

Patients should be informed that PREZISTA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of PREZISTA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with PREZISTA can reduce the risk of transmitting HIV to others.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using PREZISTA.

Patients should be advised to take PREZISTA and ritonavir (NORVIR®) with food every day as prescribed. The type of food does not affect exposure to PREZISTA. Patients should be instructed to swallow whole tablets with a drink such as water or milk. PREZISTA must always

be used with 100 mg of ritonavir (NORVIR®) in combination with other antiretroviral drugs. Patients should not alter the dose of either PREZISTA or ritonavir (NORVIR®), discontinue ritonavir (NORVIR®), or discontinue therapy with PREZISTA without consulting their physician. If a patient misses a dose of PREZISTA or ritonavir (NORVIR®) by more than 6 hours, the patient should be told to wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If the patient misses a dose of PREZISTA or ritonavir (NORVIR®) by less than 6 hours, the patient should be told to take PREZISTA and ritonavir (NORVIR®) immediately, and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If a dose of PREZISTA or ritonavir (NORVIR®) is skipped, the patient should not double the next dose. Inform the patient that he or she should not take more or less than the prescribed dose of PREZISTA or ritonavir (NORVIR®) at any one time.

PREZISTA/rtv may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort.

Patients receiving estrogen-based contraceptives should be instructed to use alternate contraceptive measures during therapy with PREZISTA/rtv because hormonal levels may decrease.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including PREZISTA/rtv, and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions

PREZISTA and ritonavir are both inhibitors of CYP3A. Co-administration of PREZISTA and ritonavir with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see Tables 10 and 11).

Drugs that are contraindicated and not recommended for co-administration with PREZISTA/rtv are included in Table 10. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 10: Drugs That Should Not Be Co-administered With PREZISTA/rtv

Drug Class: Drug Name	Clinical Comment
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. PREZISTA/rtv should not be used in combination with phenobarbital, phenytoin, or carbamazepine as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	Rifampin is a potent inducer of CYP450 metabolism. PREZISTA/rtv should not be used in combination with rifampin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Gastrointestinal Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (*Hypericum perforatum*)	PREZISTA/rtv should not be used concomitantly with products containing St. John's wort (*Hypericum perforatum)* because co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis. For dosing recommendation regarding atorvastatin and pravastatin, see Table 11: Established and Other

	Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 11: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (See CLINICAL PHARMACOLOGY for Magnitude of Interaction, Tables 4 and 5)

Concomitant Drug Class: Drug Name	**Effect on Concentration of Darunavir or Concomitant Drug**	**Clinical Comment**
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz	↓ darunavir ↑ efavirenz	Co-administration of darunavir/rtv and efavirenz decreased darunavir AUC by 13% and C_{min} by 31%. The AUC of efavirenz increased by 21% and C_{min} increased by 17%. The clinical significance has not been established. The combination of PREZISTA/rtv and efavirenz should be used with caution.
Nevirapine	↔ darunavir ↑ nevirapine	PREZISTA/rtv and nevirapine can be co-administered without any dose adjustments.
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Didanosine		It is recommended that didanosine be administered on an empty stomach. Therefore, didanosine should be administered one hour before or two hours after PREZISTA/rtv (which are administered with food).
Tenofovir Disoproxil Fumarate	↔ darunavir ↑ tenofovir	PREZISTA/rtv and tenofovir disoproxil fumarate can be co-administered without any

		dose adjustments.
HIV-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
Atazanavir (The reference regimen for atazanavir was atazanavir/ritonavir 300/100 mg q.d.)	↔ darunavir ↔ atazanavir	PREZISTA/rtv and atazanavir (300 mg q.d.) can be co-administered.
Indinavir (The reference regimen for indinavir was indinavir/ritonavir 800/100 mg b.i.d.)	↑ darunavir ↑ indinavir	The appropriate dose of indinavir in combination with PREZISTA/rtv has not been established.
Lopinavir/ritonavir	↓ darunavir ↑ lopinavir	Due to decrease in the exposure (AUC) of darunavir by 53%, appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer lopinavir/ritonavir and PREZISTA, with or without an additional low-dose of ritonavir.
Saquinavir	↓ darunavir ↔ saquinavir	Due to a decrease in the exposure (AUC) of darunavir by 26%, appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer saquinavir and PREZISTA, with or without low-dose ritonavir.
Other Agents		
Antiarrhythmics: bepridil, lidocaine (systemic), quinidine, amiodarone	↑ antiarrhythmics	Concentrations of bepridil, lidocaine, quinidine and amiodarone may be increased when co-administered with

		PREZISTA/rtv. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with PREZISTA/rtv.
Anticoagulant: warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations may be affected when co-administered with PREZISTA/rtv. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/rtv.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and PREZISTA/rtv may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A inhibitor such as PREZISTA/rtv, the combination should be used with caution and a lower dose of trazodone should be considered.
Anti-infective: clarithromycin	↑ clarithromycin	No dose adjustment of darunavir or clarithromycin is required for patients with normal renal function. For patients with renal impairment, the

		following dose adjustments should be considered: • For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%. • For subjects with CLcr of < 30 mL/min, the dose of clarithromycin should be reduced by 75%.
Antifungals: ketoconazole, itraconazole, voriconazole	↑ ketoconazole ↑ darunavir ↑ itraconazole (not studied) ↓ voriconazole (not studied)	Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole, and darunavir/ritonavir may increase plasma concentration of darunavir. Plasma concentrations of ketoconazole or itraconazole may be increased in the presence of darunavir/ritonavir. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Co-administration of voriconazole with darunavir/ritonavir has not been studied. Administration of

		voriconazole with ritonavir (100 mg twice daily) decreased the AUC of voriconazole by an average of 39%. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Antimycobacterial: rifabutin	↑ rifabutin ↓ darunavir	Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and darunavir in the presence of ritonavir is expected to increase rifabutin plasma concentrations and decrease darunavir plasma concentrations. When indicated, it is recommended to administer rifabutin at a dosage of 150 mg once every other day when co-administered with PREZISTA/rtv.
Calcium Channel Blockers: felodipine, nifedipine, nicardipine	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g. felodipine, nifedipine, nicardipine) may increase when PREZISTA/rtv are co-administered. Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: dexamethasone fluticasone propionate	↓ darunavir ↑ fluticasone propionate	Use with caution. Systemic dexamethasone induces CYP3A and can thereby decrease darunavir

		plasma concentrations. This may result in loss of therapeutic effect to PREZISTA. Concomitant use of inhaled fluticasone propionate and PREZISTA/rtv may increase plasma concentrations of fluticasone propionate. Alternatives should be considered, particularly for long term use.
HMG-CoA Reductase Inhibitors: atorvastatin, pravastatin	↑ atorvastatin ↑ pravastatin	When atorvastatin and PREZISTA/rtv is co-administered, it is recommended to start with the lowest possible dose of atorvastatin with careful monitoring. A gradual dose increase of atorvastatin may be considered based on the clinical response. When PREZISTA/rtv was administered with pravastatin, the mean increase in pravastatin AUC was 81%. However, pravastatin AUC increased by up to 5-fold in some subjects. The mechanism of the interaction is not known.
H2-Receptor Antagonists and Proton Pump Inhibitors: omeprazole, ranitidine	↔ darunavir	PREZISTA/rtv can be co-administered with H2-receptor antagonists and proton pump inhibitors without any dose adjustments.
Immunosuppressants: cyclosporine,	↑ immunosuppressants	Plasma concentrations of cyclosporine, tacrolimus or

tacrolimus, sirolimus		sirolimus may be increased when co-administered with PREZISTA/rtv. Therapeutic concentration monitoring of the immunosuppressive agent is recommended for immunosuppressant agents when co-administered with PREZISTA/rtv.
Narcotic Analgesic: methadone	↓ methadone	When methadone is co-administered with PREZISTA/rtv, patients should be monitored for opiate abstinence syndrome, as ritonavir is known to induce the metabolism of methadone, leading to a decrease in its plasma concentrations. An increase in methadone dosage may be considered based on the clinical response.
Oral Contraceptives/estrogen: ethinyl estradiol norethindrone	↓ ethinyl estradiol ↓ norethindrone	Plasma concentrations of ethinyl estradiol may be decreased due to induction of its metabolism by ritonavir. Alternative or additional contraceptive measures should be used when estrogen-based contraceptives are co-administered with PREZISTA/rtv.
PDE-5 inhibitors: sildenafil, vardenafil, tadalafil	↑ PDE-5 inhibitors	Concomitant use of PDE-5 inhibitors with PREZISTA/rtv should be done with caution. If concomitant use of PREZISTA/rtv with sildenafil, vardenafil, or

		tadalafil is required, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours, is recommended.
Selective Serotonin Reuptake Inhibitors (SSRIs): sertraline, paroxetine	↔ darunavir ↓ sertraline ↓ paroxetine	If sertraline or paroxetine is co-administered with PREZISTA/rtv, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/rtv should be monitored for antidepressant response.

Other NRTIs:
Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no drug interactions are expected for these drugs and PREZISTA/rtv.

Other protease inhibitors:
The co-administration of PREZISTA/rtv and PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir has not been studied. Therefore, such co-administration is not recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis and Mutagenesis:
Long-term carcinogenicity studies of darunavir in rodents have not been completed. Darunavir, however, was tested negative in the *in vitro* Ames reverse mutation assay and *in vitro* chromosomal aberration assay in human lymphocytes, both tested in the absence and presence of metabolic activation system. Darunavir does not induce chromosomal damage in the *in vivo* micronucleus test in mice.

Impairment of Fertility:
There were no effects on fertility and early embryonic development with darunavir in rats and darunavir has shown no teratogenic potential in mice (in the presence or absence of ritonavir), rats and rabbits.

Pregnancy
Pregnancy Category B: Reproduction studies conducted with darunavir have shown no embryotoxicity or teratogenicity in mice, rats and rabbits. Because of limited bioavailability of darunavir in animals and/or dosing limitations, the plasma exposures (AUC values) were approximately 50% in mice and rats and 5% in the rabbit of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of pups to drug substances via the milk. Sexual development, fertility or mating performance of offspring was not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

There are, however, no adequate and well-controlled studies in pregnant women. PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk.

Antiretroviral Pregnancy Registry: *To monitor maternal-fetal outcomes of pregnant women exposed to PREZISTA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.*

Nursing Mothers
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known whether darunavir is secreted in human milk, darunavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving PREZISTA**.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

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

ADVERSE REACTIONS

The safety assessment is based on all safety data from the Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis reported with the recommended dose PREZISTA/rtv 600/100 mg b.i.d. in the 458 subjects who initiated treatment with the

recommended dose (*de novo* subjects). In Studies TMC114-C213 and TMC114-C202, the mean exposure in weeks for subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and comparator PI arm was 63.5 and 31.5, respectively. The mean exposure in weeks for subjects in the TMC114-C215/C208 analysis was 23.9.

The most common treatment-emergent adverse events (> 10%) reported in the *de novo* subjects, regardless of causality or frequency, were diarrhea, nausea, headache, and nasopharyngitis.

For subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and the comparator PI arm in the pooled analysis for Studies TMC114-C213 and TMC114-C202, diarrhea was reported in 19.8% and 28.2%, nausea in 18.3% and 12.9%, headache in 15.3% and 20.2%, and nasopharyngitis in 13.7% and 10.5%, of subjects, respectively. In the randomized trials, rates of discontinuation of therapy due to adverse events were 9% in subjects receiving PREZISTA/rtv and in 5% of subjects in the comparator PI arm.

Due to the need for co-administration of PREZISTA with 100 mg of ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

Drug-related clinical adverse events of moderate or severe intensity (≥ Grade 2) occurring in ≥ 2% of subjects treated with PREZISTA/rtv for 1 to 96 weeks are presented in Table 12.

Table 12: Percentage of Subjects with Selected Treatment Emergent, Drug-Related^ Adverse Events of at least Moderate Intensity (Grades 2-4) in ≥ 2% of Adult Subjects in Any PREZISTA/rtv Treatment Groups†

System Organ Class, Preferred Term, %	Randomized Studies TMC114-C213 and TMC114-C202		Non-randomized TMC114-C215/C208 Analysis
	PREZISTA/rtv 600/100 mg b.i.d. +OBR N = 131	Comparator PI +OBR N = 124	PREZISTA/rtv 600/100 mg b.i.d. +OBR N = 327
Gastrointestinal Disorders			
Diarrhea	2.3%	3.2%	2.8%
Vomiting	1.5%	1.6%	2.4%
Abdominal Pain	2.3%	0.8%	1.2%
Constipation	2.3%	0.8%	0.6%
Nervous System Disorders			
Headache	3.8%	2.4%	0.9%

^ Includes adverse events at least possibly, probably, or very likely related to the drug
N=total number of subjects per treatment group
† Excludes laboratory abnormalities that were reported as Adverse Events (see Table 13: Treatment Emergent Grade 2 to 4 Laboratory Abnormalities Reported in ≥ 2% of Subjects)

Treatment-emergent adverse events occurring in less than 2% of *de novo* subjects (n=458) receiving PREZISTA/rtv, considered at least possibly related to treatment and of at least moderate intensity are listed below by body system:

Body as a Whole:
folliculitis, asthenia, pyrexia, fatigue, rigors, hyperthermia, peripheral edema

Cardiovascular System:
myocardial infarction, tachycardia, hypertension

Digestive System:
flatulence, abdominal distension, dry mouth, dyspepsia, abdominal pain, nausea, constipation

Metabolic and Nutritional Disorders:
anorexia, hypercholesterolemia, hyperlipidemia, diabetes mellitus, decreased appetite, obesity, fat redistribution, hyponatremia, polydipsia

Musculoskeletal System:
arthralgia, pain in extremity, myalgia, osteopenia, osteoporosis

Nervous System:
peripheral neuropathy, hypoesthesia, memory impairment, paresthesia, somnolence, transient ischemic attack, confusional state, disorientation, irritability, altered mood, nightmare, anxiety, headache

Respiratory System:
dyspnea, cough, hiccups

Skin and Appendages:
lipoatrophy, night sweats, allergic dermatitis, eczema, toxic skin eruption, alopecia, dermatitis medicamentosa, hyperhidrosis, skin inflammation, maculopapular rash, erythema multiforme, Stevens-Johnson Syndrome (reported in another ongoing clinical study)

Special Senses:
vertigo

Urogenital System:
acute renal failure, renal insufficiency, nephrolothiasis, polyuria, gynecomastia

Laboratory abnormalities:
The percentages of adult subjects treated with PREZISTA/rtv 600/100 mg b.i.d. with treatment-emergent Grade 2 to 4 laboratory abnormalities are presented in Table 13.

Table 13: Treatment Emergent Grade 2 to 4 Laboratory Abnormalities Reported in ≥ 2% of Subjects				
		Randomized Studies TMC114-C213 and TMC114-C202		**Non-randomized TMC114-C215/C208 Analysis**
Laboratory Parameter Preferred Term, %	**Limit**	**PREZISTA/ rtv 600/100 mg b.i.d. + OBR N = 131**	**Comparator PI + OBR N = 124**	**PREZISTA/ rtv 600/100 mg b.i.d. N = 327**
Biochemistry				
Aspartate Aminotransferase	> 2.5 X ULN	10.0%	13.0%	5.3%
Alanine Aminotransferase	> 2.5 X ULN	6.9%	9.8%	5.6%
Gamma Glutamyl Transferase	> 2.5 X ULN	9.2%	8.9%	8.4%
Hyperbilirubinemia	> 1.5 X ULN	2.3%	15.4%	0.9%
Alkaline Phosphatase	> 2.5 X ULN	4.6%	0%	2.8%
Pancreatic Amylase	> 1.5 X ULN	16.9%	8.9%	10.8%
Pancreatic Lipase	> 1.5 X ULN	8.5%	4.1%	6.2%
Hyperglycemia	≥ 161 mg/dL	2.3%	8.1%	5.9%
Hypoglycemia	≤ 54 mg/dL	1.5%	1.6%	3.7%
Total Cholesterol	≥ 240 mg/dL	9.2%	3.3%	8.0%
Triglycerides	> 400 mg/dL	25.4%	26.0%	18.9%
Hypoalbuminemia	< 3 g/dL	3.1%	1.6%	4.3%
Hyperuricemia	≥ 9.9 mg/dL	6.9%	6.5%	2.2%
Bicarbonate	< 15 mmol/L	3.1%	4.1%	3.4%
Hypocalcemia	≤ 7.8 mg/dL	0%	0.8%	4.0%
Hyponatremia	≤ 129 meq/L	0.8%	0%	2.5%
Hypernatremia	≥ 151 meq/L	2.3%	0%	0%
Hematology				
White Blood Cell Count decrease	< 3000 count/mm^3	15.4%	18.7%	13.0%
Total Absolute Neutrophil Count decrease	≤ 999 mm^3	6.9%	9.8%	11.5%
Lymphocytes decrease	< 1000 count/mm^3	4.6%	19.5%	10.9%
Partial Thromboplastin	> 1.66 X ULN	7.8%	4.1%	4.3%

Time increase				
Plasma Prothrombin Time increase	> 1.25 X ULN	3.9%	0.8%	0.6%
Platelet Count decrease	< 75,000/mm^3	3.1%	1.6%	2.8%

Patients co-infected with hepatitis B and/or hepatitis C virus:
Subjects co-infected with hepatitis B or C virus receiving PREZISTA/rtv, did not experience higher incidence of adverse events or clinical chemistry abnormalities than subjects receiving PREZISTA/rtv who were not co-infected. The pharmacokinetic exposure in co-infected subjects was comparable to that in subjects without co-infection. Standard clinical monitoring of patients with chronic hepatitis B and/or C is considered adequate.

OVERDOSAGE

Human experience of acute overdose with PREZISTA/rtv is limited. Single doses up to 3200 mg of the oral solution of darunavir alone and up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

There is no specific antidote for overdose with PREZISTA. Treatment of overdose with PREZISTA consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since PREZISTA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

DOSAGE AND ADMINISTRATION

Adults: The recommended oral dose of PREZISTA tablets is 600 mg (two 300 mg tablets) twice daily taken with ritonavir 100 mg twice daily and with food. The type of food does not affect exposure to darunavir.

Pediatric Patients: The safety and efficacy of PREZISTA in pediatric patients has not been established (see CLINICAL PHARMACOLOGY, *Special Populations*, *Pediatric Patients*).

Hepatic Impairment: There are no data regarding the use of PREZISTA/rtv when co-administered to patients with varying degrees of hepatic impairment; therefore, specific dosage recommendations cannot be made. PREZISTA/rtv should be used with caution in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults*, *Special Populations*, *Hepatic Impairment* and PRECAUTIONS, *Patients with co-existing conditions*, *Hepatic Impairment*).

Renal Impairment: No dose adjustment is required in patients with moderate renal impairment. There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*

in Adults, Special Populations, Renal Impairment and PRECAUTIONS, *Patients with co-existing conditions, Renal Impairment*).

HOW SUPPLIED

PREZISTA (darunavir) tablets are supplied as orange, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 300 mg of darunavir per tablet. Each tablet is debossed with "300" on one side and "TMC114" on the other side. PREZISTA tablets are packaged in bottles in the following configuration:

300 mg tablets—bottles of 120 (NDC 59676-560-01)

Storage:
Store PREZISTA tablets at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F).

Manufactured for Tibotec, Inc. by:
JOLLC, Gurabo, Puerto Rico
Distributed by:
Tibotec Therapeutics, Division of Ortho Biotech Products, L.P., Raritan NJ 08869

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