PREZISTA®

400, 600 AND 800 MG

PRODUCT NAME

PREZISTA® (darunavir)

DOSAGE FORMS AND STRENGTHS

QUALITATIVE AND QUANTITATIVE COMPOSITION

PRESENTATION	
400 mg tablet	Each film-coated tablet contains 400 mg of darunavir (corresponding to 433.64 mg of darunavir ethanolate). The film-coating of the light orange tablet contains sunset yellow FCF (E110). For a full list of excipients, see *List of Excipients*.
600 mg tablet	Each film-coated tablet contains 600 mg of darunavir (corresponding to 650.46 mg of darunavir ethanolate). For a full list of excipients, see *List of Excipients*.
800 mg tablet	Each film-coated tablet contains 800 mg of darunavir (corresponding to 867.28 mg of darunavir ethanolate). For a full list of excipients, see *List of Excipients*.

PHARMACEUTICAL FORM

PRESENTATION	
400 mg tablet	Film-coated tablet. Light orange oval-shaped tablet, debossed with 400MG on one side and TMC on the other side.
600 mg tablet	Film-coated tablet. White oval-shaped tablet, debossed with 600MG on one side and TMC on the other side.
800 mg tablet	Film-coated tablet. Dark red oval-shaped tablet, debossed with 800 on one side and T on the other side.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

Adult patients

PREZISTA, in combination with a pharmacokinetic enhancer (low dose ritonavir (PREZISTA/rtv)) and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection.

Pediatric patients

PREZISTA, in combination with low dose ritonavir (PREZISTA/rtv) and with other antiretroviral agents, is indicated for the treatment of HIV infection in treatment-experienced paediatric patients weighing 40 kg or more.

Dosage and Administration

PREZISTA must always be given with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The prescribing information of ritonavir must therefore be consulted prior to initiation of therapy with PREZISTA/rtv.
After therapy with PREZISTA has been initiated, patients should be advised not to alter the dosage, dosage form, or discontinue therapy without instruction of their physician.

Dosage – Adults

Antiretroviral treatment-naïve patients	**Antiretroviral treatment-experienced patients**	
	with no darunavir resistance associated mutations (DRV-RAMs)*	**with at least one darunavir resistance associated mutation (DRV-RAM)***
800 mg PREZISTA once daily (q.d.) taken with 100 mg ritonavir and with food	800 mg PREZISTA once daily (q.d.) taken with 100 mg ritonavir and with food	600 mg PREZISTA twice daily (b.i.d.) taken with 100 mg ritonavir and with food

* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

For antiretroviral treatment-experienced patients HIV genotypic testing is recommended. However, when HIV genotypic testing is not feasible, the once daily dosing regimen is recommended in HIV protease inhibitor-naïve patients and the twice daily dosing regimen is recommended in HIV protease inhibitor-experienced patients.

The type of food does not affect the exposure to darunavir. Ritonavir is used as a pharmacokinetic enhancer of darunavir (see *Interactions* and *Pharmacokinetic Properties*).

Pediatric patients

Antiretroviral treatment-experienced pediatric patients weighing 40 kg or more **(see *Pharmacodynamic Properties*)**

The recommended dose of PREZISTA/rtv for pediatric patients is based on body weight and should not exceed the recommended adult dose. The adult dose of PREZISTA/rtv (600/100 mg b.i.d.) may be used in pediatric patients of 40 kg or more. PREZISTA tablets should be taken with ritonavir twice daily and with food.

The type of food does not affect the exposure to darunavir. Ritonavir is used as a pharmacokinetic enhancer of darunavir (see *Interactions* and *Pharmacokinetic Properties*).

Antiretroviral treatment-experienced children weighing less than 40 kg and antiretroviral treatment naïve pediatric patients

The safety and efficacy of PREZISTA/rtv in children 3 years or more and weighing less than 40 kg and in antiretroviral treatment naïve pediatric patients have not been evaluated.

PREZISTA/rtv should not be used in children below 3 years of age (see *Warnings and Precautions* and *Toxicology*).

Pregnancy and postpartum

No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. Caution should be used in patients with concomitant medications which may further decrease darunavir exposure (see *Pregnancy, Breast-feeding and Fertility* and *Pharmacokinetic Properties-Special Populations-Pregnancy and Postpartum*).

Missed dose(s)

If using the once daily regimen: in case a dose of PREZISTA and/or ritonavir was missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of PREZISTA and ritonavir with food as soon as possible. If this was noticed later than 12 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

If using the twice daily regimen: in case a dose of PREZISTA and/or ritonavir was missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of PREZISTA and ritonavir with food as soon as possible. If this was noticed later than 6 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

Special populations

Elderly (65 years of age and older)

Limited information is available on the use of PREZISTA in patients 65 and older. Therefore PREZISTA should be used with caution in this age group (see *Warnings and Precautions*, and *Pharmacokinetic Properties-Elderly*).

Renal impairment

No dose adjustment is required in patients with renal impairment (see *Warnings and Precautions* and *Pharmacokinetic Properties*).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. There are no data regarding the use of PREZISTA when co-administered to patients with severe hepatic impairment; therefore, specific dosage recommendations cannot be made. PREZISTA should be used with caution in patients with severe hepatic impairment (see *Warnings and Precautions* and *Pharmacokinetic Properties*).

Administration

Method of administration: oral administration.

PREZISTA must be taken with food. The type of food does not affect the exposure to PREZISTA (see *Pharmacokinetic Properties-Absorption*).

Contraindications

Hypersensitivity to darunavir or to any of the excipients.

Darunavir and ritonavir are inhibitors of the cytochrome P450 3A (CYP3A) isoform. PREZISTA/rtv should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These medicinal products include alfuzosin, astemizole, cisapride, colchicine (in patients with renal and/or hepatic impairment), dronedarone, elbasvir/grazoprevir, the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine and methylergonovine), lomitapide, lovastatin, lurasidone, midazolam (oral), pimozide, ranolazine, sildenafil (when used for treatment of pulmonary arterial hypertension), simvastatin, terfenadine, and triazolam (see *Interactions*).

Patients taking PREZISTA should not use products containing rifampin or St. John's wort because co-administration may result in reduced plasma concentrations of darunavir. This may result in loss of therapeutic effect and development of resistance.

Warnings and Precautions

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

PREZISTA/rtv should not be used in children below 3 years of age in view of toxicity observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age (see *Toxicology*).

Elderly: As limited information is available on the use of PREZISTA in patients aged 65 and over, caution should be exercised in the administration of PREZISTA in elderly patients, reflecting the

greater frequency of decreased hepatic function and of concomitant disease or other therapy (see *Pharmacokinetic Properties*).

The absolute oral bioavailability of a single 600 mg dose of PREZISTA alone was approximately 37% and increased to approximately 82% in the presence of 100 mg ritonavir b.i.d. The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg PREZISTA was given orally in combination with ritonavir at 100 mg b.i.d. Therefore, PREZISTA should only be used in combination with low dose ritonavir as a pharmacokinetic enhancer (see *Pharmacokinetic Properties*).
Increasing the dose of ritonavir did not significantly affect darunavir concentrations. It is not recommended to alter the dose of ritonavir.

Severe skin reactions

During the darunavir/ritonavir clinical development program (N = 3063), severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. Stevens-Johnson Syndrome has been rarely (< 0.1%) reported; during post-marketing experience, toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), and acute generalized exanthematous pustulosis have been reported very rarely (< 0.01%). Discontinue PREZISTA 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 patients treated with PREZISTA/rtv (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 patients using PREZISTA/rtv was 0.5%.

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

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

Patients with coexisting conditions

Hepatic impairment

There are no data regarding the use of PREZISTA in patients with severe hepatic impairment; therefore, specific dosage recommendations cannot be made. PREZISTA should be used with caution in patients with severe hepatic impairment. Based on data that demonstrated that the steady-state pharmacokinetic parameters of darunavir in subjects with mild and moderate hepatic

impairment were comparable with those in healthy subjects, no dose adjustment is required in patients with mild or moderate hepatic impairment (see *Dosage and Administration* and *Pharmacokinetic Properties*).

Hepatotoxicity

Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/rtv. During the darunavir/ritonavir clinical development program (N = 3063), hepatitis was reported in 0.5% of patients receiving combination therapy with PREZISTA/rtv. 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.

Appropriate laboratory testing should be conducted prior to initiating therapy with PREZISTA 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 PREZISTA 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 PREZISTA should prompt consideration of interruption or discontinuation of treatment.

Renal impairment

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 *Dosage and Administration* and *Pharmacokinetic Properties*).

Hemophiliac patients

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 has been suggested, although the mechanism of action has not been elucidated. Hemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Hyperglycemia

New onset diabetes mellitus, hyperglycemia, or exacerbation of existing diabetes mellitus has been reported in patients receiving antiretroviral therapy, including PIs. In some of these patients the hyperglycemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycemia.

Fat redistribution & metabolic disorders

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesized. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see *Adverse Reactions*).

Immune reconstitution inflammatory syndrome

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders such as Graves' disease 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 treatment (see *Adverse Reactions*).

Interactions with medicinal products

Darunavir or ritonavir is an inhibitor of CYP3A, CYP2D6 and P-gp. Co-administration of PREZISTA and ritonavir with medicinal products primarily metabolized by CYP3A, CYP2D6, or transported by P-gp may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect and adverse events (see *Contraindications* and *Interactions*).

Darunavir and ritonavir are metabolized by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lower plasma concentrations of darunavir and ritonavir. Co-administration with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (see *Interactions*).

Interactions

PREZISTA should be used in combination with low dose ritonavir as a pharmacokinetic enhancer.

PREZISTA should not be used in combination with other antiretrovirals that also require pharmacokinetic boosting with ritonavir.

Darunavir when used in combination with ritonavir is an inhibitor of CYP3A, CYP2D6 and P-gp. Co-administration of PREZISTA/rtv and medicinal products primarily metabolized by CYP3A,

CYP2D6, or transported by P-gp may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect and adverse events.

Darunavir and ritonavir are metabolized by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lower plasma concentrations of darunavir and ritonavir. Co-administration with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir, and may result in increased plasma concentrations of darunavir and ritonavir.

The below list of drug-drug interactions is not all-inclusive.

Antiretroviral medicinal products

Integrase strand transfer inhibitors

Dolutegravir

PREZISTA/rtv (600/100 mg b.i.d.) did not have a clinically relevant effect on dolutegravir exposure. Using cross-study comparisons to historical pharmacokinetic data, dolutegravir had no clinically significant effect on the pharmacokinetics of darunavir.

PREZISTA/rtv co-administered with dolutegravir can be used without dose adjustment.

Elvitegravir

When PREZISTA/rtv (600/100 mg b.i.d.) is used in combination with elvitegravir, the dose of elvitegravir should be 150 mg once daily.

The pharmacokinetics and dosing recommendations for other doses of darunavir have not been established. Therefore, co-administration of PREZISTA/rtv in doses other than 600/100 mg b.i.d. and elvitegravir is not recommended.

Raltegravir

Some clinical studies suggest raltegravir may cause a modest decrease in darunavir plasma concentrations. At present the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically relevant.

PREZISTA co-administered with low dose ritonavir and raltegravir can be used without dose adjustments.

Nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs)

Didanosine

PREZISTA/rtv (600/100 mg b.i.d.) did not significantly affect didanosine exposure.

The combination of PREZISTA co-administered with low dose ritonavir and didanosine can be used without dose adjustments. It is recommended that didanosine be administered on an empty stomach. Didanosine should be administered 1 hour before or 2 hours after PREZISTA/rtv (which are administered with food).

Tenofovir disoproxil fumarate

The results of an interaction trial with tenofovir (tenofovir disoproxil fumarate 300 mg once daily [q.d.]) demonstrated that the systemic exposure of tenofovir was increased by 22% when co-administered with PREZISTA/rtv (300/100 mg b.i.d.). This finding is not considered to be

clinically relevant. There was no change in the urinary excretion of tenofovir or darunavir during co-administration. Tenofovir did not have a significant influence on darunavir exposure.
No dose adjustments of PREZISTA, ritonavir, or tenofovir disoproxil fumarate are required when these drugs are co-administered.

Emtricitabine/tenofovir alafenamide

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 medicinal compounds and PREZISTA/rtv.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Delavirdine

Co-administration of PREZISTA/rtv and delavirdine may increase darunavir and delavirdine concentrations (inhibition of CYP3A). The appropriate doses of PREZISTA/rtv and delavirdine have not been established. The combination of PREZISTA/rtv and delavirdine is not recommended.

Etravirine

In an interaction trial between PREZISTA/rtv (600/100 mg b.i.d.) and etravirine, there was a 37% decrease in etravirine exposure in the presence of PREZISTA/rtv and no relevant change in exposure to darunavir. Therefore, PREZISTA/rtv can be co-administered with etravirine 200 mg b.i.d. without dose adjustments.

Efavirenz

An interaction trial between PREZISTA/rtv (300/100 mg b.i.d.) and efavirenz (600 mg q.d.) has been performed. In the presence of efavirenz, a decrease of 13% for darunavir exposure was observed. Exposure to efavirenz was increased by 21% when administered in combination with PREZISTA/rtv. Since this difference is considered not to be clinically relevant, the combination of PREZISTA/rtv and efavirenz can be used without dose adjustments.

Nevirapine

The results of an interaction trial with PREZISTA/rtv (400/100 mg b.i.d.) and nevirapine (200 mg b.i.d.) demonstrated that darunavir exposure was not affected when administered concomitantly with nevirapine. Exposure to nevirapine increased by 27% (compared to historical controls) when administered in combination with PREZISTA/rtv.
Since this difference is not considered to be clinically relevant, the combination of PREZISTA/rtv and nevirapine can be used without dose adjustments.

Rilpivirine

In an interaction trial between PREZISTA/rtv (800/100 mg q.d.) and rilpivirine (150 mg q.d.), no clinically relevant effect on darunavir exposure was observed. Exposure to rilpivirine increased by 130% (2.3-fold) when administered in combination with PREZISTA/rtv.
Since this difference is not considered to be clinically relevant, the combination of PREZISTA/rtv and rilpivirine can be used without dose adjustments.

HIV protease inhibitors (PIs)

Ritonavir

The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg PREZISTA was given orally in combination with ritonavir at 100 mg b.i.d.
Therefore, PREZISTA should only be used in combination with a pharmacokinetic enhancer such as low dose ritonavir (see *Warnings and Precautions* and *Pharmacokinetic Properties*).

Lopinavir/ritonavir

Results of interaction trials with PREZISTA with or without ritonavir and lopinavir/ritonavir (1200 mg darunavir b.i.d. with or without 100 mg ritonavir b.i.d. and lopinavir/ritonavir 400/100 mg b.i.d. or 533/133.3 mg b.i.d.) demonstrated a decrease in the exposure (AUC) of darunavir by 40%.
The appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer PREZISTA/rtv with lopinavir/ritonavir.

Saquinavir

In an interaction trial between PREZISTA (400 mg b.i.d.), saquinavir (1000 mg b.i.d.) and ritonavir (100 mg b.i.d.), darunavir exposure was decreased by 26% in the presence of saquinavir/rtv; saquinavir exposure was not affected by the presence of PREZISTA/rtv.
It is not recommended to combine saquinavir and PREZISTA, with or without low dose ritonavir.

Atazanavir

An interaction trial between PREZISTA/rtv (400/100 mg b.i.d.) and atazanavir (300 mg q.d.) demonstrated that systemic exposure to darunavir and atazanavir was not significantly affected when co-administered.
Atazanavir can be co-administered with PREZISTA/rtv.

Indinavir

In an interaction trial between PREZISTA/rtv (400/100 mg b.i.d.) and indinavir (800 mg b.i.d.), darunavir exposure was increased by 24% in the presence of indinavir/rtv; indinavir exposure was increased by 23% in the presence of PREZISTA/rtv.
When used in combination with PREZISTA/rtv, dose adjustment of indinavir from 800 mg b.i.d. to 600 mg b.i.d. may be warranted in case of intolerance.

Other HIV PIs

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

CCR5 antagonist

When used in combination with PREZISTA/rtv, the dose of maraviroc should be 150 mg twice daily. An interaction trial between PREZISTA/rtv (600/100 mg b.i.d.) and maraviroc (150 mg b.i.d.) demonstrated that in the presence of PREZISTA/rtv the exposure of maraviroc was increased by 305%. There was no apparent effect of maraviroc on darunavir/ritonavir exposure.

Other medicinal products

Acid reducing agents

Antacids

e.g. Aluminium/magnesium hydroxide, calcium carbonate

No interaction is expected between antacids and PREZISTA/rtv.

PREZISTA/rtv and antacids can be used concomitantly without dose adjustments.

H_2-receptor antagonists

e.g. Cimetidine, famotidine, nizatidine, ranitidine

Co-administration of ranitidine (150 mg b.i.d.) and PREZISTA/rtv (400/100 mg b.i.d.) did not affect the exposure to darunavir.

PREZISTA/rtv can be co-administered with H_2-receptor antagonists without dose adjustments.

Proton pump inhibitors

e.g. Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

Co-administration of omeprazole (20 mg q.d.) and PREZISTA/rtv (400/100 mg b.i.d.) did not affect the exposure to darunavir.

PREZISTA/rtv and proton pump inhibitors can be co-administered without dose adjustment.

Alpha 1-adrenoreceptor antagonist

Alfuzosin

Exposure to alfuzosin may be increased when co-administered with PREZISTA/rtv.

Concomitant use of PREZISTA/rtv with alfuzosin is contraindicated.

Anti-anginal

Ranolazine

Exposure to ranolazine may be increased (CYP3A inhibition) when co-administered with PREZISTA/rtv.

Concomitant use of PREZISTA/rtv with ranolazine is contraindicated.

Antiarrhythmics

Amiodarone, bepridil, disopyramide, dronedarone, flecainide, mexiletine, propafenone, systemic lidocaine, and quinidine

Exposure to these antiarrhythmics may be increased when co-administered with PREZISTA/rtv. Caution is warranted and therapeutic drug monitoring of antiarrhythmics is recommended when available.

Concomitant use of PREZISTA/rtv with dronedarone is contraindicated.

Digoxin

An interaction trial with PREZISTA/rtv (600/100 mg b.i.d.) and a single dose of digoxin (0.4 mg) showed an increase of digoxin AUC_{last} of 77% (ratio of Least Square Means (LSM) was 1.77 with a 90% CI of 0.90 to 3.50).

It is recommended that the lowest dose of digoxin should initially be prescribed and digoxin dose should be titrated to obtain the desired clinical effect when co-administered with PREZISTA/rtv. Serum digoxin concentrations should be monitored to assist in the titration.

Antibacterial

Clarithromycin

An interaction trial between PREZISTA/rtv (400/100 mg b.i.d.) and clarithromycin (500 mg b.i.d.) showed an increase in exposure to clarithromycin by 57%, while exposure to darunavir was not affected.

PREZISTA/rtv and clarithromycin can be used without dose adjustment in patients with normal renal function. For patients with renal impairment, a dose reduction of clarithromycin should be considered. Consult the prescribing information for clarithromycin for the recommended dosage.

Anticoagulants

Direct Oral Anticoagulants (DOACs): apixaban, dabigatran, edoxaban, rivaroxaban

DOACs are primarily metabolized by CYP3A4 and/or transported by P-gp. Co-administration with PREZISTA/rtv may result in increased plasma concentrations of the DOAC, which may lead to an increased bleeding risk.

Co-administration of a DOAC affected by both P-gp and CYP3A4, including apixaban and rivaroxaban, is not recommended with PREZISTA/rtv.

Clinical monitoring and/or dose adjustment is recommended when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran and edoxaban, is co-administered with PREZISTA/rtv.

Warfarin

Warfarin concentrations may be affected when co-administered with PREZISTA/rtv.

It is recommended that the international normalized ratio (INR) is monitored when warfarin is combined with PREZISTA/rtv.

Anticonvulsants

Phenobarbital and phenytoin

Phenobarbital and phenytoin are inducers of CYP450 enzymes. PREZISTA/rtv should not be used in combination with these medicines, as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.

Carbamazepine

An interaction trial between PREZISTA/rtv (600/100 mg b.i.d.) and carbamazepine (200 mg b.i.d.) showed that the exposure to darunavir, co-administered with ritonavir, was unaffected by carbamazepine. Ritonavir exposure (AUC_{12h}) was decreased by 49%. For carbamazepine, AUC_{12h} was increased by 45%.

No dose adjustment for PREZISTA/rtv is recommended. If there is a need to combine PREZISTA/rtv and carbamazepine, patients should be monitored for potential carbamazepine-related adverse events. Carbamazepine concentrations should be monitored and its dose should be titrated for adequate response. Based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of PREZISTA/rtv.

Clonazepam

Co-administration of PREZISTA/rtv with clonazepam may increase concentrations of clonazepam.

Clinical monitoring is recommended when co-administering PREZISTA/rtv with clonazepam.

Antidepressants

Paroxetine and sertraline

In an interaction trial between paroxetine (20 mg q.d.) or sertraline (50 mg q.d.) and PREZISTA/rtv (400/100 mg b.i.d.), the exposure to darunavir was not affected by the presence of sertraline or paroxetine. Exposure to sertraline and paroxetine, was decreased by 49% and 39%, respectively, in the presence of PREZISTA/rtv.

If SSRIs are 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 an antidepressant response.

Amitriptyline, desipramine, imipramine, nortriptyline, and trazodone

Concomitant use of PREZISTA/rtv and these antidepressants may increase concentrations of the antidepressant (inhibition of CYP2D6 and/or CYP3A).

Clinical monitoring is recommended when co-administering PREZISTA/rtv with these antidepressants and a dose adjustment of the antidepressant may be needed.

Antifungals

Itraconazole, ketoconazole, posaconazole, and voriconazole

Itraconazole, ketoconazole, posaconazole, and voriconazole are potent inhibitors of CYP3A and some are substrates of CYP3A.

Concomitant systemic use of these antifungals with PREZISTA/rtv may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of some of these antifungals may be increased by PREZISTA/rtv. This was confirmed in an interaction trial where the concomitant administration of ketoconazole (200 mg b.i.d.) with PREZISTA/rtv (400/100 mg b.i.d.) increased exposure of ketoconazole and darunavir by 212% and 42%, respectively.

Plasma concentrations of voriconazole may be decreased in the presence of PREZISTA/rtv. Voriconazole should not be administered to patients receiving PREZISTA/rtv unless an assessment of the benefit/risk ratio justifies the use of voriconazole.

Clinical monitoring is recommended when co-administering PREZISTA/rtv with posaconazole.

When co-administration is required the daily dose of ketoconazole or itraconazole should not exceed 200 mg.

Clotrimazole and fluconazole

Co-administration of PREZISTA/rtv with these antifungals may increase concentrations of darunavir, ritonavir and/or the antifungal.

Clinical monitoring is recommended when co-administering PREZISTA/rtv with these antifungals.

Anti-gout

Colchicine

Concomitant use of colchicine and PREZISTA/rtv may increase the exposure to colchicine.

The following dose adjustments are recommended for colchicine. For the treatment of gout-flares in patients on PREZISTA/rtv, the recommended dose of colchicine is 0.6 mg, followed by 0.3 mg 1 hour later. Treatment course to be repeated no earlier than 3 days. For the prophylaxis of gout-flares in patients on PREZISTA/rtv, the recommended dose of colchicine is 0.3 mg q.d. or

q.o.d. For the treatment of familial Mediterranean fever in patients on PREZISTA/rtv, the maximum dose of colchicine is 0.6 mg q.d. (may be given as 0.3 mg b.i.d.).
Co-administration of PREZISTA/rtv with colchicine in patients with renal or hepatic impairment is contraindicated.

Antihistamines

Astemizole, terfenadine

Exposure to these antihistamines may be increased when co-administered with PREZISTA/rtv.
Concomitant use of PREZISTA/rtv with astemizole and terfenadine is contraindicated.

Antimalarial

Artemether/lumefantrine

An interaction trial between PREZISTA/rtv (600/100 mg b.i.d.) and artemether/lumefantrine (80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours) showed an increase in exposure to lumefantrine by 2.75-fold, while exposure to darunavir was not affected. The exposure to artemether and its active metabolite, dihydroartemisinin, decreased by 16% and 18%, respectively. The combination of PREZISTA/rtv and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.

Antimycobacterials

Rifampin and rifapentine

Co-administration of PREZISTA/rtv with rifampin and rifapentine may decrease darunavir concentrations (induction of CYP3A), which may result in loss of therapeutic effect of PREZISTA.
Co-administration of PREZISTA/rtv with rifampin is contraindicated.
Co-administration of PREZISTA/rtv with rifapentine is not recommended.

Rifabutin

Rifabutin is a substrate of CYP450 enzymes. In an interaction trial, an increase of systemic exposure to darunavir by 57% was observed, when PREZISTA/rtv (600/100 mg b.i.d.) was administered with rifabutin (150 mg once every other day [q.o.d.]). Based on the safety profile of PREZISTA/rtv, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for PREZISTA/rtv. The interaction trial showed a comparable systemic exposure for rifabutin between treatment at 300 mg q.d. alone and at 150 mg q.o.d. in combination with PREZISTA/rtv (600/100 mg b.i.d.) with an increase in exposure to the active metabolite 25-O-desacetylrifabutin.
A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg q.o.d.) and increased monitoring for rifabutin-related adverse events is warranted in patients receiving the combination.

Antineoplastics

Dasatinib, everolimus, nilotinib, vinblastine, vincristine

The plasma concentrations of these antineoplastics are expected to increase with co-administration of PREZISTA/rtv (inhibition of CYP3A), resulting in the potential for adverse events usually associated with these agents.
Caution should be exercised when combining one of these antineoplastic agents with PREZISTA/rtv.

Concomitant use of everolimus and PREZISTA/rtv is not recommended.

Antipsychotics/neuroleptics

Lurasidone

Concomitant use of lurasidone and PREZISTA/rtv may increase the exposure to lurasidone (inhibition of CYP3A4).
Concomitant use of PREZISTA/rtv with lurasidone is contraindicated.

Pimozide

Concomitant use of pimozide and PREZISTA/rtv may increase the exposure to pimozide (inhibition of CYP3A and CYP2D6).
Concomitant use of PREZISTA/rtv with pimozide is contraindicated.

Perphenazine

Co-administration of PREZISTA/rtv and perphenazine may increase concentrations of the neuroleptic (inhibition of CYP3A or CYP2D6).
Clinical monitoring is recommended when co-administering PREZISTA/rtv with perphenazine and a lower dose of the neuroleptic should be considered.

Risperidone, thioridazine

Concomitant use of risperidone or thioridazine and PREZISTA/rtv may increase the exposure to these antipsychotics (inhibition CYP2D6 and/or P-gp).
Decrease of risperidone or thioridazine dose may be needed when co-administered with PREZISTA/rtv.

Quetiapine

Concomitant use of quetiapine and PREZISTA/rtv may increase the exposure to quetiapine (inhibition of CYP3A).
The quetiapine dose should be substantially reduced when co-administered with PREZISTA. For details, refer to the quetiapine prescribing information.

β-Blockers

Carvedilol, metoprolol, timolol

Co-administration of PREZISTA/rtv and beta-blockers may increase concentrations of the beta-blocker (inhibition of CYP2D6).
Clinical monitoring is recommended when co-administering PREZISTA/rtv with beta-blockers and a lower dose of the beta-blocker should be considered.

Calcium channel blockers

Amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil

The exposure to calcium channel blockers may increase when PREZISTA/rtv are used concomitantly (inhibition of CYP2D6 and/or CYP3A).
Caution is warranted and careful clinical monitoring is recommended.

Contraceptives

Ethinylestradiol and norethindrone

The results of an interaction trial between PREZISTA/rtv (600/100 mg b.i.d.) and ethinylestradiol and norethindrone demonstrated that at steady-state systemic exposures to ethinylestradiol and norethindrone are decreased by 44% and 14%, respectively.

Ethinylestradiol and drospirenone

The effect of PREZISTA/rtv on drospirenone exposure is not known.

When PREZISTA/rtv is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential of hyperkalemia.

No data are available to make recommendations on the use of PREZISTA/rtv with other hormonal contraceptives. Therefore, additional or alternative (non-hormonal) methods of contraception are recommended.

Corticosteroids: systemic/inhaled/nasal

Corticosteroids primarily metabolized by CYP3A *(betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone)*

Concomitant use of corticosteroids and PREZISTA/rtv may increase plasma concentrations of these corticosteroids. Concomitant use may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.

Clinical monitoring is recommended when co-administering PREZISTA/rtv with corticosteroids. Alternatives should be considered, particularly for long term use.

Systemic dexamethasone

Systemic dexamethasone induces CYP3A and thereby may decrease darunavir exposure. This may result in loss of therapeutic effect.

Therefore this combination should be used with caution.

Endothelin receptor antagonist

Bosentan

Concomitant use of bosentan and PREZISTA/rtv may increase plasma concentrations of bosentan. In patients who have been receiving PREZISTA/rtv for at least 10 days, start bosentan at 62.5 mg q.d. or q.o.d. based upon individual tolerability. For patients on bosentan and initiating PREZISTA/rtv, discontinue the use of bosentan at least 36 hours prior to initiation of PREZISTA/rtv. After at least 10 days following the initiation of PREZISTA/rtv, resume bosentan at 62.5 mg q.d. or q.o.d. based upon individual tolerability.

Ergot alkaloids

e.g., Ergotamine, ergonovine, dihydroergotamine, and methylergonovine

Exposure to the ergot alkaloids may be increased when co-administered with PREZISTA/rtv.

Concomitant use of PREZISTA/rtv with ergot alkaloids is contraindicated.

Gastrointestinal motility agent

Cisapride

Exposure to cisapride may be increased when co-administered with PREZISTA/rtv.

Concomitant use of PREZISTA/rtv with cisapride is contraindicated.

Hepatitis C virus (HCV) direct-acting antivirals

Boceprevir

In an interaction trial between PREZISTA/rtv (600/100 mg b.i.d.) and boceprevir (800 mg three times daily), darunavir exposure was reduced by 44% and boceprevir exposure was reduced by 32%.

It is not recommended to co-administer PREZISTA/rtv with boceprevir.

Elbasvir/Grazoprevir

Concomitant use of elbasvir/grazoprevir and PREZISTA/rtv may increase the exposure to grazoprevir (inhibition of CYP3A).

Concomitant use of PREZISTA/rtv with elbasvir/grazoprevir is contraindicated.

Glecaprevir/Pibrentasvir

Concomitant use of glecaprevir/pibrentasvir and PREZISTA/rtv may increase the exposure to glecaprevir and pibrentasvir (inhibition of P-gp, BCRP and/or OATP1B1/3).

Co-administration of PREZISTA/rtv with glecaprevir/pibrentasvir is not recommended.

Simeprevir

Co-administration of PREZISTA/rtv (800/100 mg q.d.) and simeprevir increased darunavir and simeprevir concentrations (inhibition of CYP3A). In an interaction trial between PREZISTA/rtv (800/100 mg q.d.) and simeprevir (50 mg q.d.), simeprevir exposure increased 2.59-fold and darunavir exposure increased by 1.18-fold.

The combination of PREZISTA/rtv and simeprevir is not recommended.

Telaprevir

In an interaction trial between PREZISTA/rtv (600/100 mg b.i.d.) and telaprevir (750 mg every 8 hours), darunavir exposure was reduced by 40% and telaprevir exposure was reduced by 35%.

It is not recommended to co-administer PREZISTA/rtv with telaprevir.

Herbal product

St. John's wort

Co-administration of PREZISTA/rtv with products containing St. John's wort (*Hypericum perforatum*) may cause significant decreases in darunavir concentrations (induction of CYP3A), which may result in loss of therapeutic effect to PREZISTA.

Co-administration of PREZISTA/rtv with products containing St. John's wort (*Hypericum perforatum*) is contraindicated.

HMG-CoA reductase inhibitors

Atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin

HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A metabolism, are therefore expected to have markedly increased plasma concentrations when co-administered with PREZISTA/rtv. Increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis.

Concomitant use of PREZISTA/rtv with lovastatin and simvastatin is contraindicated.

The results of an interaction trial with atorvastatin show that atorvastatin (10 mg q.d.) in combination with PREZISTA/rtv (300/100 mg b.i.d.) provides an exposure to atorvastatin, which is only 15% lower than that obtained with atorvastatin (40 mg q.d.) alone. When administration of atorvastatin and PREZISTA/rtv is desired, it is recommended to start with an atorvastatin dose of 10 mg q.d. A gradual dose increase of atorvastatin may be tailored to the clinical response.
PREZISTA/rtv (600/100 mg b.i.d.) increased exposure to a single dose of pravastatin (40 mg) by approximately 80%, but only in a subset of subjects.
When administration of pravastatin and PREZISTA/rtv is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effects while monitoring safety.

An interaction study evaluating PREZISTA/rtv (600/100 mg b.i.d.) in combination with rosuvastatin (10 mg q.d.) resulted in an increase in rosuvastatin exposure.
When administration of rosuvastatin and PREZISTA/rtv is desired, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.

An interaction study evaluating PREZISTA/rtv (800/100 mg q.d.) in combination with pitavastatin (4 mg q.d.) resulted in a decrease in pitavastatin exposure, which is not considered clinically relevant.
PREZISTA/rtv and pitavastatin can be co-administered without dose adjustment.

Other lipid modifying agents

Lomitapide
PREZISTA/rtv is expected to increase the exposure of lomitapide when co-administered. Co-administration is contraindicated.

Immunosuppressants

Cyclosporin, everolimus, sirolimus, tacrolimus
Exposure to these immunosuppressants may be increased when co-administered with PREZISTA/rtv.
Therapeutic drug monitoring of the immunosuppressive agent is recommended when co-administered with PREZISTA/rtv.
Concomitant use of everolimus and PREZISTA/rtv is not recommended.

Inhaled beta agonist

Salmeterol
Concomitant use of salmeterol and PREZISTA/rtv is not recommended.
The combination may result in increased risk of cardiovascular adverse events with salmeterol, including QT prolongation, palpitations and sinus tachycardia.

Narcotic analgesics/treatment of opioid dependence

Buprenorphine/naloxone
The results of an interaction trial with PREZISTA/rtv and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when administered with PREZISTA/rtv. Exposure of the active metabolite, norbuprenorphine, increased by 46%.

No dose adjustment for buprenorphine was required. Careful clinical monitoring is recommended if PREZISTA/rtv and buprenorphine are co-administered.

Fentanyl, oxycodone, tramadol

Co-administration of PREZISTA/rtv with fentanyl, oxycodone or tramadol may increase concentrations of the analgesic.

Clinical monitoring is recommended when co-administering PREZISTA/rtv with these analgesics.

Methadone

An interaction trial investigating the effect of PREZISTA/rtv (600/100 mg b.i.d.) on a stable methadone maintenance therapy showed an AUC decrease of 16% for R-methadone.

Based on pharmacokinetic and clinical findings, no adjustment of methadone dosage is required when initiating co-administration of PREZISTA/rtv. However, clinical monitoring is recommended as maintenance therapy may need to be adjusted in some patients.

PDE-5 inhibitors

Treatment of erectile dysfunction:

Avanafil, sildenafil, tadalafil, vardenafil

In an interaction trial a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with PREZISTA/rtv (400/100 mg b.i.d.).

Concomitant use of PDE-5 inhibitors for the treatment of erectile dysfunction with PREZISTA/rtv should be done with caution. If concomitant use of PREZISTA/rtv with sildenafil, vardenafil, or tadalafil is indicated, 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.

Co-administration of PREZISTA/rtv and avanafil is not recommended.

Treatment of pulmonary arterial hypertension:

Sildenafil, tadalafil

A safe and effective dose of sildenafil when combined with PREZISTA/rtv for the treatment of pulmonary arterial hypertension has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope).

Therefore, co-administration of PREZISTA/rtv with sildenafil when used for pulmonary arterial hypertension is contraindicated.

For the treatment of pulmonary arterial hypertension with tadalafil co-administered with PREZISTA/rtv, a dose adjustment for tadalafil is warranted. In patients who have been receiving PREZISTA/rtv for at least 1 week, start tadalafil at 20 mg q.d., and increase to 40 mg q.d. based upon individual tolerability. For patients on tadalafil and initiating PREZISTA/rtv, discontinue the use of tadalafil at least 24 hours prior to initiating PREZISTA/rtv and avoid the use of tadalafil during the initiation of PREZISTA/rtv. After at least 1 week following the initiation of PREZISTA/rtv, resume tadalafil at 20 mg q.d. and increase to 40 mg q.d. based upon individual tolerability.

Pharmacokinetic enhancer

PREZISTA should be used in combination with a pharmacokinetic enhancer such as low dose ritonavir.
PREZISTA should not be used in combination with other antiretrovirals that also require pharmacokinetic boosting with ritonavir.

Platelet aggregation inhibitors

Ticagrelor
Co-administration of PREZISTA/rtv with ticagrelor may increase concentrations of ticagrelor.
Co-administration of PREZISTA/rtv and ticagrelor is not recommended.

Sedatives/hypnotics

Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem
Co-administration of PREZISTA/rtv with these sedatives/hypnotics may increase concentrations of the sedative/hypnotic (inhibition of CYP3A).
Co-administration of PREZISTA/rtv with oral midazolam or triazolam is contraindicated.
Co-administration of parenteral midazolam should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral midazolam should be considered, especially if more than a single dose of midazolam is administered.
Clinical monitoring is recommended when co-administering PREZISTA/rtv with the other sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered.

Pregnancy, Breast-feeding and Fertility

Pregnancy

There are no adequate and well-controlled studies on pregnancy outcome with darunavir in pregnant women. Studies in animals have not shown evidence of developmental toxicity or effect on reproductive function and fertility (see *Toxicology*).

To monitor maternal-fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry has been established (http://www.apregistry.com). This is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products. For darunavir, sufficient first trimester exposures are available to allow detection of at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

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. 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). Virologic response was preserved throughout the study period in both arms. No mother to child transmission occurred in the infants born to the 31 subjects who stayed on the antiretroviral treatment through delivery. 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 (see *Pharmacokinetic Properties-Special Populations-Pregnancy and Postpartum*).

PREZISTA/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk.

Breast-feeding

It is not known whether darunavir is excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk. Because of both the potential for HIV transmission and the potential for serious adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving PREZISTA.

Fertility

There was no effect on mating or fertility with PREZISTA treatment in rats (see *Toxicology*).

Effects on Ability to Drive and Use Machines

No trials on the effects of PREZISTA in combination with ritonavir on the ability to drive or use machines have been performed. However, dizziness has been reported in some patients during treatment with regimens containing PREZISTA and should be borne in mind when considering a patient's ability to drive or operate machinery (see *Adverse Reactions*).

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of darunavir based on the comprehensive assessment of the available adverse event information. A causal relationship with darunavir cannot be reliably established in individual cases. Further, 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.

The overall safety profile of PREZISTA is based on all available clinical trial and post-marketing data, and is consistent with the data presented below.

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

Adverse reactions to PREZISTA/rtv identified in clinical trials in adults

Adverse reactions to PREZISTA/rtv 800/100 mg q.d. identified in antiretroviral treatment-naïve adult patients

The safety assessment is based on all safety data up to 192 weeks of treatment from the Phase III ARTEMIS trial comparing PREZISTA/rtv 800/100 mg q.d. versus lopinavir/ritonavir 800/200 mg per day in antiretroviral naïve HIV-1 infected adult patients. The total patient years exposure in the PREZISTA/rtv arm and the lopinavir/rtv arm was 1072.0 and 1021.4, respectively.

The majority of the ARs reported during treatment with PREZISTA/rtv were mild in severity. The most frequent (≥ 5%) ARs of moderate to severe (grade 2-4) intensity were diarrhea, headache, and abdominal pain.

The most frequent (≥ 1%) ARs of severe (grade 3 or 4) intensity were related to laboratory abnormalities. All other grade 3 or 4 ARs were reported in less than 1% of the patients. 2.3% of the patients in the PREZISTA/rtv arm discontinued treatment due to ARs.

Adverse Reactions to PREZISTA/rtv 800/100 mg q.d. of at least moderate intensity (grade 2-4) in antiretroviral treatment naïve HIV-1 infected adult patients are presented in Table 1.

Table 1: Adverse Reactions at Least Grade 2 Intensity Reported in ARTEMIS (192 Weeks)

System Organ Class Adverse Reaction*	**PREZISTA/rtv 800/100 mg q.d. + TDF/FTC[#] N = 343**	**Lopinavir/rtv 800/200 mg per day + TDF/FTC[#] N = 346**
Nervous system disorders		
Headache	6.7%	5.5%
Gastrointestinal disorders		
Abdominal pain	5.8%	6.1%
Acute pancreatitis	0.6%	0.6%
Diarrhea	8.7%	15.9%
Dyspepsia	0.3%	0.3%
Flatulence	0.9%	0.9%
Nausea	4.1%	3.8%
Vomiting	2.0%	3.5%
Skin and subcutaneous tissue disorders		
Angioedema[+]	0.6%	0%
Lipodystrophy (lipohypertrophy, lipodystrophy, and lipoatrophy)	0.9%	1.7%
Pruritus	1.2%	0.9%
Rash	2.9%	4.6%
Stevens-Johnson Syndrome	0.3%	0%
Urticaria[+]	1.2%	0.6%
Musculoskeletal and connective tissue disorders		
Myalgia	0.6%	1.4%
Osteonecrosis[+]	0.3%	0%
Metabolism and nutrition disorders		
Anorexia	1.5%	0.9%
Diabetes mellitus	0.6%	0.9%

General disorders and administration site conditions		
Asthenia	0.9%	0%
Fatigue	0.9%	2.9%
Immune system disorders		
(Drug) Hypersensitivity+	0.6%	1.4%
Immune reconstitution inflammatory syndrome	0.3%	0.3%
Hepatobiliary disorders		
Acute hepatitis	0.3%	0.9%
Psychiatric disorders		
Abnormal dreams	0.3%	0.3%

* Excluding laboratory abnormalities reported as ARs
\# Tenofovir disoproxil fumarate/emtricitabine
\+ Adverse reactions identified from post-marketing experience

913 Laboratory abnormalities, grade 2-4, considered ARs, in antiretroviral treatment naïve HIV-1
914 infected adult patients are shown in Table 2.
915

Table 2: Laboratory Abnormalities, Grade 2-4, Considered ARs in ARTEMIS 192 Week Analyses

Laboratory parameter*	**Limit**	**PREZISTA/rtv 800/100 mg q.d. + TDF/FTC# N = 343**	**Lopinavir/rtv 800/200 mg per day + TDF/FTC# N = 346**
ALT			
Grade 2	> 2.5 to ≤ 5.0 x ULN	8.8%	9.4%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.9%	3.5%
Grade 4	> 10.0 x ULN	0.9%	2.9%
AST			
Grade 2	> 2.5 to ≤ 5.0 x ULN	7.3%	9.9%
Grade 3	> 5.0 to ≤ 10.0 x ULN	4.4%	2.3%
Grade 4	> 10.0 x ULN	1.2%	2.6%
ALP			
Grade 2	> 2.5 to ≤ 5.0 x ULN	1.5%	1.5%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0%	0.6%
Grade 4	> 10.0 x ULN	0%	0%
Triglycerides			
Grade 2	500-750 mg/dl	2.6%	9.9%
Grade 3	751-1200 mg/dl	1.8%	5.0%
Grade 4	> 1200 mg/dl	1.5%	1.2%
Total cholesterol*			
Grade 2	240-300 mg/dl	22.9%	27.1%
Grade 3	> 300 mg/dl	1.5%	5.5%
LDL cholesterol*			
Grade 2	160-190 mg/dl	14.1%	12.3%
Grade 3	≥ 191 mg/dl	8.8%	6.1%

Elevated glucose levels			
Grade 2	126-250 mg/dl	10.8%	9.6%
Grade 3	251-500 mg/dl	1.2%	0.3%
Grade 4	> 500 mg/dl	0%	0%
Pancreatic lipase			
Grade 2	> 1.5 to ≤ 3.0 x ULN	2.6%	1.7%
Grade 3	> 3.0 to ≤ 5.0 x ULN	0.6%	1.2%
Grade 4	> 5.0 x ULN	0%	0.9%
Pancreatic amylase			
Grade 2	> 1.5 to ≤ 2.0 x ULN	4.7%	2.3%
Grade 3	> 2.0 to ≤ 5.0 x ULN	4.7%	4.1%
Grade 4	> 5.0 x ULN	0%	0.9%

* Grade 4 data not applicable in Division of AIDS grading scale

Tenofovir disoproxil fumarate/emtricitabine

Adverse reactions to PREZISTA/rtv 600/100 mg b.i.d. identified in antiretroviral treatment-experienced adult patients

The safety assessment is based on all safety data from the Phase III trial TITAN comparing PREZISTA/rtv 600/100 mg b.i.d. versus lopinavir/ritonavir 400/100 mg b.i.d. in antiretroviral treatment-experienced HIV-1 infected adult patients. The total patient years of exposure in the PREZISTA/rtv arm and the lopinavir/rtv arm was 462.5 and 436.1, respectively.

The majority of the ARs reported during treatment with PREZISTA/rtv were mild in severity. The most frequent (≥ 5%) ARs of moderate to severe (grade 2-4) intensity were diarrhoea, hypertriglyceridaemia, hypercholesterolaemia, nausea, abdominal pain, vomiting, lipodystrophy, hepatic enzymes increased, and rash.

The most frequent (≥ 1%) severe (grade 3 or 4) ARs were lipodystrophy or related to laboratory abnormalities. All other grade 3 or 4 ARs were reported in less than 1% of the patients. 4.7 % of the patients discontinued treatment due to ARs.

Adverse Reactions to PREZISTA/rtv 600/100 mg b.i.d. of at least moderate intensity (grade 2-4) in antiretroviral treatment-experienced HIV-1 infected adult patients in the TITAN trial are mentioned in Table 3.

Table 3: Adverse Reactions at Least Grade 2 Intensity Reported in TITAN Trial (96 Weeks)

System Organ Class Adverse Reaction*	**PREZISTA/rtv 600/100 mg b.i.d. + OBR# N = 298**	**Lopinavir/rtv 400/100 mg b.i.d. + OBR# N = 297**
Nervous system disorders		
Headache	2.7%	3.0%

Gastrointestinal disorders		
Abdominal distension	2.0%	0.3%
Abdominal pain	5.7%	2.7%
Acute pancreatitis	0.3%	0.3%
Diarrhea	14.4%	19.9%
Dyspepsia	2.0%	1.0%
Flatulence	0.3%	1.0%
Nausea	7.0%	6.4%
Vomiting	5.4%	2.7%
Skin and subcutaneous tissue disorders		
Lipodystrophy (lipohypertrophy, lipodystrophy, and lipoatrophy)	5.4%	4.4%
Pruritus	1.0%	1.0%
Rash	5.0%	2.0%
Urticaria[+]	0.3%	0%
Musculoskeletal and connective tissue disorders		
Myalgia	1.0%	0.7%
Metabolism and nutrition disorders		
Anorexia	1.7%	2.0%
Diabetes mellitus	1.7%	0.3%
General disorders and administration site conditions		
Asthenia	3.4%	1.0%
Fatigue	2.0%	1.3%
Immune system disorders		
Immune reconstitution syndrome	0.3%	0%
Reproductive system and breast disorders		
Gynaecomastia	0.3%	0.3%
Psychiatric disorders		
Abnormal dreams	0.7%	0%

[*] Excluding laboratory abnormalities reported as ARs
[#] Optimized Background Regimen
[+] Adverse reactions identified from post-marketing experience

938
939 Laboratory abnormalities, grade 2-4, considered ARs, in antiretroviral treatment-experienced
940 HIV-1 infected adult patients in the TITAN trial are shown in Table 4.
941

Table 4: Laboratory Abnormalities, Grade 2-4, Considered ARs in TITAN 96 Week Analyses

Laboratory parameter*	**Limit**	**PREZISTA/rtv 600/100 mg b.i.d. + OBR# N = 298**	**Lopinavir/rtv 400/100 mg b.i.d. + OBR# N = 297**

ALT			
Grade 2	> 2.5 to ≤ 5.0 x ULN	6.9%	4.8%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.4%	2.4%
Grade 4	> 10.0 x ULN	1.0%	1.7%
AST			
Grade 2	> 2.5 to ≤ 5.0 x ULN	5.5%	6.2%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.4%	1.7%
Grade 4	> 10.0 x ULN	0.7%	1.7%
ALP			
Grade 2	> 2.5 to ≤ 5.0 x ULN	0.3%	0%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0.3%	0.3%
Grade 4	> 10.0 x ULN	0%	0%
Triglycerides			
Grade 2	500-750 mg/dl	10.4%	11.4%
Grade 3	751-1200 mg/dl	6.9%	9.7%
Grade 4	> 1200 mg/dl	3.1%	6.2%
Total cholesterol*			
Grade 2	240-300 mg/dl	24.9%	23.2%
Grade 3	> 300 mg/dl	9.7%	13.5%
LDL cholesterol*			
Grade 2	160-190 mg/dl	14.4%	13.5%
Grade 3	≥ 191 mg/dl	7.7%	9.3%
Elevated glucose levels			
Grade 2	126-250 mg/dl	10.0%	11.4%
Grade 3	251-500 mg/dl	1.4%	0.3%
Grade 4	> 500 mg/dl	0.3%	0%
Pancreatic lipase			
Grade 2	> 1.5 to ≤ 3.0 x ULN	2.8%	3.5%
Grade 3	> 3.0 to ≤ 5.0 x ULN	2.1%	0.3%
Grade 4	> 5.0 x ULN	0.3%	0%
Pancreatic amylase			
Grade 2	> 1.5 to ≤ 2.0 x ULN	6.2%	7.3%
Grade 3	> 2.0 to ≤ 5.0 x ULN	6.6%	2.8%
Grade 4	> 5.0 x ULN	0%	0%

* Grade 4 data not applicable in Division of AIDS grading scale

Optimized Background Regimen

Additional adverse reactions to PREZISTA/rtv identified in adult patients in other clinical trials

Not Applicable.

Adverse reactions to PREZISTA/rtv identified in pediatric patients

The safety assessment in children and adolescents is based on the safety data from the week 48 analysis of three Phase II trials: DELPHI, in which 80 antiretroviral treatment-experienced HIV-1 infected pediatric patients aged from 6 to < 18 years and weighing at least 20 kg received

PREZISTA tablets in combination with low dose ritonavir and other antiretroviral agents (see *Pharmacodynamic Properties*).

Frequency, type, and severity of adverse reactions in pediatric patients were comparable to those observed in adults.

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience. The frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/ 1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports.

In Table 5, adverse reactions identified during post-marketing experience are presented by frequency category based on spontaneous reporting rates.

Table 5: Post-marketing ARs Presented by Frequency Category Based on Spontaneous Reporting Rates

System Organ Class	Adverse Reaction	Incidence
Skin and subcutaneous tissue disorders	DRESS	very rare
	Toxic Epidermal Necrolysis	very rare
	Acute Generalized Exanthematous Pustulosis	very rare

Effects of combination antiretroviral therapy

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy, and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has also been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia.

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (immune reconstitution inflammatory syndrome). Autoimmune disorders such as Graves' disease have also been reported in the context of immune reconstitution inflammatory syndrome (see *Warnings and Precautions*).

There have been reports of increased spontaneous bleeding in hemophilia patients receiving PIs.

Increased CPK, myalgia, myositis, and rarely, rhabdomyolysis have been reported with the use of HIV protease inhibitors, particularly in combination with NRTIs[#].

Special populations

Patients co-infected with hepatitis B and/or hepatitis C virus

In patients co-infected with hepatitis B or C virus receiving PREZISTA/rtv, the incidence of adverse events and clinical chemistry abnormalities was not higher than in patients receiving PREZISTA/rtv who were not co-infected, except for increased hepatic enzymes (see *Warnings and Precautions*). The pharmacokinetic exposure in co-infected patients was comparable to that in patients without co-infection.

Overdose

Symptoms and signs

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

Treatment

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Antivirals for systemic use, ATC code: J05A-E010.

Mechanism of action

Darunavir is an inhibitor of the dimerization and of the catalytic activity of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.
Darunavir tightly binds to the HIV-1 protease with a KD of 4.5 × 10-12 M. Darunavir shows resilience to the effects of HIV protease inhibitors Resistance-Associated Mutations (RAMs).
Darunavir is not an inhibitor of any of 13 tested human cellular proteases.

Pharmacodynamic effects

Microbiology

Antiviral activity in vitro

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC50 values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity *in vitro* 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 < 0.1 to 4.3 nM. These EC50 values are well below the 50% cellular toxicity concentration range of 87 µM to > 100 µM.

The EC50 value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir showed synergistic antiviral activity when studied in combination with the protease inhibitors ritonavir, nelfinavir, or amprenavir and additive antiviral activity when studied in combination with the protease inhibitors indinavir, saquinavir, lopinavir, atazanavir, or tipranavir, the N(t)RTIs zidovudine, lamivudine, zalcitabine, didanosine, stavudine, abacavir, emtricitabine, or tenofovir, the NNRTIs etravirine, nevirapine, delavirdine, rilpivirine, or efavirenz and the fusion inhibitor enfuvirtide. No antagonism was observed between darunavir and any of those antiretrovirals.

Resistance in vitro

In vitro selection of darunavir-resistant virus from wildtype HIV-1 was lengthy (> 3 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23-50-fold) harbored 2 to 4 amino acid substitutions in the protease gene. The decreased susceptibility to darunavir of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations.

In vitro selection of darunavir-resistant HIV-1 (range: 53-641-fold change in EC50 values [FC]) from 9 HIV-1 strains harboring multiple PI RAMs resulted in the overall emergence of 22 mutations in the protease, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were present in more than 50% of the 9 darunavir-resistant isolates. A minimum of 8 of these darunavir *in vitro* selected mutations, from which at least 2 were already present in the protease prior to selection, were required in the HIV-1 protease to render a virus resistant (FC > 10) to darunavir.

In 1113 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and/or tipranavir and in 886 baseline isolates from the patients enrolled in the POWER 1 and POWER 2 trials and in the POWER 3 analysis, only the subgroups with > 10 PI RAMs showed a median FC for darunavir > 10.

Cross-resistance in vitro

Cross-resistance has been observed among HIV protease inhibitors. Darunavir has a < 10-fold decreased susceptibility against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and/or tipranavir showing that viruses resistant to most PIs remain susceptible to darunavir.

Seven of the 9 darunavir-resistant viruses selected from PI-resistant viruses had phenotypic data for tipranavir. Six of those showed a FC < 3 for tipranavir, indicative of limited cross-resistance between these 2 protease inhibitors.

Cross-resistance between darunavir and the nucleoside/nucleotide reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors, the entry inhibitors, or the integrase inhibitors, is unlikely because the viral targets for those inhibitors are different.

Pharmacokinetic Properties

The pharmacokinetic properties of PREZISTA, co-administered with ritonavir, have been evaluated in healthy adult volunteers and in HIV-1 infected patients. Exposure to darunavir was higher in HIV-1 infected patients than in healthy subjects. The increased exposure to darunavir in HIV-1 infected patients compared to healthy subjects may be explained by the higher concentrations of alpha-1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG and, therefore, higher plasma concentrations.
Darunavir is primarily metabolized by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

Absorption

Darunavir was rapidly absorbed following oral administration. Maximum plasma concentration of darunavir in the presence of low dose ritonavir is generally achieved within 2.5-4.0 hours.
The absolute oral bioavailability of a single 600 mg dose of PREZISTA alone was approximately 37% and increased to approximately 82% in the presence of 100 mg b.i.d. ritonavir. The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg PREZISTA was given orally in combination with ritonavir at 100 mg b.i.d. (see *Warnings and Precautions*).
When administered without food, the relative bioavailability of PREZISTA in the presence of low dose ritonavir is 30% lower as compared to intake with food. Therefore, PREZISTA tablets should be taken with ritonavir and with food. The type of food does not affect exposure to darunavir.

Distribution

Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma alpha-1-acid glycoprotein.

Metabolism

In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by the hepatic CYP system and almost exclusively by isozyme CYP3A4. A ^{14}C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg PREZISTA/rtv dose was due to the parent drug. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 10-fold less than the activity of darunavir against wildtype HIV.

Elimination

After a 400/100 mg ^{14}C-darunavir/rtv dose, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir could be retrieved in 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 combined with ritonavir.
The intravenous clearance of darunavir alone (150 mg) and in the presence of low dose ritonavir was 32.8 l/h and 5.9 l/h, respectively.

Special populations

Pediatrics (17 years of age and younger)

The pharmacokinetics of darunavir in combination with ritonavir in 74 treatment-experienced pediatric patients, aged 6 to < 18 years and weighing at least 20 kg, showed that the administered weight-based dosages resulted in darunavir exposure comparable to that in adults receiving PREZISTA/rtv 600/100 mg b.i.d. (see *Dosage and Administration*). Median (range) darunavir AUC_{12h} and C_{0h} values in this pediatric population were 61.6 (35.9–100.8) mcg.h/mL and 3.7 (1.8–7.2) mcg/mL, respectively.

Elderly (65 years of age and older)

Population pharmacokinetic analysis in HIV infected patients showed that PREZISTA pharmacokinetics are not considerably different in the age range (18-75 years) evaluated in HIV infected patients (see *Warnings and Precautions*).

Renal impairment

Results from a mass balance study with ^{14}C-darunavir/rtv showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine as unchanged drug.
Although PREZISTA has not been studied in patients with renal impairment, population pharmacokinetic analysis showed that the pharmacokinetics of PREZISTA were not significantly affected in HIV infected patients with moderate renal impairment (CrCl between 30-60 mL/min, n = 20) (see *Dosage and Administration* and *Warnings and Precautions*).

Hepatic impairment

Darunavir is primarily metabolized and eliminated by the liver. In a multiple dose study with PREZISTA co-administered with ritonavir (600/100 mg) twice daily, it was demonstrated that the steady-state pharmacokinetic parameters of darunavir in subjects with mild (Child-Pugh Class A, n = 8) and moderate (Child-Pugh Class B, n = 8) hepatic impairment were comparable with those in healthy subjects. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see *Dosage and Administration* and *Warnings and Precautions*).

Gender

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

Pregnancy and postpartum

The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 600/100 mg b.i.d and darunavir/ritonavir 800/100 mg q.d. as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum (see Table 6 and Table 7). However, for unbound (i.e., active) darunavir, the pharmacokinetic parameters were less reduced during pregnancy

compared to postpartum, due to an increase in the unbound fraction of darunavir during pregnancy compared to postpartum.

Table 6: Pharmacokinetic Results of Total Darunavir After Administration of Darunavir/Ritonavir at 600/100 mg bid as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

Pharmacokinetics of total darunavir (mean ± SD)	**2nd Trimester of pregnancy (n=12)[a]**	**3rd Trimester of pregnancy (n=12)**	**Postpartum (6-12 Weeks) (n=12)**
C_{max}, ng/mL	4668 ± 1097	5328 ± 1631	6659 ± 2364
AUC_{12h}, ng.h/mL	39370 ± 9597	45880 ± 17360	56890 ± 26340
C_{min}, ng/mL	1922 ± 825	2661 ± 1269	2851 ± 2216

[a] n=11 for AUC_{12h}

Table 7: Pharmacokinetic Results of Total Darunavir After Administration of Darunavir/Ritonavir at 800/100 mg qd as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

Pharmacokinetics of total darunavir (mean ± SD)	**2nd Trimester of pregnancy (n=17)**	**3rd Trimester of pregnancy (n=15)**	**Postpartum (6-12 Weeks) (n=16)**
C_{max}, ng/mL	4964 ± 1505	5132 ± 1198	7310 ± 1704
AUC_{24h}, ng.h/mL	62289 ± 16234	61112 ± 13790	92116 ± 29241
C_{min}, ng/mL	1248 ± 542	1075 ± 594	1473 ± 1141

In women receiving darunavir/ritonavir 600/100 mg b.i.d during the 2nd trimester of pregnancy, mean intra-individual values for total darunavir C_{max}, AUC_{12h} and C_{min} were 28%, 26% and 26% lower, respectively, as compared with postpartum; during the 3rd trimester of pregnancy, total darunavir C_{max}, AUC_{12h} and C_{min} values were 18%, 16% lower and 2% higher, respectively, as compared with postpartum.

In women receiving darunavir/ritonavir 800/100 mg q.d. during the 2nd trimester of pregnancy, mean intra-individual values for total darunavir C_{max}, AUC_{24h} and C_{min} were 33%, 31% and 30% lower, respectively, as compared with postpartum; during the 3rd trimester of pregnancy, total darunavir C_{max}, AUC_{24h} and C_{min} values were 29%, 32% and 50% lower, respectively, as compared with postpartum.

NON-CLINICAL INFORMATION

Carcinogenicity and Mutagenicity

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450, and 1000 mg/kg were administered to mice and doses of 50, 150, and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal

enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg once daily).

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

Toxicology

Animal toxicology studies have been conducted with darunavir alone, in mice, rats, dogs, and in combination with ritonavir in rats and dogs.

In chronic toxicology studies in rats and dogs, there were only limited effects of treatment with darunavir. In the rat, the key target organs identified were the hematopoietic system, the blood coagulation system, liver, and thyroid, observed at 100 mg/kg/day and above and at exposures below clinical levels. A variable but limited decrease in red blood cell-related parameters was observed, together with increases in activated PTT. The observed liver and thyroid changes were considered to reflect an adaptive response to enzyme induction in the rat rather than an adverse effect. In combination toxicity studies with ritonavir, no additional target organs of toxicity were reported in rats. In the dog, no major toxicity findings or key target organs were identified at doses up to 120 mg/kg/day and exposures equivalent to clinical exposure at the recommended dose.

Reproductive Toxicology

In a study conducted in rats, there were no effects on mating or fertility with PREZISTA treatment up to 1000 mg/kg/day and exposure levels below (AUC-0.5 fold) of that in humans at the clinically recommended dose. Up to same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone, nor in mice when treated in combination with ritonavir. The exposure levels were lower than those with the recommended clinical dose in humans. In addition, rats treated with combination with ritonavir showed no teratogenicity with the increase in exposure levels which are higher than those with the recommended clinical dose in humans.

Juvenile Toxicity

In a pre and postnatal development assessment in rats, darunavir with and without ritonavir caused a transient reduction in body weight of the offspring during lactation. This was attributed to drug exposure via the milk. No post weaning functions were affected with darunavir alone or in combination with ritonavir. In juvenile rats directly dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age, mortality was observed and, in some of the animals, convulsions. Within this age range, exposures in plasma, liver, and brain were dose and age dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood brain barrier. No treatment related mortalities were noted in juvenile rats dosed at 1000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats. Due to uncertainties regarding the rate of development of the human

blood brain barrier and liver enzymes, PREZISTA/rtv should not be used in pediatric patients below 3 years of age.

PHARMACEUTICAL INFORMATION

List of Excipients

Tablet core (all tablet formulations)

Colloidal anhydrous silica, crospovidone, magnesium stearate, microcrystalline cellulose.
The 800 mg tablet core also contains hypromellose.

Tablet film-coat:

Presentation	
400 mg	LIGHT ORANGE TABLET: Polyvinyl alcohol – partially hydrolyzed Macrogol 3350 Titanium dioxide (E171) Talc Sunset Yellow FCF (E110)
600 mg	WHITE TABLET: Polyvinyl alcohol – partially hydrolyzed Macrogol 3350 Titanium dioxide (E171) Talc
800 mg	DARK RED TABLET: Polyvinyl alcohol – partially hydrolyzed Macrogol 3350 Titanium dioxide (E171) Talc Iron Oxide Red (E172)

Incompatibilities

Not applicable

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Do not store above 30°C.
Keep out of the sight and reach of children.

Nature and Contents of Container

Tablets

PREZISTA film-coated tablets are provided in high density polyethylene (HDPE) plastic bottles, fitted with polypropylene (PP) child resistant closures.

Tablet strength	Presentation (tablets/bottle)
400 mg	60
600 mg	60
800 mg	30

Instructions for Use and Handling

No special requirements.

MANUFACTURED BY

Janssen Ortho LLC, Gurabo, Puerto Rico

Tablet strength	Marketing Authorization Numbers	Date of Authorization
400 mg	1C 22/56 (NC)	11 March 2013
600 mg	1C 111/53 (N)	18 July 2012
800 mg	1C 39/59 (NC)	22 September 2016

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