PRODUCT NAME
PREZISTA® 75 mg film-coated tablets.
PREZISTA® 150 mg film-coated tablets.
PREZISTA® 400 mg film-coated tablets.
PREZISTA® 600 mg film-coated tablets.
PREZISTA® 800mg film-coated tablets.

DOSAGE FORMS AND STRENGTHS
Film-coated tablet
- 75mg white caplet-shaped tablet, debossed with 75 on one side and TMC on the other side; contains 75 mg of darunavir (corresponding to 81.31 mg of darunavir ethanolate).
- 150mg white oval-shaped tablet, debossed with 150 on one side and TMC on the other side; contains 150 mg of darunavir (corresponding to 162.62 mg of darunavir ethanolate).
- 400mg light orange oval-shaped tablet, debossed with 400MG on one side and TMC on the other side; 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).
- 600mg orange oval-shaped tablet, debossed with 600MG on one side and TMC on the other side; contains 600 mg of darunavir (corresponding to 650.46 mg of darunavir ethanolate). The film-coating of the orange tablet contains sunset yellow FCF (E110).
- 800mg dark red oval-shaped tablet, debossed with 800 on one side and T on the other side; contains 800mg of darunavir (corresponding to 867.28mg of darunavir ethanolate). The film coating of the dark red tablet contains Iron Oxide Red.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION
Indications
Adult patients
PREZISTA®, in combination with 100 mg 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 pediatric patients of 6 years and above and at least 20kg body weight.

In treatment-experienced adult and pediatric patients, the following points should be considered when initiating therapy with PREZISTA®/rtv:
- Treatment history and, when available, genotypic or phenotypic testing should guide the use of PREZISTA®/rtv.

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 or discontinue therapy without instruction of their physician.

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*).

Dosage - Adults

Treatment-Naïve Adult Patients

The recommended oral dose of PREZISTA® tablets is 800 mg (one 800 mg tablet or two 400 mg tablets) taken with ritonavir 100 mg once daily and with food.

Treatment-Experienced Adult Patients

Treatment-Experienced Adult Patients	
With no darunavir resistance associated substitutions*	With at least one darunavir resistance associated substitution*
800 mg PREZISTA® once daily with ritonavir 100 mg once daily and with food	600 mg PREZISTA® twice daily taken with ritonavir 100 mg twice daily and with food

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

For antiretroviral treatment-experienced patients, HIV genotypic testing is recommended. However, when HIV genotypic testing is not feasible, the PREZISTA®/ritonavir 600/100 mg twice daily dosing is recommended.

The type of food does not affect the exposure to darunavir. Ritonavir (100 mg) is used as a pharmacokinetic enhancer of darunavir (see *Interactions* and *Pharmacokinetic properties*).

Dosage - Pediatrics

Antiretroviral treatment-experienced pediatric patients (6 to < 18 years of age)

The recommended dose of PREZISTA®/rtv for pediatric patients (6 to < 18 years of age and weighing at least 20 kg) is based on body weight (see table below) and should not exceed the recommended adult dose (600/100 mg b.i.d.). PREZISTA® tablets should be taken with ritonavir twice daily and with food. The type of food does not affect exposure to darunavir.

Recommended dose for treatment-experienced pediatric patients (6 to < 18 years of age) for PREZISTA® tablet(s) and ritonavir tablets, capsules (100mg) or oral solution (80 mg/mL)*	
Body weight (kg)	**Dose**
≥ 20 kg to < 30 kg	375 mg PREZISTA® with 0.6mL (50 mg) ritonavir b.i.d.
≥ 30 kg to < 40 kg	450 mg PREZISTA® with 0.8mL (60 mg) ritonavir b.i.d.
≥ 40 kg	600 mg PREZISTA® with 100 mg (1.2mL) ritonavir b.i.d.

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

Antiretroviral treatment-experienced children less than 6 years of age and antiretroviral treatment-naïve pediatric patients

The safety and efficacy of PREZISTA®/rtv in antiretroviral treatment-experienced children aged 3 to less than 6 years and in antiretroviral treatment-naïve pediatric patients have not been established.
PREZISTA®/rtv should not be used in children below 3 years of age (See *Warnings and Precautions* and *Non-Clinical Information*).

Pregnancy and postpartum

No dose adjustment is required for PREZISTA®/rtv 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 of 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 pharmacokinetic or safety data available for subjects with severe hepatic impairment, therefore, PREZISTA®/rtv must not be used 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 both 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). Examples include alfuzosin, astemizole, cisapride, colchicine (in patients with renal and/or hepatic impairment), dapoxetine, dronedarone, elbasvir/grazoprevir, the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine and methylergonovine), ivabradine, lomitapide, lovastatin, lurasidone, midazolam (oral), naloxegol, pimozide, ranolazine, sildenafil (when used for treatment of pulmonary arterial hypertension), simvastatin, terfenadine, ticagrelor, and triazolam (see *Interactions*).

Patients taking PREZISTA® should not use products containing potent CYP3A inducers such as 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.

Do not administer PREZISTA®/rtv in children below 3 years of age in view of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1,000 mg/kg) up to days 23 to 26 of age (see *Toxicology*).

The safety and efficacy of PREZISTA®/rtv in antiretroviral treatment-experienced children aged 3 to less than 6 years and in antiretroviral treatment naïve pediatric patients have not been established.

Elderly: As limited information is available on the use of PREZISTA®/rtv 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 clinical development program (N = 3,063), 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® (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.

Hepatotoxicity

Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA®/rtv. During the 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.

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

Appropriate laboratory testing should be conducted prior to initiating therapy with PREZISTA®/rtv 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®/rtv treatment. If there is 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®/rtv, interruption or discontinuation of treatment must be considered.

Patients with coexisting conditions

Hepatic impairment

There are no data regarding the use of PREZISTA®/rtv when co-administered to patients with severe hepatic impairment; therefore, PREZISTA®/rtv is not recommended for use 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*).

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.

Metabolic disorders

Hyperglycemia/Diabetes mellitus

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.

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, generalised 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 and autoimmune hepatitis 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 when used in combination with ritonavir is an inhibitor of CYP3A, CYP2D6 and P-gp. Co-administration of PREZISTA® and ritonavir with medicinal products primarily metabolised 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 event (see *Contraindications* and *Interactions*).

Darunavir and ritonavir are metabolised 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*). Co-administration of PREZISTA®/rtv with drugs that have active metabolite(s), formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect (see *Interactions*).

Interactions

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 and 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. Co-administration of PREZISTA®/rtv with drugs that have active metabolite(s), formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect.

Darunavir and ritonavir are metabolised 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.
Drug-drug interactions presented by drug class including drug name examples are presented below.This list of examples of drug-drug interactions is not comprehensive and therefore the label of each drug that is co-administered with PREZISTA® should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

Antiretroviral medicinal products

Integrase strand tranfer 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 150mg once daily. The pharmacokinetics and dosing recommendations for other doses of darunavir or with elvitegravir/cobicistat 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.
Co-administration of PREZISTA®/rtv and elvitegravir in the presence of cobicistat 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

The results of an interaction trial with tenofovir (tenofovir alafenamide 10 mg once daily [q.d.]) demonstrated that the systemic exposure of tenofovir was increased by 105% when co-administered with PREZISTA®/rtv (800/100 mg q.d.). The recommended dose of emtricitabine/tenofovir alafenamide is 200/10 mg once daily when used with PREZISTA®/rtv (800/100 mg q.d.).

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 low dose ritonavir as a pharmacokinetic enhancer.

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

H_2-receptor antagonists
e.g. CIMETIDINE, FAMOTIDINE, NIZATIDINE, RANITIDINE
Co-administration of ranitidine (150 mg b.i.d.) and PREZISTA®/rtv (400/100mg 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 adjustments.

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.

Antianginals/ Antiarrhythmics
RANOLAZINE
Exposure to ranolazine may be increased (CYP3A inhibition) when co-administered with PREZISTA®/rtv. Concomitant use of PREZISTA®/rtv with ranolazine is contraindicated.

IVABRADINE
Concomitant use of PREZISTA®/rtv with ivabradine is contraindicated.

AMIODARONE, BEPRIDIL, DISOPYRAMIDE, DRONEDARONE, FELCAINIDE, 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.

Antibacterials

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.

Antiemetics

DOMPERIDONE
Use with caution: monitor for domperidone adverse reactions.

Antifungals

ITRACONAZOLE, ISAVUCONAZOLE, KETOCONAZOLE, POSACONAZOLE AND VORICONAZOLE
Itraconazole, isavuconazole, ketoconazole, posaconazole, and voriconazole are moderate to potent inhibitors of CYP3A and/or 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 or isavuconazole.

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.

Antimalarials

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® and artemether/lumefantrine can be used without dose adjustments. The combination should be used with caution as increase in lumefantrine exposure may increase the risk of QT prolongation.

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, IRINOTECAN, 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 or irinotecan and PREZISTA®/rtv is not recommended.

Antiplatelets

CLOPIDOGREL

Co-administration of PREZISTA®/rtv with clopidogrel is expected to decrease clopidogrel active metabolite plasma concentration, which may reduce the antiplatelet activity of clopidogrel. Co-administration of PREZISTA®/rtv with clopidogrel is not recommended.

PRASUGREL

PREZISTA®/rtv is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite of prasugrel.

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 these antipsychotics (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 beta-blocker should be considered.

Calcium channel blockers

AMLODIPINE, DILTIAZEM, FELODIPINE, NICARDIPINE, NIFEDIPINE, VERAPAMIL

The exposure to calcium channel blockers (e.g., felodipine, nifedipine, nicardipine) 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. Therefore, additional or alternative (non-hormonal) methods of contraception are recommended.

ETHINYLESTRADIOL AND DROSPIRENONE

The effect of PREZISTA®/rtv on drospirenone exposure is not known. Therefore, additional or alternative (non-hormonal) methods of contraception are recommended.

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

OTHER HORMONAL CONTRACEPTIVES

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

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.

For co-administration of cutaneously-administered corticosteroids sensitive to CYP3A inhibition, refer to the prescribing information of the corticosteroid for conditions or uses that augment its systemic absorption.

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 agents

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 OATP1B and 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 simprevir 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 Products

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

CYCLOSPOTIN, 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 analgesic/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.

Opioid antagonist

NALOXEGOL

Co-administration of PREZISTA®/rtv with naloxegol is contraindicated.

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 and ticagrelor is contraindicated. Co-administration of PREZISTA®/rtv with ticagrelor may increase concentrations of ticagrelor.

Sedatives/Hypnotics

BUSPIRONE, CLORAZEPATE, DIAZEPAM, 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.

Treatment of premature ejaculation

Co-administration of PREZISTA®/rtv with dapoxetine is contraindicated.

Urinary antispasmodics

FESOTERODINE, SOLIFENACIN
Use with caution: monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary.

Pregnancy, Breast-feeding and Fertility

Pregnancy

There are no adequate and well controlled studies 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®/rtv and should be borne in mind when considering a patient's ability to drive or operate machinery.

Adverse Reactions
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.

a. Summary of the safety profile
During the clinical development program (N=1,968 treatment-experienced subjects who initiated therapy with PREZISTA®/rtv 600/100 mg b.i.d.), 49.5% of subjects experienced at least one adverse reaction. The total mean treatment duration for subjects was 48.58 weeks. For treatment-naïve patients, see the information below the table. The most frequent adverse reactions reported in clinical trials and as

spontaneous reports are diarrhea, immune reconstitution syndrome, nausea, pyrexia and rash. The most frequent serious reactions are diarrhea, hepatitis, immune reconstitution syndrome, pyrexia and rash.

b. Tabulated summary of adverse reactions

Adverse reactions are listed by system organ class (SOC) and frequency category. Within each frequency category, adverse reactions are presented in order of decreasing seriousness.
Frequency categories are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and not known (frequency cannot be estimated from the available data).

Adverse reactions in clinical trials and post-marketing in adult patients

SOC Frequency category	**Adverse reaction**
Infections and infestations	
Uncommon	herpes simplex
Blood and lymphatic system disorders	
Uncommon	thrombocytopenia, neutropenia, anemia, increased eosinophil count, leukopenia
Immune system disorders	
Uncommon	Immune reconstitution inflammatory syndrome, (drug) hypersensitivity
Endocrine disorders	
Uncommon	hypothyroidism, increased blood thyroid stimulating hormone
Metabolism and nutrition disorders	
common	hypertriglyceridemia, hypercholesterolemia, hyperlipidemia
Uncommon	diabetes mellitus, gout, anorexia, decreased appetite, decreased weight, increased weight, hyperglycemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase
Psychiatric disorders	
Common	Insomnia
Uncommon	depression, confusional state, disorientation, anxiety, altered mood, sleep disorder, abnormal dreams, nightmare, decreased libido, restlessness
Nervous system disorders	
Common	headache, peripheral neuropathy, dizziness
Uncommon	syncope, convulsion, lethargy, paresthesia, hypoesthesia, ageusia, dysgeusia, disturbance in attention, memory impairment, somnolence, sleep phase rhythm disturbance
Eye disorders	
Uncommon	Visual disturbance, conjunctival hyperemia, dry eye
Ear and labyrinth disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	acute myocardial infarction, myocardial infarction, angina

	pectoris, prolonged electrocardiogram QT, sinus bradycardia, tachycardia, palpitations
Vascular disorders	
Uncommon	Hypertension, flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon	dyspnoea, cough, epistaxis, rhinorrhoea, throat irritation
Gastrointestinal disorders	
Very common	Diarrhea
Common	vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence
Uncommon	Pancreatitis, gastritis, gastrooesophageal reflux disease, aphthous stomatitis, stomatitis, retching, hematemesis, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysesthesia, cheilitis, dry lip, coated tongue
Hepatobiliary disorders	
Common	increased alanine aminotransferase, increased aspartate aminotransferase
Uncommon	hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-glutamyltransferase
Skin and subcutaneous tissue disorders	
Common	Rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus
Uncommon	Angioedema, generalised rash, allergic dermatitis, urticaria, dermatitis, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, seborrhoeic dermatitis, skin lesion, xeroderma, dry skin, nail pigmentation
Rare	Erythema multiforme, Stevens-Johnson syndrome
Very Rare	Acute generalized exanthematous pustulosis, Toxic epidermal necrolysis, Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	
Uncommon	myalgia, osteonecrosis, muscle spasms, muscular weakness, musculoskeletal stiffness, arthritis, arthralgia, joint stiffness, pain in extremity, osteoporosis, increased blood creatine phosphokinase
Renal and urinary disorders	
Uncommon	acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, decreased creatinine renal clearance, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria
Reproductive system and breast disorders	
Uncommon	erectile dysfunction, gynecomastia
General disorders and administration site conditions	
Common	Asthenia, fatigue

Uncommon	pyrexia, chest pain, peripheral oedema, malaise, chills, abnormal feeling, feeling hot, irritability, pain, xerosis

The safety profile of PREZISTA®/rtv 800/100 mg q.d. in treatment-naïve subjects is similar to that seen with PREZISTA®/rtv 600/100 mg b.i.d. in treatment-experienced subjects except for nausea which was observed more frequently in treatment-naïve subjects. This was driven by mild intensity nausea

c. Description of selected adverse reactions

Rash

In clinical trials, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In cases of severe skin reaction see the warning in section *Warnings and Precautions*.

Metabolic abnormalities

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, hyperglycemia and hyperlactatemia (see *Warnings and Precautions***)**.

Musculoskeletal abnormalities

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

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see *Warnings and Precautions***)**.

Immune reconstitution syndrome

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 and autoimmune hepatitis have also been reported in the context of immune reconstitution inflammatory syndrome (see *Warnings and Precautions***)**.

Bleeding in hemophiliac patients

There have been reports of increased spontaneous bleeding in hemophilia patients receiving protease inhibitors (see *Warnings and Precautions***)**.

d. Pediatric population

The safety assessment in children and adolescents is based on the safety data from the Phase 2 trial DELPHI in which 80 ART-experienced HIV-1 infected pediatric patients aged from 6 to 17 years and weighing at least 20 kg received PREZISTA® with low dose ritonavir in combination with other antiretroviral agents (see *Pharmacodynamic properties*).

Overall, the safety profile in these 80 children and adolescents was similar to that observed in the adult population.

e. Other special Populations

Patients co-infected with hepatitis B and/or hepatitis C virus
Among 1,968 treatment-experienced patients receiving PREZISTA® co-administered with ritonavir 600/100 mg b.i.d., 236 patients were co-infected with hepatitis B or C. Co-infected patients were more likely to have baseline and treatment emergent hepatic transaminase elevations than those without chronic viral hepatitis (see *Warnings and Precautions*).

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 dimerisation 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 K_D 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 EC_{50} 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 EC_{50} values ranging from < 0.1 to 4.3 nM.

These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 µM to > 100 µM.
The EC_{50} 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) harboured 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 EC_{50} values [FC]) from 9 HIV-1 strains harbouring 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 inhibitor, is unlikely because the viral targets for those inhibitors are different.

Clinical studies

Description of clinical studies in adults

Efficacy of PREZISTA®/rtv in treatment- of naïve adult patients

The evidence of efficacy of PREZISTA®/rtv 800/100 mg q.d. is based on the analyses of 192 week data from the randomised, controlled, open-label Phase 3 trial ARTEMIS in antiretroviral treatment naïve HIV-1 infected patients comparing PREZISTA®/rtv 800/100 mg q.d. with lopinavir/rtv 800/200 mg per day (given as a twice-daily or as a once-daily regimen). Both arms used a fixed background regimen consisting of tenofovir disoproxil fumarate 300 mg q.d. (TDF) and emtricitabine 200 mg q.d. (FTC).

HIV-1 infected patients who were eligible for this trial had plasma HIV-1 RNA > 5000 copies/mL. Randomisation was stratified by screening plasma viral load and screening CD4+ cell count. Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 50 copies/mL.

Demographics and baseline characteristics were balanced between the PREZISTA®/rtv arm and the lopinavir/rtv arm. The 343 patients on PREZISTA®/rtv 800/100 mg q.d. had a median age of 34 years (range 18-70), 70% were male, 40% white, 23% black, 23% hispanic, and 13% asian. The mean baseline plasma HIV-1 RNA was 4.86 $\log_{10}$ copies/mL and the median baseline CD4+ cell count was 228×10^6 cells/L (range $4 – 750 \times 10^6$ cells/L).

The table below shows the efficacy data of the 48 week and 192 week analyses from the ARTEMIS trial:

	At week 48[a]			**At week 192 [b]**		
Outcomes	**PREZISTA®/ rtv 800/100 mg q.d. N = 343**	**Lopinavir/ rtv 800/200 mg per day N = 346**	**Treatment difference (95% CI of difference)**	**PREZISTA®/ rtv 800/100 mg q.d. N = 343**	**Lopinavir/ rtv 800/200 mg per day N = 346**	**Treatment difference (95% CI of difference)**
HIV-1 RNA < 50 copies/mL[c]	287 (83.7%)	271 (78.3%)	5.3 (-0.5; 11.2)[d]	236 (68.8%)	198 (57.2%)	11.6 (4.4; 18.8)[d]
HIV-1 RNA < 400 copies/mL[c]	301 (87.8%)	295 (85.3%)	2.5 (-2.6; 7.6)[b]	258 (75.2%)	225 (65.0%)	10.2 (3.4; 17.0)
mean HIV-1 RNA log change from baseline ($\log_{10}$ copies/mL)[e]	-2.77	-2.65	-0.11[f] (-0.30; 0.07)[d]	-2.35	-2.03	-0.32[f] (-0.55; -0.09)
median CD4+ cell count change from baseline ($\times 10^6$/L)[e]	137	141		258	263	

[a] Data based on analyses at week 48

[b] Data based on analyses at week 192

[c] Imputations according to the TLOVR algorithm

[d] Based on normal approximation to the difference in % response

[e] Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0

[f] Difference in means

Analyses of data at 192 weeks of treatment in the ARTEMIS trial demonstrated sustained antiretroviral efficacy and immunological benefit of the PREZISTA®/rtv arm. In the 192 weeks analysis, virologic response (HIV-1 RNA < 50 copies/mLL) was 68.8% and 57.2% for the PREZISTA®/rtv and lopinavir/rtv arm, respectively. Non-inferiority in virologic response was demonstrated ($p < 0.001$) for both ITT and OP population. Furthermore, statistical superiority of the PREZISTA®/rtv arm over the lopinavir/rtv arm was demonstrated ($p = 0.002$) for both ITT and OP population.

Efficacy of PREZISTA®/rtv 800/100 mg q.d. in treatment-experienced adult patients

The evidence of comparable efficacy of PREZISTA®/rtv 800/100 mg q.d. and PREZISTA®/rtv 600/100 mg b.i.d. in treatment-experienced patients with no darunavir RAMs is based on the 48 week analysis of the Phase 3 trial ODIN.

ODIN is a randomised, open-label trial comparing PREZISTA®/rtv 800/100 mg q.d. to PREZISTA®/rtv 600/100 mg b.i.d. in treatment-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a viral load of >1,000 HIV-1 RNA copies/mL. Both arms used an optimised background regimen consisting of ≥2 NRTIs selected by the investigator.

Demographics and baseline characteristics were balanced between the PREZISTA®/rtv q.d. arm and the PREZISTA®/rtv b.i.d. arm. The 590 patients in total had a median age of 40 years (range 18-77), 64% were male, 36% white, 26% black, 18% hispanic, and 15% asian. The mean baseline plasma HIV-1 RNA was 4.16 $\log_{10}$ copies/mL and the median baseline CD4+ cell count was 228 x 10^6 cells/L (range 24 – 1306 x 10^6 cells/L).

The table below shows the efficacy data of the 48 week analysis from the ODIN trial:

Outcomes	**PREZISTA®/rtv 800/100 mg q.d. + OBR N = 294**	**PREZISTA®/rtv 600/100 mg b.i.d. + OBR N = 296**	**Treatment difference (95% CI of difference)**
HIV-1 RNA < 50 copies/mL[a]	212 (72.1%)	210 (70.9%)	1.2% (-6.1; 8.5)[b]
mean HIV-1 RNA log change from baseline ($\log_{10}$ copies/mL)[e]	-1.84	-1.80	-0.04[d] (-0.24; 0.16)
mean CD4+ cell count change from baseline (× 10^6/L)[c]	108	112	-5[d] (-25; 16)

[a] Imputations according to the TLOVR algorithm

[b] Based on a normal approximation of the difference in % response

[c] Last Observation Carried Forward imputation

[d] Difference in means

[e] NC=F

In the 48 week analysis, the virologic response defined as a confirmed plasma HIV-1 RNA viral load < 50 copies/mL, was 72.1% for the PREZISTA®/rtv q.d. arm and 70.9% for the PREZISTA®/rtv b.i.d. arm. Statistical comparisons between the treatment arms at week 48 confirmed non-inferiority of PREZISTA®/rtv q.d. versus PREZISTA®/rtv b.i.d. for both the ITT and OP population (p-value < 0.001).

Efficacy of PREZISTA®/rtv 600/100mg b.i.d.in treatment-experienced adult patients

The evidence of efficacy of PREZISTA®/rtv 600/100mg b.i.d. in treatment-experienced patients is based on the 96week analysis of the Phase 3 trial TITAN in treatment-experienced, lopinavir/rtv naïve patients and on the analyses of 96 week data from the Phase 2b trials POWER 1, 2 and 3, in patients with high level of PI resistance.

TITAN is a randomised, controlled, open-label Phase 3 trial comparing PREZISTA®/rtv 600/100 mg b.i.d. versus lopinavir/rtv 400/100 mg b.i.d. in antiretroviral treatment-experienced,

lopinavir/rtv naïve HIV-1 infected adult patients. Both arms used an optimised background regimen (OBR) consisting of at least 2 antiretrovirals (NRTIs with or without NNRTIs).
HIV-1 infected patients who were eligible for this trial had plasma HIV-1 RNA > 1,000 copies/mL and were on a highly active antiretroviral therapy regimen (HAART) for at least 12 weeks.

Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 400 copies/mL. Analyses included 595 patients in the TITAN trial who had completed 96 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the PREZISTA®/rtv arm and the lopinavir/ritonavir arm. The 298 patients on PREZISTA®/rtv 600/100 mg b.i.d. had a median age of 40 years (range 18-68), 77% were male, 54% white, 18% black, 15% hispanic, and 9% asian. The mean baseline plasma HIV-1 RNA was 4.33 $\log_{10}$ copies/mL and the median baseline CD4+ cell count was 235 x 10^6 cells/L (range 3 – 831 x 10^6 cells/L).

The table below shows the efficacy data of the 48 week and 96 week analyses from the TITAN trial:

Outcomes	**At week 48[a]**			**At week 96[b]**		
	PREZISTA®/ rtv 600/100 mg b.i.d. + OBR N = 298	**Lopinavir/ rtv 400/100 mg b.i.d. + OBR N = 297**	**Treatment difference (95% CI of difference)**	**PREZISTA®/ rtv 600/100 mg b.i.d. + OBR N = 298**	**Lopinavir/ rtv 400/100 mg b.i.d. + OBR N = 297**	**Treatment difference (95% CI of difference)**
HIV-1 RNA < 400 copies/mL[c]	228 (76.5%)	199 (67.0%)	9.5% (2.3; 16.7)[d]	199 (66.8%)	175 (58.9%)	7.9% (0.1; 15.6)[d]
HIV-1 RNA < 50 copies/mL[c]	211 (70.8%)	179 (60.3%)	10.5% (2.9; 18.1)[d]	180 (60.4%)	164 (55.2%)	5.2% (-2.8; 13.1)[d]
mean HIV-1 RNA log change from baseline ($\log_{10}$ copies/mL)[e]	-1.95	-1.72	-0.23[f] (-0.44; -0.02)[d]	–1.71	–1.52	–0.19[f] (–0.40; 0.03)
median CD4+ cell count change from baseline (x 10^6/L)[e]	88	81		81	93	

[a] Data based on analyses at week 48
[b] Data based on analyses at week 96
[c] Imputations according to the TLOVR algorithm
[d] Based on a normal approximation of the difference in % response
[e] NC=F
[f] Difference in means

At 48 weeks non-inferiority in virologic response to the PREZISTA®/ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 400 and < 50 copies/mL, was demonstrated (at the pre-defined 12% non-inferiority margin) for both ITT and OP populations. These results were confirmed in the analysis of data at 96 weeks of treatment in the TITAN trial, with 60.4% of patients in the PREZISTA®/rtv arm having HIV-1 RNA < 50 copies/mL at week 96 compared to 55.2% in the lopinavir/rtv arm [difference: 5.2%, 95% CI (-2.8–13.1)].

POWER 1 and POWER 2 are randomised, controlled Phase 2b trials in adult patients with a high level of PI resistance, consisting of 2 parts: an initial partially blinded, dose-finding part and a second long

term part in which all patients randomised to PREZISTA®/rtv received the recommended dose of 600/100 mg b.i.d.

HIV-1 infected patients who were eligible for these trials had plasma HIV-1 RNA > 1000 copies/mL, had prior treatment with PI(s), NNRTI(s) and NRTI(s), had at least 1 primary PI mutation at screening and were on a stable PI-containing regimen at screening for at least 8 weeks. Randomisation was stratified by the number of PI mutations, screening viral load and the use of enfuvirtide.

Demographics and baseline characteristics were balanced between the PREZISTA®/rtv arm and the comparator arm. In both studies combined, the 131 patients on PREZISTA®/rtv 600/100 mg b.i.d. had a median age of 43 years (range 27-73), 89% were male, 81% white, 10% black and 7% hispanic. The mean baseline plasma HIV-1 RNA was 4.61 $\log^{10}$ copies/mL and the median baseline CD4+ cell count was 153×10^6 cells/L (range $3 – 776 \times 10^6$ cells/L). The median darunavir FC was 4.3. In the PREZISTA®/rtv 600/100 mg b.i.d. arm patients had prior exposure to a mean of 4 PIs, 5 NRTIs and 1 NNRTI versus 4 PIs, 6 NRTIs and 1 NNRTI in the comparator arm. Twenty percent of the patients in the PREZISTA®/rtv arm had prior use of enfuvirtide versus 17% in the comparator arm.

The virologic response, defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 $\log^{10}$ versus baseline, was evaluated in patients receiving PREZISTA®/rtv plus an optimised background regimen (OBR) versus a control arm receiving an investigator-selected PI(s) regimen plus an OBR. The OBR consisted of at least 2 NRTIs with or without enfuvirtide (ENF). Based on resistance testing and prior medical history, selected PIs in the control arm included: lopinavir/ritonavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%. Twenty-three percent of the control patients used dual-boosted PIs. Approximately 47% of all patients used enfuvirtide and 35% of the use was in patients who were ENF-naïve.

POWER 3: additional data on the efficacy of PREZISTA® co-administered with ritonavir 600/100 mg b.i.d. with OBR have been obtained in similar treatment-experienced patients participating in the non-randomised trial TMC114-C215. Entry criteria were the same as and baseline characteristics were comparable to those of POWER 1 and POWER 2.

The table below shows the efficacy data of the 48-week analyses on the recommended 600 mg dose of PREZISTA® co-administered with 100 mg ritonavir b.i.d. from the pooled POWER 1 and POWER 2 trials as well as from the POWER 3 trial.

	POWER 1 and POWER 2 pooled data			POWER 3
Outcome at 48 weeks				
Baseline characteristics				
Mean plasma HIV-1 RNA	4.61 $\log_{10}$ copies/mL (PREZISTA®/ritonavir) 4.49 $\log_{10}$ copies/mL (control)			4.58 $\log_{10}$ copies/mL
Median CD4+ cell count	153×10^6 cells/L (PREZISTA®/ritonavir) 163×10^6 cells/L (control)			120×10^6 cells/L
Outcomes	**PREZISTA®/rtv 600/100 mg b.i.d. N = 131**	**Control N = 124**	**Treatment difference (95% Cl of**	**PREZISTA®/rtv 600/100 mg b.i.d. N = 334**

			difference)	
HIV-1 RNA log_{10} mean change from baseline (log_{10} copies/mL)[a]	-1.69	-0.37	1.32 (1.58; 1.05) [d]	-1.62
CD4+ cell count mean change from baseline ($\times 10^6$/L)[b]	103	17	86 (57; 114) [d]	105
HIV RNA ≥ 1 log_{10} below baseline[c]	81 (61.8%)	20 (16.1%)	45.7% (35.0%; 56.4%)[d]	196 (58.7%)
HIV RNA < 400 copies/mL[c]	72 (55.0%)	18 (14.5%)	40.4% (29.8%; 51.1%) [d]	183 (54.8%)
HIV RNA < 50 copies/mL[c]	59 (45.0%)	14 (11.3%)	33.7% (23.4%; 44.1%) [d]	155 (46.4%)

[a] Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0
[b] Last Observation Carried Forward imputation
[c] Imputations according to the TLOVR algorithm
[d] 95% confidence intervals.

In the pooled POWER 1 and POWER 2 analysis, the proportion of patients in the PREZISTA®/rtv (600/100 mg b.i.d.) arm provided superior decreases in log_{10} viral load from baseline compared to the comparator arm. At week-48, the proportion of patients in the PREZISTA®/rtv arm resulted in 62% of patients with a decrease of at least 1.0 log^{10} in viral load, compared to 16% in the comparator arm. The proportion of patients with HIV-1 RNA < 50 copies/mL was 45% in the PREZISTA®/rtv arm compared to 11% for the comparator arm.

The 48-week efficacy POWER 3 analysis confirmed the viral load reduction and CD4+ increase observed in the POWER 1 and POWER 2 trials. Of the 334 patients included in the week 48 analysis, 59% had a virologic response defined as a decrease of at least 1.0 log_{10} in plasma viral load versus baseline and 46% of the patients reached less than 50 HIVRNA copies/mL.

Analyses of data through 96 weeks of treatment in the POWER trials demonstrated sustained antiretroviral efficacy and immunological benefit. Treatment with PREZISTA®/rtv (600/100 mg b.i.d.) resulted in 56.5% (POWER 1 and 2) and 52.2% (POWER 3) of patients with a decrease of at least 1 log_{10} in HIV-1 RNA from baseline. 38.9% (POWER 1 and 2) and 42.1% (POWER 3) of patients reached an HIV-1 RNA level < 50 copies/mL. At 96 weeks, 49.6% (POWER 1 and 2) and 50.0% (POWER 3) of patients reached less than 400 HIV-1 RNA copies/mL. The mean decrease in HIV-1 RNA level compared to baseline was 1.58 (POWER 1 and 2) and 1.43 (POWER 3) log_{10} copies/mL and a mean increase in CD4+ cell count of 133 $\times 10^6$ cells/L (POWER 1 and 2) and 103 $\times 10^6$ cells/L (POWER 3) was observed. Out of the 206 patients who responded with complete viral suppression (< 50 copies/mL) at week 48, 177 patients (86% of the responders at week 48) remained responders at week 96.

In vivo selection of viral resistance during PREZISTA®/rtv therapy

In the 192 week analysis of the ARTEMIS trial, the number of virologic failures was lower in the group of patients receiving PREZISTA®/rtv 800/100 mg q.d. than in patients receiving lopinavir/ritonavir 800/200 mg per day (16.0% vs. 20.5%, respectively). In the virologic failures of the PREZISTA®/rtv

group, 4 patients with developing PI RAMs were identified. In the virologic failures of the lopinavir/rtv group, 9 patients with developing PI RAMs were identified. None of the developing mutations in the PREZISTA®/rtv group or in the lopinavir/rtv group were primary (i.e. major) PI mutations. In 4 virologic failures of the PREZISTA®/rtv group and 7 virologic failures of the lopinavir/rtv group, a maximum of 2 developing NRTI RAMs were identified. The development of the NRTI RAM at position 184 (n = 9) was associated with a decreased susceptibility to FTC included in the background regimen.

In the 48 week analysis of the ODIN trial the number of virologic failures was comparable in the PREZISTA®/rtv 800/100 mg q.d. group and the PREZISTA®/rtv 600/100 mg b.i.d. group (22.1% vs. 18.2%, respectively). In the virologic failures in the PREZISTA®/rtv 800/100 mg q.d. group 7 subjects (12%) with developing PI RAMs were identified, compared to 4 subjects (10%) in the PREZISTA®/rtv 600/100 mg b.i.d. group. One subject in the PREZISTA®/rtv 800/100 mg q.d. group developed primary (i.e. major) PI mutations, which included 3 DRV RAMs, resulting in decreased susceptibility to darunavir. All the virologic failures from the PREZISTA®/rtv 600/100 mg b.i.d. group retained susceptibility to darunavir. Four (6.7%) and 3 (7.1%) virologic failures developed 1 or 2 NRTI RAMs in the PREZISTA®/rtv 800/100 mg q.d. and the PREZISTA®/rtv 600/100 mg b.i.d. groups, respectively. In 3 and 2 of these virologic failures in the PREZISTA®/rtv 800/100 mg q.d. and the PREZISTA®/rtv 600/100 mg b.i.d. groups, respectively, the development of these NRTI RAMs was associated with a decreased susceptibility to a NRTI included in the treatment regimen.

In a pooled analysis of the POWER and DUET trials, the identified amino acid substitutions that developed on PREZISTA®/rtv 600/100 mg b.i.d. in ≥ 20% of the isolates from patients who experienced virological failure by rebound were V32I, I54L, and L89V. Amino acid substitutions that developed in 10 to 20% of the isolates were V11I, I13V, L33F, I50V, and F53L.

In vivo cross-resistance with other HIV protease inhibitors

Of the viruses isolated from subjects receiving PREZISTA®/rtv 800/100 mg q.d. experiencing virologic failure in the ODIN trial, 98% remained susceptible to darunavir after treatment. In the same group of subjects, 96% to 100% that were susceptible at baseline to amprenavir, atazanavir, indinavir, lopinavir, saquinavir or tipranavir remained susceptible to these protease inhibitors after treatment. In the virologic failures receiving PREZISTA®/rtv 600/100 mg b.i.d. no cross-resistance with other PIs was observed.

Of the viruses isolated from patients experiencing virologic failure by rebound from the PREZISTA®/rtv 600/100 mg b.i.d. group of the POWER and DUET trials, 85% that were susceptible to Darunavir at baseline developed decreased susceptibility to darunavir during treatment. In the same group of patients, 71% of viruses that were susceptible to tipranavir at baseline remained susceptible after treatment. In the POWER trials, patients with resistance to tipranavir (FC > 3) at baseline showed a mean change in viral load at week-24 of -1.38 $\log_{10}$. Cross-resistance with the other PIs could not be studied in the POWER and DUET trials, since most of the baseline viruses were already resistant to these PIs. Patients with no susceptible PI at baseline (excluding tipranavir) showed a mean change in viral load at week-24 of -1.57 $\log^{10}$.

Baseline genotype or phenotype and virologic outcome

In a pooled analysis of the 600/100 b.i.d groups of the POWER and DUET trials, the presence at baseline of three or more of the mutations V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V was associated with a decreased virologic response to PREZISTA®/rtv.

Response (HIV-1 RNA, < 50 Copies/mL at Week 24) to PREZISTA®/rtv 600/100 mg b.i.d. by Baseline Genotype* and by Use of Enfuvirtide: As-Treated Analysis (POWER and DUET Trials)

Number of mutations at baseline*	**All % (n/N)**	**No/non-naïve use of ENF % (n/N)**	**Naïve use of ENF % (n/N)**
All ranges	45% (455/1014)	39% (290/741)	60% (165/273)
0-2	54% (359/660)	50% (238/477)	66% (121/183)
3	39% (67/172)	29% (35/120)	62% (32/52)
≥ 4	12% (20/171)	7% (10/135)	28% (10/36)

* Number of mutations from the list of mutations associated with a diminished response to PREZISTA®/rtv (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V)

Baseline darunavir phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome.

Response rates assessed by baseline darunavir phenotype are shown in the table below. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to darunavir.

Response (HIV-1 RNA <50 Copies/mL at Week 24) to PREZISTA®/rtv 600/100 mg b.i.d. by Baseline Darunavir Phenotype and by Use of Enfuvirtide: As-Treated Analysis (POWER AND DUET Trials) :

Baseline darunavir phenotype	**All % (n/N)**	**No/non-naive use of ENF % (n/N)**	**Naive use of ENF % (n/N)**
All ranges	45% (455/1014)	39% (290/741)	60% (165/273)
≤ 10	55% (364/659)	51% (244/477)	66% (120/182)
10-40	29% (59/203)	17% (25/147)	61% (34/56)
> 40	8% (9/118)	5% (5/94)	17% (4/24)

In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the treatment history and to resistance testing results where available.

Description of the clinical study in pediatric patients

DELPHI is an open-label, Phase 2 trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of PREZISTA®/rtv in 80 antiretroviral treatment-experienced HIV-1 infected pediatric patients aged 6 to < 18 years and weighing at least 20 kg. At week 24, the virologic response rate was evaluated in pediatric patients receiving PREZISTA®/rtv in combination with other antiretroviral agents (see Table "Recommended dose for treatment-experienced pediatric patients (6 to < 18 years of age) for PREZISTA® tablets and ritonavir"). Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 $\log_{10}$ versus baseline. The mean baseline plasma HIV-1 RNA was 4.64 $\log_{10}$ copies/mL, and the median baseline CD4+ cell count was 330×10^6 cells/L (range: 6 - 1505×10^6 cells/L).

In the study, patients who were at risk of discontinuing therapy due to intolerance of ritonavir oral solution (e.g. taste aversion) were allowed to switch to the capsule formulation. Of the 44 patients taking ritonavir oral solution, 23 switched to the 100 mg capsule formulation and exceeded the weight-based ritonavir dose without changes in observed safety.

At week 24, 73.8% of the pediatric patients had at least 1.0 $\log_{10}$ HIV-1 RNA decrease from baseline. The proportion of pediatric patients reaching undetectable viral load (< 50 HIV-1 RNA copies/mL) was 50.0%, and the proportion of pediatric patients with < 400 HIV-1 RNA copies/mL was 63.8%. The mean change in plasma HIV-1 RNA from baseline was -1.98 $\log_{10}$ copies/mL. The mean CD4+ cell count increase from baseline was 117×10^6 cells/L.

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 metabolised by the hepatic CYP system and almost exclusively by isozyme CYP3A. 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 63,670 (33,527; 115,360) ng.h/mL and 3,888 (1,836; 7,821) ng.h/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 to 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 metabolised 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

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 tables below). 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.

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}

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_{12h} 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.

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

Colloidal silicon dioxide
Crospovidone
Magnesium stearate
Microcrystalline cellulose
Hypromellose (For PREZISTA® 800-mg only)

Tablet film-coat

Poly(vinyl alcohol) – partially hydrolyzed
PEG 3350
Titanium dioxide
Talc
FD&C Yellow #6 (For PREZISTA® 400-mg and 600-mg tablet only)
Iron Oxide Red (For PREZISTA® 800-mg only)

Incompatibilities

(None known)

Shelf Life

Please refer to Outer Carton

Storage Conditions

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

Nature and Contents of Container

PREZISTA® film-coated tablets are provided in high density polyethylene (HDPE) plastic bottles fitted with polypropylene (PP) child resistant closures.
PREZISTA® 75 mg: 480 tablets
PREZISTA® 150 mg: 240 tablets
PREZISTA® 400 mg: 60 tablets
PREZISTA® 600 mg: 60 tablets
PREZISTA® 800 mg: 30 tablets

Instructions for Use and Handling

The plastic bottle comes with a child resistant cap and should be opened as follows:

- Push the plastic screw cap down while turning it counter clockwise.
- Remove the unscrewed cap.

PRODUCT REGISTRANT

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BATCH RELEASER

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