AUSTRALIAN PRODUCT INFORMATION

PREZISTA®

DARUNAVIR

FILM-COATED TABLET

1. NAME OF THE MEDICINE

Darunavir

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PREZISTA darunavir is available as 75 mg, 400 mg, 600 mg and 800 mg film-coated tablets (the 75 mg and 400 mg tablets are not currently marketed). Each film-coated tablet contains 75 mg, 400 mg, 600 mg or 800 mg of darunavir, as 81.31 mg, 433.64 mg, 650.46 mg or 867.28 mg of darunavir ethanolate, respectively.

For a full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

PREZISTA 75 mg film-coated tablets are white caplet-shaped tablets, debossed with 75 on one side and TMC on the other side (currently not marketed).

PREZISTA 400 mg film-coated tablets are light orange oval shaped tablets, debossed with 400MG on one side and TMC on the other side (currently not marketed).

PREZISTA 600 mg film-coated tablets are orange oval shaped tablets, debossed with 600MG on one side and TMC on the other side.

PREZISTA 800 mg film-coated tablets are dark red oval-shaped tablets, debossed with 800 on one side and T on the other side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Adult patients

PREZISTA (with low dose ritonavir as a pharmacokinetic enhancer) is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adult patients.

Paediatric patients

PREZISTA (with low dose ritonavir as a pharmacokinetic enhancer) is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in treatment-experienced paediatric patients aged 6 years and older, weighing at least 20 kg.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

Adults:

For antiretroviral treatment-experienced patients, HIV-1 genotype testing is recommended.

Once Daily Dose

The recommended dose of PREZISTA is 800 mg once daily with ritonavir 100 mg once daily taken with food. The once daily dose regimen is recommended for the following patients:

- Antiretroviral treatment-naive patients
- Antiretroviral treatment-experienced patients with no darunavir resistance associated mutations* and who have plasma HIV-1 RNA <100,000 copies/mL
- Antiretroviral treatment-experienced but HIV protease inhibitor-naive patients for whom HIV-1 genotype testing is unavailable

Twice Daily Dose

The recommended dose of PREZISTA is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. The twice daily dose regimen is recommended for the following patients:

- Antiretroviral treatment-experienced patients with at least one darunavir resistance associated mutation*
- HIV protease inhibitor treatment-experienced patients for whom HIV-1 genotype testing is unavailable
- Antiretroviral treatment-experienced patients with plasma HIV-1 RNA ≥100,000 copies/mL

* Darunavir resistance associated mutations: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V

Paediatric patients:

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

The recommended dose of PREZISTA/ ritonavir (rtv) for paediatric patients (6 to < 18 years of age and weighing at least 20 kg) is based on body weight (see Table 1 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.

Table 1: Recommended dose for treatment-experienced paediatric patients (6 to < 18 years of age) for PREZISTA tablets and ritonavir (see section 5.1 Pharmacodynamic Properties, Clinical Trials)

Body weight (kg)	Dose
≥ 20 kg–< 30 kg	375 mg PREZISTA/50 mg ritonavir b.i.d.
≥ 30 kg–< 40 kg	450 mg PREZISTA/60 mg ritonavir b.i.d.
≥ 40 kg	600 mg PREZISTA/100 mg ritonavir b.i.d.

Antiretroviral treatment-experienced children less than 6 years of age and antiretroviral treatment naïve paediatric 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 paediatric patients have not been established.

PREZISTA/rtv should not be used in children below 3 years of age (see section 4.4 Special Warnings and Precautions for Use).

Method of 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/ritonavir.

PREZISTA with ritonavir should be taken with food. The type of food does not affect the exposure to darunavir.

After therapy with PREZISTA has been initiated patients should be advised not to alter the dosage or discontinue therapy without consulting their physician.

Do not halve tablets. Dose equivalence when tablets are divided has not been established.

For combination use with cobicistat and darunavir please refer to the PREZCOBIX (darunavir/ cobicistat) or TYBOST (cobicistat) Product Information.

Special populations

Pregnancy and postpartum:

No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. Caution should be used in patients with concomitant medications which may further decrease darunavir exposure (see sections 5.2 Pharmacokinetic Properties and 4.6 Fertility, Pregnancy and Lactation).

Treatment with darunavir/cobicistat during pregnancy results in low darunavir exposure (see sections 5.2 Pharmacokinetic Properties). Therefore, therapy with PREZISTA/cobicistat should not be initiated during pregnancy, and women who become pregnant during therapy with PREZISTA/cobicistat should be switched to an alternative regimen (see section 4.6 Fertility, Pregnancy and Lactation). PREZISTA/ritonavir may be considered as an alternative.

Hepatic impairment:

No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however PREZISTA should be used with caution in these patients due to increased darunavir exposure and adverse events. No pharmacokinetic data are available in patients with severe hepatic impairment. Therefore, PREZISTA should not be used in patients with severe hepatic impairment (see section 4.4 Special Warnings and Precautions for Use).

Renal impairment:

No dose adjustment is required in patients with renal impairment (see section 4.4 Special Warnings and Precautions for Use).

4.3. CONTRAINDICATIONS

Hypersensitivity to darunavir or to any of the excipients.

Darunavir, ritonavir and cobicistat are inhibitors of the CYP3A isoform. PREZISTA/rtv and PREZISTA/cobicistat 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 astemizole, apixaban, alfuzosin, sildenafil (when used for treatment of pulmonary arterial hypertension), terfenadine, midazolam (oral), triazolam, cisapride, colchicine (in patients with renal and/or hepatic impairment), dapoxetine, dronedarone, elbasvir/grazoprevir, pimozide, ranolazine, the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine and methylergonovine), lomitapide, ivabradine, lovastatin, lurasidone, naloxegol, simvastatin and antiarrhythmic drugs (e.g. amiodarone, bepridil, flecainide, systemic lidocaine, quinidine) (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

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

Due to the need for co-administration of PREZISTA with low dose ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications and precautions.

In addition, potent CYP3A inducers such as carbamazepine, phenobarbital and phenytoin are also contraindicated for use with PREZISTA/cobicistat (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions). For further information on combination use with darunavir and cobicistat please refer to the PREZCOBIX (darunavir/cobicistat) or TYBOST (cobicistat) Product Information.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

PREZISTA (darunavir) must be co-administered with ritonavir and food to exert its therapeutic effect (see section 4.2 Dose and Method of Administration). Failure to correctly administer PREZISTA with ritonavir and food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired therapeutic effect.

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.

Hepatotoxicity

Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/rtv. During the clinical development program (N=3063), hepatitis has been 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.

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; and during post-marketing experience toxic epidermal necrolysis, (Drug reaction with eosinophilia and systemic symptoms) (DRESS) and acute generalised 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 section 4.8 Adverse Effects (Undesirable Effects)). 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 patients receiving regimens containing PREZISTA/rtv + raltegravir compared to patients receiving PREZISTA/rtv without raltegravir or raltegravir without PREZISTA/rtv.

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.

Haemophiliac patients

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis in patients with haemophilia type A and B treated with HIV 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. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Metabolic disorders

Diabetes mellitus/hyperglycaemia

New onset diabetes mellitus, hyperglycaemia, or exacerbation of existing diabetes mellitus has been reported in patients receiving antiretroviral therapy, including HIV PIs. In some of these patients the hyperglycaemia 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 hyperglycaemia.

Consideration should be given to measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8 Adverse Effects (Undesirable Effects)).

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 section 4.8 Adverse Effects (Undesirable Effects)).

Interactions with medicinal products

See section 4.3 Contraindications and section 4.5 Interactions with Other Medicines and Other Forms of Interactions.

Darunavir, ritonavir and cobicistat are metabolized by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir, ritonavir and cobicistat resulting in lower plasma concentrations of darunavir, ritonavir and cobicistat.

Darunavir boosted with cobicistat is more sensitive to CYP3A induction than darunavir boosted with ritonavir. (see section 4.3 Contraindications and section 4.5 Interactions with Other Medicines and Other Forms of Interactions.) Co-administration with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir, ritonavir and cobicistat and may result in increased plasma concentrations of darunavir, ritonavir and cobicistat (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Co-administration of PREZISTA/cobicistat or 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 section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Use in hepatic impairment

The safety and efficacy of PREZISTA have not been established in patients with severe hepatic impairment. Therefore, PREZISTA should not be used in patients with severe hepatic impairment. Due to an increase in unbound darunavir plasma concentrations, PREZISTA

should be used with caution in patients with mild or moderate hepatic impairment (see sections 5.2 Pharmacokinetic Properties and 4.2 Dose and Method of Administration).

Use in renal impairment

There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease. 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 haemodialysis or peritoneal dialysis (see sections 5.2 Pharmacokinetic Properties and 4.2 Dose and Method of Administration).

Use in the 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 section 5.2 Pharmacokinetic Properties).

Paediatric use

PREZISTA/rtv should not be used in children below 3 years of age in view of toxicity observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1,000 mg/kg) up to days 23 to 26 of age (see section 4.6 Fertility, Pregnancy and Lactation).

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

Effects on laboratory tests

No data available.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The interaction profile of PREZISTA depends on whether ritonavir or cobicistat is used as a pharmacokinetic enhancer. PREZISTA may therefore have different recommendations for concomitant medications depending on whether PREZISTA is boosted with ritonavir or cobicistat. No interaction studies have been performed with PREZISTA/cobicistat.

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

Darunavir, when used in combination with ritonavir or cobicistat, is an inhibitor of CYP3A, CYP2D6 and P-gp. Co-administration with medicinal products primarily metabolized by CYP3A, CYP2D6, or transported by P-gp may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect and adverse events (see Tables 2 and 3). Co-administration of PREZISTA/cobicistat or 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, ritonavir and cobicistat are metabolized by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir, ritonavir and cobicistat resulting in lower plasma concentrations of darunavir, ritonavir and cobicistat.

Darunavir boosted with cobicistat is more sensitive to CYP3A induction than darunavir boosted with ritonavir. Co-administration with other medicinal products that inhibit CYP3A may decrease

the clearance of darunavir, ritonavir and cobicistat and may result in increased plasma concentrations of darunavir, ritonavir and cobicistat.

For further information on combination use with cobicistat and darunavir please refer to the PREZCOBIX (darunavir/ cobicistat) or TYBOST (cobicistat) Product Information.

Drugs that are contraindicated and not recommended for concomitant administration with PREZISTA/rtv are included in Table 2. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Drug-drug interactions presented by drug class including drug name examples are presented below. The list of examples of drug-drug interactions in Tables 2 and 3 are not comprehensive and therefore the Product Information 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.

Table 2: Drugs that should not be concomitantly administered with PREZISTA/rtv or PREZISTA/cobicistat

Drug class: drug name examples	Clinical comment
Alpha blocker: alfuzosin	Exposure to alfuzosin may be increased when co-administered with PREZISTA/rtv or PREZISTA/cobicistat. Concomitant use of PREZISTA/rtv or PREZISTA/cobicistat with alfuzosin is contraindicated.
Antianginals: ranolazine, ivabradine	Exposure to ranolazine may be increased (CYP3A inhibition) when co-administered with PREZISTA/rtv or PREZISTA/cobicistat. Concomitant use of PREZISTA/rtv or PREZISTA/cobicistat with ranolazine is contraindicated. Concomitant use of PREZISTA/rtv or PREZISTA/cobicistat with ivabradine is contraindicated.

Drug class: drug name examples	Clinical comment
Anticoagulants: Direct Oral Anticoagulants (DOACs): apixaban, dabigatran etexilate, edoxaban, rivaroxaban	DOACs are primarily metabolized by CYP3A4 and/or transported by P-gp. Co-administration with PREZISTA/rtv or PREZISTA/cobicistat 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 rivaroxaban, is not recommended with PREZISTA/rtv or PREZISTA/cobicistat. Co-administration of apixaban with PREZISTA/rtv or PREZISTA/cobicistat is contraindicated. The results of a drug-drug interaction study between darunavir 800 mg, ritonavir 100 mg and dabigatran etexilate 150 mg in healthy participants showed a 1.7-fold increase in dabigatran plasma AUC after single dosing of darunavir and ritonavir, and a 1.2-fold increase in dabigatran plasma AUC after repeated dosing of darunavir and ritonavir. The study demonstrated a 1.6-fold increase in dabigatran plasma Cmax after single dosing of darunavir and ritonavir, and a 1.2-fold increase in dabigatran plasma Cmax after repeated dosing of darunavir and ritonavir. Clinical monitoring and/or dose reduction of the DOAC should be considered when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with PREZISTA/rtv. The results of a drug-drug interaction study between darunavir/cobicistat 800/150 mg and dabigatran etexilate 150 mg in healthy participants showed a 2.6-fold increase in dabigatran plasma AUC after single dosing of darunavir/cobicistat, and a 1.9-fold increase in dabigatran plasma AUC after repeated dosing of darunavir/cobicistat. The study demonstrated a 2.6-fold increase in dabigatran plasma Cmax after single dosing of darunavir/cobicistat and a 2.0-fold increase in dabigatran plasma Cmax after repeated dosing of darunavir/cobicistat. Clinical monitoring is required when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with PREZISTA/cobicistat. A dose reduction of the DOAC may be needed.

Drug class: drug name examples	Clinical comment
Antiarrhythmics: amiodarone, bepridil, disopyramide, dronedarone, flecainide, mexiletine, propafenone, lidocaine (systemic), quinidine	Concentrations of these antiarrhythmics may be increased when co-administered with PREZISTA/rtv or PREZISTA/cobicistat. Concomitant use of these antiarrhythmics and PREZISTA/rtv or PREZISTA/cobicistat is contraindicated.
Antihistamines: astemizole, terfenadine	Exposure to these antihistamines may be increased when co-administered with PREZISTA/rtv or PREZISTA/cobicistat. Concomitant use of PREZISTA/rtv or PREZISTA/cobicistat with astemizole and terfenadine is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials: rifampicin, rifapentine	Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with rifampicin and rifapentine may decrease darunavir concentrations (induction of CYP3A), which may result in loss of therapeutic effect of PREZISTA. Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with rifampicin is contraindicated. Co- administration of PREZISTA/rtv or PREZISTA/cobicistat with rifapentine is not recommended.
Antiplatelets: clopidogrel	Co-administration of PREZISTA/cobicistat or PREZISTA/rtv with clopidogrel is expected to decrease clopidogrel active metabolite plasma concentration, which may reduce the antiplatelet activity of clopidogrel. Coadministration of PREZISTA/cobicistat or PREZISTA/rtv with clopidogrel is not recommended.
Ergot alkaloids: dihydroergotamine, ergonovine, ergotamine, methylergonovine	Contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues. Exposure to the ergot alkaloids may be increased when co-administered with PREZISTA/rtv or PREZISTA/cobicistat. Concomitant use of PREZISTA/rtv or PREZISTA/cobicistat with ergot alkaloids is contraindicated.
Gastrointestinal motility agent: cisapride	Exposure to cisapride may be increased when co -administered with PREZISTA/rtv or PREZISTA/cobicistat. Concomitant use of PREZISTA/rtv or PREZISTA/cobicistat with cisapride is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

Drug class: drug name examples	Clinical comment
Gout agents: colchicine	Concomitant use of colchicine and PREZISTA/rtv or PREZISTA/cobicistat 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 or PREZISTA/cobicistat, 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 or PREZISTA/cobicistat, 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 or PREZISTA/cobicistat, the maximum dose of colchicine is 0.6 mg q.d. (may be given as 0.3 mg b.i.d.). Patients should be monitored for clinical symptoms of colchicine toxicity. Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with colchicine in patients with renal or hepatic impairment is contraindicated.
Herbal products: St. John's wort (*Hypericum perforatum*)	PREZISTA/rtv or PREZISTA/cobicistat should not be used concomitantly with products containing St. John's wort (*Hypericum perforatum*) because co-administration may cause significant decreases in darunavir or cobicistat plasma concentrations (induction of CYP3A). This may result in loss of therapeutic effect to PREZISTA. Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with products containing St John's wort (Hypericum perforatum) is contraindicated.
Antipsychotic/neuroleptic: pimozide, lurasidone	Concomitant use of pimozide and PREZISTA/rtv or PREZISTA/cobicistat may increase the exposure to pimozide (inhibition of CYP3A and CYP2D6). Concomitant use of PREZISTA/rtv or PREZISTA/cobicistat with pimozide is contraindicated due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias. Concomitant use of lurasidone and PREZISTA/rtv or PREZISTA/cobicistat may increase the exposure to lurasidone (inhibition of CYP3A4). Concomitant use of PREZISTA/rtv or PREZISTA/cobicistat with lurasidone is contraindicated.
Sedative/hypnotics: midazolam, triazolam	Contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with oral midazolam or triazolam is contraindicated.
HIV-protease inhibitor: lopinavir/ritonavir	Results of interaction trials with PREZISTA with or without ritonavir and lopinavir/ritonavir (1200 mg PREZISTA 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%. This may significantly affect the therapeutic effect of PREZISTA in HIV-1 infected patients. The appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer PREZISTA/rtv with lopinavir/ritonavir.

Drug class: drug name examples	Clinical comment
HIV-protease inhibitor: saquinavir	An interaction trial between darunavir (400 mg b.i.d.), saquinavir (1000 mg b.i.d.), and low-dose ritonavir (100 mg b.i.d.) demonstrated that darunavir exposure was decreased by 26% when co-administered with saquinavir and ritonavir; saquinavir exposure was not affected when administered concomitantly with darunavir/ritonavir. It is not recommended to co-administer saquinavir and PREZISTA, with or without low-dose ritonavir.
Anticonvulsants: phenobarbital, phenytoin, carbamazepine	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. Co-administration of phenobarbital and phenytoin with PREZISTA/cobicistat may decrease cobicistat plasma concentrations and that of darunavir, which may result in loss of therapeutic effect and development of resistance. Co-administration of these drugs with PREZISTA/cobicistat is contraindicated. Co-administration of carbamazepine with PREZISTA/cobicistat may decrease cobicistat plasma concentrations and that of darunavir, which may result in loss of therapeutic effect and development of resistance. Co-administration of carbamazepine with PREZISTA/cobicistat is contraindicated. No dose adjustment for PREZISTA/rtv is recommended with co-administration of carbamazepine and PREZISTA/rtv, however the carbamazepine dose may need to be reduced by 25% to 50% (For further information, see Table 3).
HMG-CoA reductase inhibitors: atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A metabolism, are expected to have markedly increased plasma concentrations when co-administered with PREZISTA/rtv or PREZISTA/cobicistat. Increased concentrations of HMGCoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of PREZISTA/rtv or PREZISTA/cobicistat with lovastatin or simvastatin is contraindicated. For information regarding atorvastatin, rosuvastatin and pravastatin, see Table 3.
Other lipid modifying agents: lomitapide	PREZISTA/rtv or PREZISTA/cobicistat is expected to increase the exposure of lomitapide when co-administered. Co-administration is contraindicated.
PDE-5 inhibitors for pulmonary arterial hypertension: sildenafil, tadalafil	A safe and effective dose of sildenafil 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) when co-administered with PREZISTA/rtv or PREZISTA/cobicistat. Therefore, co-administration of PREZISTA/rtv or PREZISTA/cobicistat with sildenafil when used for pulmonary arterial hypertension is contraindicated. For information regarding tadalafil, see Table 3.

Drug class: drug name examples	Clinical comment
Hepatitis C Virus (HCV) direct-acting antivirals (NS3-4A inhibitors): elbasvir/grazoprevir, glecaprevir/pibrentasvir	Concomitant use of elbasvir/grazoprevir and PREZISTA/rtv or PREZISTA/cobicistat may increase the exposure to grazoprevir (inhibition of OATP1B and CYP3A). Concomitant use of PREZISTA/rtv or PREZISTA/cobicistat with elbasvir/grazoprevir is contraindicated. Concomitant use of glecaprevir/pibrentasvir and PREZISTA/rtv or PREZISTA/cobicistat may increase the exposure to glecaprevir and pibrentasvir (inhibition of P-gp, BCRP and/or OATP1B1/3). Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with glecaprevir/pibrentasvir is not recommended.
Opioid antagonist: naloxegol	Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with naloxegol is contraindicated.
Treatment of premature ejaculation: dapoxetine	Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with dapoxetine is contraindicated.

Table 3: Established and other potentially significant drug interactions: Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interactions

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
HIV-Antiviral agents: Integrase strand transfer inhibitors		
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 or PREZISTA/cobicistat and raltegravir can be used without dose adjustments.
elvitegravir		When PREZISTA/ritonavir (600/100 mg b.i.d) is used in combination with elvitegravir, the dose of elvitegravir should be 150 mg daily. The pharmacokinetics and dosing recommendations for other doses of darunavir or with elvitegravir/cobicistat have not been established. Therefore, co-administration of PREZISTA/ritonavir in doses other than 600/100 mg b.i.d and elvitegravir is not recommended. Co-administration of PREZISTA/ritonavir and elvitegravir in the presence of cobicistat is not recommended.
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 or PREZISTA/cobicistat co-administered with dolutegravir can be used without dose adjustment.
HIV-Antiviral agents: Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
delavirdine	↑ darunavir ↑ delavirdine	Co-administration of PREZISTA/ritonavir or PREZISTA/cobicistat and delavirdine may increase darunavir, cobicistat and delavirdine concentrations (inhibition of CYP3A). The appropriate doses of PREZISTA/ritonavir or PREZISTA/cobicistat and delavirdine have not been established. The combination of PREZISTA/ritonavir or PREZISTA/cobicistat and delavirdine is not recommended.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
efavirenz	↓ darunavir ↑ efavirenz	An interaction trial between darunavir (300 mg twice daily [b.i.d.]), low-dose ritonavir (100 mg b.i.d.), and efavirenz (600 mg once daily) has been performed. In the presence of efavirenz, a decrease of 13% for darunavir exposure was observed. Exposure to efavirenz increased by 21% when administered in combination with darunavir and ritonavir. Since this difference is not considered to be clinically relevant, the combination of PREZISTA/rtv and efavirenz can be used without dose adjustments. Co-administration of PREZISTA/cobicistat with efavirenz may decrease darunavir and/or cobicistat concentrations which may result in loss of therapeutic effect and development of resistance. Co-administration with PREZISTA/cobicistat with efavirenz is not recommended.
etravirine	↔ darunavir ↓ etravirine	A pharmacokinetic interaction study between darunavir/rtv and etravirine in healthy patients indicated that etravirine has no significant effect on the pharmacokinetics of darunavir. In this study, when 100 mg b.i.d. of etravirine was co-administered with 600/100 mg b.i.d. darunavir/rtv a 37% decrease in etravirine plasma levels was observed. However, when 200 mg b.i.d. etravirine was co-administered, exposure was increased by 80% compared with etravirine alone. Based on the results of this study, a dose adjustment for darunavir is not considered necessary when co-administered with 200 mg etravirine and 100 mg rtv. Co-administration with PREZISTA/cobicistat with etravirine may decrease darunavir and/or cobicistat concentrations which may result in loss of therapeutic effect and development of resistance. Co-administration with PREZISTA/cobicistat is not recommended.
nevirapine	↔ darunavir ↑ nevirapine	The results of an interaction trial with darunavir (400 mg b.i.d.), low-dose ritonavir (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 darunavir and ritonavir. Since this difference is not considered to be clinically relevant, the combination of PREZISTA/rtv and nevirapine can be used without dose adjustments. Co-administration of PREZISTA/cobicistat with nevirapine may decrease darunavir and/or cobicistat concentrations which may result in loss of therapeutic effect and development of resistance. Nevirapine concentrations may be increased when co-administered with PREZISTA/cobicistat. Co-administration of PREZISTA/cobicistat with nevirapine is not recommended.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
rilpivirine	↑ rilpivirine ↔ darunavir	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 the difference is not considered to be clinically relevant, the combination of PREZISTA/rtv or PREZISTA/cobicistat and rilpivirine can be used without dose adjustment.
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine	↔ didanosine	PREZISTA/rtv (600/100 mg b.i.d) did not significantly affect didanosine exposure. The combination of PREZISTA co-administered with 100 mg ritonavir or PREZISTA/cobicistat and didanosine can be used without dose adjustments. It is recommended that didanosine be administered on an empty stomach. Didanosine should be administered one hour before or two hours after PREZISTA/rtv or PREZISTA/cobicistat (which are administered with food).
tenofovir disoproxil fumarate	↔ darunavir ↑ tenofovir	The results of an interaction trial between darunavir (300 mg b.i.d.), low-dose ritonavir (100 mg b.i.d.), and tenofovir disoproxil fumarate (300 mg once daily) demonstrated that darunavir exposure was not significantly affected when administered concomitantly with tenofovir disoproxil fumarate. Exposure to tenofovir disoproxil fumarate increased by 22% when administered in combination with darunavir and ritonavir. This finding is not considered to be clinically relevant. There was no change in the urinary excretion of tenofovir disoproxil fumarate or darunavir during co administration. The combination of PREZISTA/rtv or PREZISTA/cobicistat and tenofovir disoproxil fumarate can be used without dose adjustments.
HIV-Antiviral agents: HIV Protease Inhibitors (HIV PIs)		
ritonavir	↑ darunavir	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 darunavir 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 sections 5.2 Pharmacokinetic Properties and 4.4 Special Warnings and Precautions for Use).

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
atazanavir	↔ darunavir ↔ atazanavir	An interaction trial between darunavir (400 mg b.i.d.), low-dose ritonavir (100 mg b.i.d.), and atazanavir (300 mg once daily) demonstrated that exposure to darunavir and atazanavir was not significantly affected when co-administered. Atazanavir can be co-administered with PREZISTA/rtv.
Indinavir	↑ darunavir ↑ indinavir	An interaction trial between darunavir (400 mg b.i.d.), low-dose ritonavir (100 mg b.i.d.), and indinavir (800 mg b.i.d.) demonstrated that darunavir exposure was increased by 24% when co-administered with indinavir and ritonavir; indinavir exposure was increased by 23% when administered concomitantly with darunavir/ritonavir. 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.
emtricitabine/tenofovir alafenamide	↔ tenofovir alafenamide ↑ tenofovir	Tenofovir exposure is increased when PREZISTA/rtv is used in combination with emtricitabine/tenofovir alafenamide. The recommended dose of emtricitabine/tenofovir alafenamide when used in combination with PREZISTA/rtv is 200/10 mg daily.
HIV-Antiviral agents: CCR5 antagonist		
maraviroc	↑ maraviroc ↔ darunavir	When used in combination with PREZISTA/rtv or PREZISTA/cobicistat, 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 Agents		
Analgesics: fentanyl, oxycodone, tramadol	↑ fentanyl ↑ oxycodone ↑ tramadol	Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with fentanyl, oxycodone or tramadol may increase concentrations of the analgesic with potential to cause respiratory depression. Clinical monitoring is recommended when co-administering PREZISTA/rtv with these analgesics. Patients should be warned of the increased risk associated with use or abuse of these products while on treatment with PREZISTA/rtv or PREZISTA/cobicistat.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
Antiarrhythmic: digoxin	↑ 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). The pharmacokinetics of digoxin were significantly influenced by PREZISTA/rtv. Therefore, it is recommended that the lowest possible dose of digoxin should initially be prescribed in case digoxin is given to patients on PREZISTA/rtv or PREZISTA/cobicistat therapy. Given that digoxin has a narrow therapeutic index, the digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject.
Anticoagulants: warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations may be affected when co-administered with PREZISTA/rtv or PREZISTA/cobicistat. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/rtv or PREZISTA/cobicistat.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
Anticonvulsant: carbamazepine	↑ carbamazepine ↔ darunavir	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. Co-administration of carbamazepine with PREZISTA/cobicistat may decrease cobicistat plasma concentrations and that of darunavir, which may result in loss of therapeutic effect and development of resistance. Co-administration of carbamazepine with PREZISTA/cobicistat is contraindicated (Refer also to Table 2).
clonazepam	↑ clonazepam	Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with clonazepam may increase concentrations of clonzepam. Clinical monitoring is recommended when co-administering PREZISTA/rtv or PREZISTA/cobicistat with clonazepam.
oxcarbazepine	↓ darunavir ↓ cobicistat	Co-administration of PREZISTA/cobicistat with oxcarbazepine may decrease darunavir and/or cobicistat concentrations, which may result in loss of therapeutic effect and development of resistance. Co-administration of PREZISTA/cobicistat with oxcarbazepine is not recommended. Alternative anticonvulsants should be considered. No dose adjustment is needed for PREZISTA/rtv and oxcarbazepine.
Anti-infective: clarithromycin	↑ clarithromycin	An interaction trial between darunavir (400 mg b.i.d.), low-dose ritonavir (100 mg b.i.d.), and clarithromycin (500 mg b.i.d.) demonstrated an increase in exposure to clarithromycin by 57%, while exposure to darunavir was not affected. PREZISTA/rtv or PREZISTA/cobicistat 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.
Anti-emetics: domperidone	↑ domperidone	Use with caution: monitor for domperidone adverse reactions.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
Antifungals: clotrimazole, fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole	↑ clotrimazole ↑ fluconazole ↑ ketoconazole ↑ posaconazole ↑ darunavir ↑ isavuconazole ↑ itraconazole (not studied) ↓ voriconazole (not studied)	Clotrimazole, fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole are moderate to potent inhibitors of CYP3A and/or some are substrates of CYP3A. Concomitant systemic use of these antifungals and PREZISTA/rtv or PREZISTA/cobicistat may increase plasma concentrations of darunavir or cobicistat. Simultaneously, plasma concentrations of some of these antifungals may be increased by PREZISTA/rtv or PREZISTA/cobicistat. This was confirmed in an interaction trial where the concomitant administration of ketoconazole (200 mg b.i.d.) with darunavir (400 mg b.i.d.) and ritonavir (100 mg b.i.d.) increased exposure of ketoconazole and darunavir by 212% and 42%, respectively. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Clinical monitoring is recommended when co-administering PREZISTA/rtv or PREZISTA/cobicistat with posaconazole or isavuconazole. Plasma concentrations of voriconazole may be decreased in the presence of PREZISTA/rtv and the effect in the presence of PREZISTA/cobicistat is unknown. Voriconazole should not be administered to patients receiving PREZISTA/rtv or PREZISTA/cobicistat unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Antimalarials: artemether/lumefantrine	↓ artemether ↑ lumefantrine ↔ darunavir ↑ dihydroartemisinin	An interaction trial between darunavir/rtv (600/100 mg b.i.d. from day 1 to day 22) and artemether/lumefantrine (80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours, from day 8 to 11) showed an increase in (AUC_{24h}) to lumefantrine by 2.75-fold (90% CI; 2.46, 3.08), while darunavir (AUC_{12h} and C_{min}) was not affected (AUC:LS means ratio 0.96 (90% CI:0.90,1.03); C_{min}: LS means ratio 0.87 (90% CI: 0.77, 0.98)). The (AUC_{last}) of artemether and its active metabolite, dihydroartemisinin, decreased by 16% (LS means ratio 0.84 (90% CI: 0.69,1.02)) and 18% (LS means ratio 0.82 (90% CI: 0.74, 0.91)), respectively. The combination of PREZISTA/rtv or PREZISTA/cobicistat and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution due to the potential risk of prolonged QT interval.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
Antimycobacterial: rifabutin	↑ rifabutin ↑ darunavir	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 once daily 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. Co-administration of PREZISTA/cobicistat with rifabutin is not recommended. If combination of rifabutin and PREZISTA/cobicistat is required, the recommended dose of rifabutin is 150 mg every other day. Clinical monitoring is recommended when co-administering PREZISTA/cobicistat with rifabutin.
Anti-neoplastics: dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine	↑ dasatinib ↑ everolimus ↑ irinotecan ↑ nilotinib ↑ vinblastine ↑ vincristine	The plasma concentrations of these antineoplastics are expected to increase with co-administration of PREZISTA/rtv or PREZISTA/cobicistat (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 or PREZISTA/cobicistat. Concomitant use of everolimus or irinotecan and PREZISTA/rtv or PREZISTA/cobicistat is not recommended.
Antiplatelets: prasugrel	↔prasugrel active metabolite	PREZISTA/cobicistat or PREZISTA/rtv is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite of prasugrel.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
Antipsychotics/ neuroleptics: perphenazine, risperidone, thioridazine, quetiapine	↑ perphenazine ↑ risperidone ↑ thioridazine ↑ quetiapine	Concomitant use of perphenazine and PREZISTA/rtv or PREZISTA/cobicistat may increase concentrations of the neuroleptic (inhibition of CYP3A4 or CYP2D6). Clinical monitoring is recommended when co-administering PREZISTA/rtv or PREZISTA/cobicistat with perphenazine and a lower dose of the neuroleptic should be considered. Concomitant use of risperidone or thioridazine and PREZISTA/rtv or PREZISTA/cobicistat 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 or PREZISTA/cobicistat. Concomitant use of quetiapine and PREZISTA/rtv or PREZISTA/cobicistat may increase the exposure to quetiapine (inhibition of CYP3A). The quetiapine dose should be substantially reduced when co-administered with PREZISTA.
Beta agonists: salmeterol	↑ salmeterol	Concomitant use of salmeterol and PREZISTA/rtv or PREZISTA/cobicistat is not recommended. The combination may result in increased risk of cardiovascular adverse events with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Beta-blockers: carvedilol, metaprolol, timolol	↑ carvedilol ↑ metaprolol ↑ timolol	Co-administration of PREZISTA/rtv or PREZISTA/cobicistat and beta-blockers may increase concentrations of the beta-blocker (inhibition of CYP2D6). Clinical monitoring is recommended when co-administering PREZISTA/rtv or PREZISTA/cobicistat with beta-blockers and a lower dose of the beta-blocker should be considered.
Calcium channel blockers: amlopidine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g. felodipine, nifedipine, nicardipine, amlopidine, diltiazem and verapamil) may increase when PREZISTA/rtv or PREZISTA/cobicistat are co-administered (inhibition of CYP2D6 and/or CYP3A). Caution is warranted and clinical monitoring of patients is recommended.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
Corticosteroids: betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone	↑ betamethasone ↑ budesonide ↑ fluticasone ↑ mometasone ↑ prednisone ↑ triamcinolone	Concomitant use of corticosteroids primarily metabolized by CYP3A (betamethasone, budesonide, fluticasone, mometasone, prednisone or triamcinolone) and PREZISTA/rtv or PREZISTA/cobicistat 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 or PREZISTA/cobicistat 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	↓ darunavir	Systemic dexamethasone induces CYP3A and can thereby decrease darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA. Therefore this combination should be used with caution.
Endothelin receptor antagonist: bosentan	↑ bosentan	Concomitant use of bosentan and PREZISTA/rtv or PREZISTA/cobicistat may increase plasma concentrations of bosentan. In patients who have been receiving PREZISTA/rtv or PREZISTA/cobicistat 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 or PREZISTA/cobicistat, discontinue the use of bosentan at least 36 hours prior to initiation of PREZISTA/rtv or PREZISTA/cobicistat. After at least 10 days following the initiation of PREZISTA/rtv or PREZISTA/cobicistat, resume bosentan at 62.5 mg q.d. or q.o.d. based upon individual tolerability.
Eugeroics: armodafinil, modafinil	↓ darunavir ↓ cobicistat	Co-administration of PREZISTA/cobicistat with armodafanil or modafinil may decrease darunavir and/or cobicistat concentrations, which may result in loss of therapeutic effect and development of resistance. Co-administration of PREZISTA/cobicistat and armodafanil or modafinil is not recommended. No dose adjustment is needed for PREZISTA/rtv and modafinil or armodafinil.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
Gout therapy: colchicine	↑ colchicine	Concomitant use of colchicine and PREZISTA/rtv or PREZISTA/cobicistat 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 or PREZISTA/cobicistat, 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 or PREZISTA/cobicistat, 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 or PREZISTA/cobicistat, the maximum dose of colchicine is 0.6 mg q.d. (may be given as 0.3 mg b.i.d.). Patients should be monitored for clinical symptoms of colchicine toxicity. Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with colchicine in patients with renal or hepatic impairment is contraindicated.
Oestrogen-based contraceptive: ethinyl oestradiol and norethindrone	↓ ethinyl oestradiol and norethindrone	The results of an interaction trial between PREZISTA/rtv (600/100 mg b.i.d.) and ethinyl oestradiol and norethindrone demonstrated that at steady-state systemic exposures to ethinyl oestradiol and norethindrone are decreased by 44% and 14%, respectively. The effect of PREZISTA/cobicistat on ethinyl oestradiol and norethindrone exposure is not known.
ethinyl oestradiol and drospirenone	↓ ethinyl oestradiol and drospirenone	The results of an interaction trial between PREZISTA/cobicistat (800/150 mg q.d.) and ethinyl oestradiol and drospirenone demonstrated that single dose systemic exposures to ethinyl oestradiol and drospirenone are decreased by 30% and increased by 58%, respectively. The effect of PREZISTA/rtv on drospirenone exposure is not known. When PREZISTA/rtv or PREZISTA/cobicistat is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential of hyperkalemia. No data are available to make recommendations on the use of PREZISTA/rtv or PREZISTA/cobicistat with other hormonal contraceptives. Therefore, additional or alternative (non-hormonal) methods of contraception are recommended.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
HMG-CoA reductase inhibitors: atorvastatin, pravastatin, rosuvastatin, pitavastatin	↑ HMG-CoA reductase inhibitors	An interaction trial between darunavir (300 mg b.i.d.), low-dose ritonavir (100 mg b.i.d.), and atorvastatin (10 mg once daily) demonstrated that exposure to atorvastatin was only 15% lower when co-administered with darunavir and ritonavir than when atorvastatin (40 mg once daily) was administered alone. The results of an interaction trial with PREZISTA/cobicistat (800/150 mg q.d.) and atorvastatin (10 mg q.d.) showed a 3.9-fold increase in exposure to atorvastatin. When administration of atorvastatin and PREZISTA/rtv or PREZISTA/cobicistat is desired, it is recommended to start with an atorvastatin dose of 10 mg once daily. A gradual dose increase of atorvastatin may be tailored to the clinical response. An interaction trial between darunavir/ritonavir (600/100 mg b.i.d.) and pravastatin (40 mg, single dose) demonstrated that darunavir/ritonavir did not increase exposure to a single dose of pravastatin in most patients but up to 5-fold in a limited subset of patients. When administration of pravastatin and PREZISTA co-administered with low dose ritonavir or cobicistat is required, it is recommended to start with the lowest possible dose of pravastatin and titrate it up to the desired clinical effect while monitoring for safety. An interaction study evaluating PREZISTA/rtv (600/100 mg twice daily) in combination with rosuvastatin (10 mg q.d.) resulted in a significant increase (2.44 fold [90% CI, 1.65-3.59, P=0.0001]) in rosuvastatin exposure. The results of an interaction trial with PREZISTA/cobicistat (800/150 mg q.d.) and rosuvastatin (10 mg q.d.) showed a 1.9-fold increase in exposure to rosuvastatin. When administration of rosuvastatin and PREZISTA/rtv or PREZISTA/cobicistat 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. The effect of PREZISTA/cobicistat is not known. PREZISTA/rtv and pitavastatin can be co-administered without dose adjustment. Clinical monitoring is recommended when co-administering PREZISTA/cobicistat with pitavastatin and a lower dose of pitavastatin should be considered.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
Acid reducing agents proton pump inhibitors: esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	↔ darunavir	Co-administration of omeprazole (20 mg once daily) and darunavir (400 mg b.i.d.) in the presence of low-dose ritonavir (100 mg b.i.d.) did not affect the exposure to darunavir. Based on these results, PREZISTA/rtv or PREZISTA/cobicistat can be co-administered with proton pump inhibitors without dose adjustments.
H_2-receptor antagonists: cimetidine, famotidine, nizatidine, ranitidine	↔ darunavir	Co-administration of ranitidine (150 mg b.i.d.) and PREZISTA/rtv (400/100 mg b.i.d.) did not affect the exposure to darunavir. PREZISTA/rtv or PREZISTA/cobicistat can be co-administered with H_2-receptor antagonists without dose adjustments.
Antacids: Aluminium/magnesium hydroxide, calcium carbonate	↔ darunavir	No interaction is expected between antacids and PREZISTA/rtv or PREZISTA/cobicistat. PREZISTA/rtv or PREZISTA/cobicistat and antacids can be used concomitantly without dose adjustments.
Immunosuppressants: cyclosporin, everolimus, sirolimus, tacrolimus	↑ immuno-suppressants	Exposure to these immunosuppressants may be increased when co-administered with PREZISTA/rtv or PREZISTA/cobicistat. Therapeutic concentration monitoring of the immunosuppressive agent is recommended when co-administered with PREZISTA/rtv or PREZISTA/cobicistat. Concomitant use of everolimus and PREZISTA/rtv or PREZISTA/cobicistat is not recommended.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
Narcotic analgesic/treatment of opioid dependence: methadone, buprenorphine/naloxone	↔ methadone, ↔ buprenorphine /naloxone	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 or PREZISTA/cobicistat. However, clinical monitoring is recommended as maintenance therapy may need to be adjusted in some patients. 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 metabolite, norbuprenorphine, increased by 46%. No dose adjustment for buprenorphine was required. Careful monitoring of clinical signs and symptoms of opiate toxicity is recommended if PREZISTA/rtv or PREZISTA/cobicistat and buprenorphine or buprenorphine/naloxone is co-administered.
PDE-5 inhibitors for treatment of erectile dysfunction: avanafil, sildenafil, vardenafil, tadalafil	↑ PDE-5 inhibitors	Treatment of erectile dysfunction: In an interaction trial, a comparable systemic exposure to sildenafil was observed for a single dose of 100 mg sildenafil alone and a single dose of 25 mg sildenafil co-administered with darunavir (400 mg b.i.d.) and low-dose ritonavir (100 mg b.i.d.). Concomitant use of PDE-5 inhibitors with PREZISTA/rtv or PREZISTA/cobicistat should be done with caution. If concomitant use of PREZISTA/rtv or PREZISTA/cobicistat 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 or PREZISTA/cobicistat and avanafil is not recommended.
PDE-5 inhibitors for pulmonary arterial hypertension: sildenafil, tadalafil		Treatment of pulmonary arterial hypertension: co-administration of PREZISTA/rtv or PREZISTA/cobicistat with sildenafil when used for pulmonary arterial hypertension is contraindicated (see Table 9). For co-administration of PREZISTA/rtv or PREZISTA/cobicistat with tadalafil, refer to the Product Information for tadalafil.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
Antidepresssants: paroxetine, sertraline	↔ darunavir ↓ sertraline ↓ paroxetine	An interaction trial between paroxetine (20 mg once daily) or sertraline (50 mg once daily) and darunavir (400 mg b.i.d.) and low-dose ritonavir (100 mg b.i.d.) demonstrated that exposure to darunavir was not affected by the co-administration of sertraline or paroxetine. Exposure to sertraline or paroxetine decreased by 49% and 39%, respectively, when co-administered with darunavir and ritonavir. The effect of PREZISTA/cobicistat on the exposure to sertraline or paroxetine is not known. If sertraline or paroxetine is co-administered with PREZISTA/rtv, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/rtv should be monitored for an antidepressant response. Clinical monitoring is recommended when co-administering PREZISTA/cobicistat with these antidepressants and a dose adjustment of the antidepressant may be needed.
amitriptyline, desipramine, imipramine, nortriptyline, trazodone	↑ amitriptyline ↑ desipramine ↑ imipramine ↑ nortriptyline ↑ trazodone	Concomitant use of PREZISTA/rtv or PREZISTA/cobicistat and the antidepressants amitriptyline, desipramine, imipramine, nortriptyline and trazodone may increase concentrations of the antidepressant (inihibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when co-administering PREZISTA/rtv or PREZISTA/cobicistat with these antidepressants and a dose adjustment of the antidepressant may be needed.
Platelet aggregation inhibitors: ticagrelor	↑ ticagrelor	Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with ticagrelor may increase concentrations of ticagrelor. Co-administration of PREZISTA/rtv or PREZISTA/cobicistat and ticagrelor is not recommended.

Drug class: drug name example	Effect on concentration of darunavir or drug	Clinical comment
Sedatives/hypnotics: buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem	↔ darunavir ↑ sedative/hypnotic	Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with these sedatives/hypnotics may increase concentrations of the sedative/hypnotic (inhibition of CYP3A). Clinical monitoring is recommended when co-administering PREZISTA/rtv or PREZISTA/cobicistat with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. 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. Co-administration of PREZISTA/rtv or PREZISTA/cobicistat with oral midazolam or triazolam is contraindicated (see Table 2).
Urinary antispasmodics: fesoterodine, solifenacin	↑ urinary antispasmodics	Use with caution: monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary.

Other NRTIs:

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

Other HIV protease inhibitors:

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

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a study conducted in rats, there were no effects on mating with PREZISTA treatment up to 1000 mg/kg/day, but exposure levels were below (AUC - 0.5 fold) that in humans at the clinically recommended dose. The number of corporea lutea and hence the number of live young was lower for females at 1000 mg/kg/day PREZISTA, and correlated with lower maternal body weight; the NOAEL for effects on fertility was 200 mg/kg/day PREZISTA (corresponding to an exposure level 0.3 – fold that in humans at the recommended clinical dose).

Use in Pregnancy - Category B2

There are no adequate and well controlled studies on pregnancy outcome with darunavir in pregnant women.

To monitor maternal-fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry has been established. This is a voluntary prospective, exposure registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products (ARVs). Prevalence of birth defects with first trimester exposure to any ARV was 2.8 (230 babies with birth defects out of 8277 live births as of data cut-off date of 31 July 2016). This rate is similar to 2nd and 3rd trimester exposure to the darunavir and other ARVs, as compared to overall prevalence of birth defects.

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 section 5.2 Pharmacokinetic Properties).

Darunavir/cobicistat (800/150 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 7 pregnant women during the second and third trimesters, and postpartum (6-12 weeks). The pharmacokinetic data demonstrate that exposure to darunavir and cobicistat was substantially lower during pregnancy compared with postpartum (see section 5.2 Pharmacokinetic Properties). Virologic response was sustained throughout the study period in 5 out of 6 women who completed the study; the subject with virologic failure was not compliant with study medication.

Therapy with PREZISTA/cobicistat should not be initiated during pregnancy, and women who become pregnant during therapy with PREZISTA/cobicistat should be switched to an alternative regimen (see section 4.2 Dose and Method of Administration). PREZISTA/ritonavir may be considered as an alternative.

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

In animal studies with PREZISTA treatment up to 1000 mg/kg/day, there was no teratogenicity with darunavir in mice, rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. However, the exposure levels in mice and rats were about half those with the recommended clinical dose in humans, and only 5% in rabbits. In a pre-and post-natal rat study the pups had lower birth weight following maternal treatment with 1000 mg/kg/day darunavir.

Use in lactation

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 breast-feeding infants, mothers should be instructed not to breastfeed if they are receiving PREZISTA.

In a pre- and post-natal development assessment in rats, darunavir with and without ritonavir, caused a reduction in body weight gain 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 paediatric patients below 3 years of age.

4.7. EFFECT 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.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The overall safety profile of PREZISTA is based on all available clinical trial data (Phase 2b trials POWER 1, 2 and 3, and TMC114-C208 and the Phase 3 trials ARTEMIS, ODIN, TITAN, TMC114-C209, DUET 1 (TMC125-C206) and DUET 2 (TMC125-C216)) and post-marketing data, and is consistent with the data presented below.

Please refer to the ritonavir Product Information for ritonavir-associated adverse reactions.

For combination use with cobicistat and darunavir please refer to the PREZCOBIX (darunavir/ cobicistat) or TYBOST (cobicistat) Product Information.

Adverse drug reactions to PREZISTA/rtv identified in the safety assessment of the clinical trials in adults

Adverse drug reactions to PREZISTA/rtv (800/100 mg once daily) identified in antiretroviral treatment naïve adult patients:

The safety assessment is based on all safety data from the Phase 3 trial ARTEMIS comparing PREZISTA/rtv 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day in antiretroviral naïve HIV-1 infected adult patients. The total patient years exposure in the PREZISTA/rtv arm and the lopinavir/rtv arm was 626.6 and 608.1, respectively.

The majority of the ADRs reported during treatment with PREZISTA/rtv were mild in severity.

The most frequent (≥ 5%) ADRs of moderate to severe (grade 2-4) intensity were diarrhoea, headache and abdominal pain.

The most frequent (>1%) ADRs of severe (grade 3 or 4) intensity were related to laboratory abnormalities. All other grade 3 or 4 ADRs were reported in less than 1% of the patients.

2.3% of the patients in the PREZISTA/rtv arm discontinued treatment due to ADRs.

Table 4: Adverse Drug Reactions to PREZISTA/rtv 800/100 mg once daily of at least moderate intensity (grade 2-4) in antiretroviral treatment naïve HIV-1 infected adult patients are presented in the table below*:

System Organ Class Adverse Drug Reaction	**PREZISTA/rtv 800/100 mg once daily. + TDF/FTC#** N=343	**lopinavir/rtv 800/200 mg per day + TDF/FTC#** N=346
Nervous system disorders		
Headache	5. 8%	4.6%
Gastrointestinal disorders		
Abdominal pain	5.2%	5.8%
Acute pancreatitis	0.3%	0. 6%
Diarrhoea	7.6%	14.7%
Dyspepsia	0.3%	0%
Flatulence	0.9%	0.9%
Nausea	2.6%	3.5%
Vomiting	1.5%	3.2%
Skin and subcutaneous tissue disorders		
Angioedema†	0.3%	0%
Pruritus	0.9%	0.6%
Rash	1.7%	4.0%
Stevens-Johnson Syndrome	0.3%	0%
Urticaria†	0.9%	0.3%
Musculoskeletal and connective tissue disorders		
Myalgia	0.6%	1.2%
Metabolism and nutrition disorders		
Anorexia	1.5%	0. 9%
Diabetes mellitus	0.6%	0.6%
General disorders and administration site conditions		
Asthenia	0.9%	0%
Fatigue	0.3%	2.6%
Immune system disorders		
(Drug) hypersensitivity†	0.6%	1.4%
Immune reconstitution inflammatory syndrome	0.3%	0.3%

System Organ Class Adverse Drug Reaction	**PREZISTA/rtv 800/100 mg once daily. + TDF/FTC#** N=343	**lopinavir/rtv 800/200 mg per day + TDF/FTC#** N=346
Hepatobiliary disorders Hepatitis acute, cytolytic hepatitis, hepatotoxicity	0.3%	0.6%
Psychiatric disorders Abnormal dreams	0.3%	0.3%

* Excluding laboratory abnormalities reported as ADRs
# Tenofovir disoproxil fumarate/emtricitabine
† Adverse drug reactions identified from post-marketing experience

Table 5: Laboratory abnormalities, grade 2-4, considered ADRs, in antiretroviral treatment naïve HIV-1 infected adult patients are shown in the table below*:

Laboratory parameter	**Limit**	**PREZISTA/rtv 800/100 mg once daily + TDF/FTC#** N=343	**lopinavir/rtv 800/200 mg per day + TDF/FTC#** N=346
ALT			
Grade 2	> 2.5 to ≤ 5.0 x ULN	7.3%	6.1%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.9%	2.6%
Grade 4	> 10.0 x ULN	0.9%	2.9%
AST			
Grade 2	> 2.5 to ≤ 5.0 x ULN	6.1%	6.1%
Grade 3	> 5.0 to ≤ 10.0 x ULN	4.1%	1.8%
Grade 4	> 10.0 x ULN	1.2%	2.3%
ALP			
Grade 2	> 2.5 to ≤ 5.0 x ULN	1.5%	1.2%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0%	0.3%
Grade 4	> 10.0 x ULN	0%	0%
Triglycerides			
Grade 2	5.64 to 8.47 mmol/L	2.6%	7.9%
Grade 3	> 8.47 to 13.55 mmol/L	1.2%	4.7%
Grade 4	> 13.55 mmol/L	0.6%	0.9%

Laboratory parameter	Limit	PREZISTA/rtv 800/100 mg once daily + TDF/FTC# N=343	lopinavir/rtv 800/200 mg per day + TDF/FTC# N=346
Total cholesterol*			
Grade 2	6.19 to 7.77 mmol/L	16.4%	23.0%
Grade 3	> 7.77 mmol/L	1.2%	4.7%
LDL cholesterol*			
Grade 2	4.12 to 4.90 mmol/L	13.5%	9.6%
Grade 3	> 4.90 mmol/L	4.7%	5.0%
Elevated glucose levels			
Grade 2	6.95 to < 13.89 mmol/L	7.3%	7.6%
Grade 3	13.89 to < 27.75 mmol/L	0.9%	0%
Grade 4	≥ 27.75 mmol/L	0%	0%
Pancreatic lipase			
Grade 2	> 1.5 to ≤ 3.0 x ULN	1.8%	1.2%
Grade 3	> 3.0 to ≤ 5.0 x ULN	0.6%	0.6%
Grade 4	> 5.0 x ULN	0%	0.6%
Pancreatic amylase			
Grade 2	> 1.5 to ≤ 2.0 x ULN	4.7%	1.7%
Grade 3	> 2.0 to ≤ 5.0 x ULN	2.6%	2.9%
Grade 4	> 5.0 x ULN	0%	0.6%

* Grade 4 data not applicable in Division of AIDS grading scale
\# Tenofovir disoproxil fumarate/emtricitabine

Adverse drug reactions to PREZISTA/rtv (800/100 mg once daily and 600/100 mg twice daily) identified in antiretroviral treatment-experienced adult patients with no darunavir associated mutations

The safety assessment is based on all safety data from the Phase 3 trial ODIN comparing PREZISTA/rtv 800/100 mg once daily to PREZISTA/rtv 600/100 mg b.i.d. in antiretroviral treatment-experienced HIV-1 infected adult patients with no darunavir-resistance associated mutations. The total patient years of exposure in the PREZISTA/rtv once daily arm and the PREZISTA/rtv b.i.d. arm was 253.5 and 245.1, respectively.

The majority of the ADRs reported with either PREZISTA/rtv treatment arm were mild in severity.

The most frequent (≥ 5%) ADRs of moderate to severe (grade 2-4) intensity were diarrhoea, nausea and vomiting.

The most frequent ADRs of severe (grade 3 or 4) intensity in either treatment arm were abdominal pain, diabetes, and increased blood cholesterol. All other grade 3 or 4 ADRs were reported in less than 1% of the patients.

Less than two percent of the patients in either treatment arm discontinued treatment due to ADRs.

Table 6: Adverse Drug Reactions to PREZISTA/rtv 800/100 mg once daily and PREZISTA/rtv 600/100 mg b.i.d. of at least moderate intensity (grade 2-4) in antiretroviral treatment experienced HIV-1 infected adult patients with no darunavir-resistance associated mutations are presented in the table below*:

System Organ Class Adverse Drug Reaction	**PREZISTA/rtv 800/100 mg once daily + OBR#** N=294	**PREZISTA/rtv 600/100 mg b.i.d. + OBR#** N=296
Nervous system disorders		
Headache	3.4%	4.4%
Gastrointestinal disorders		
Abdominal distention	0.3%	0.3%
Abdominal pain	3.1%	2.4%
Diarrhoea	5.8%	5.4%
Dyspepsia	0.3%	1.4%
Flatulence	0.7%	0%
Nausea	4.8%	5.1%
Vomiting	3.4%	5.4%
Skin and subcutaneous tissue disorders		
Angioedema	0%	0.3%
Pruritus	0.3%	0.3%
Rash	2.0%	2.0%
Urticaria	0%	0.3%
Musculoskeletal and connective tissue disorders		
Myalgia	0.7%	1.4%
Metabolism and nutrition disorders		
Anorexia	0.3%	1.4%
Diabetes mellitus	0.3%	1.0%
General disorders and administration site conditions		
Asthenia	0.3%	0.3%
Fatigue	0.3%	0.3%

System Organ Class Adverse Drug Reaction	**PREZISTA/rtv 800/100 mg once daily + OBR#** N=294	**PREZISTA/rtv 600/100 mg b.i.d. + OBR#** N=296
Hepatobiliary disorders		
Hepatitis acute	0%	0.7%

* Excluding laboratory abnormalities reported as ADRs
# Optimized Background Regimen

Table 7: Laboratory abnormalities, grade 2-4, considered ADRs, in antiretroviral treatment-experienced HIV-1 infected adult patients with no darunavir-resistance associated mutations are shown in the table below*:

Laboratory parameter	**Limit**	**PREZISTA/rtv 800/100 mg once daily + OBR#** N=294	**PREZISTA/rtv 600/100 mg b.i.d. + OBR#** N=296
ALT			
Grade 2	> 2.5 to ≤ 5.0 x ULN	1.7%	2.5%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0%	0.7%
Grade 4	> 10.0 x ULN	0%	0.4%
AST			
Grade 2	> 2.5 to ≤ 5.0 x ULN	1.4%	2.5%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0.7%	0.7%
Grade 4	> 10.0 x ULN	0%	0.4%
ALP			
Grade 2	> 2.5 to ≤ 5.0 x ULN	0.7%	0.4%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0%	0%
Grade 4	> 10.0 x ULN	0%	0%
Triglycerides			
Grade 2	5.64 to 8.47 mmol/L	3.5%	7.1%
Grade 3	> 8.47 to 13.55 mmol/L	1.4%	2.8%
Grade 4	> 13.55 mmol/L	0.3%	1.1%
Total cholesterol*			
Grade 2	6.19 to 7.77 mmol/L	7.7%	14.9%
Grade 3	> 7.77 mmol/L	2.4%	5.7%
LDL cholesterol*			
Grade 2	4.12 to 4.90 mmol/L	7.0%	12.8%
Grade 3	> 4.90 mmol/L	2.8%	3.9%

Laboratory parameter	Limit	PREZISTA/rtv 800/100 mg once daily + OBR# N=294	PREZISTA/rtv 600/100 mg b.i.d. + OBR# N=296
Elevated glucose levels			
Grade 2	6.95 to < 13.89 mmol/L	6.6%	5.3%
Grade 3	13.89 to < 27.75 mmol/L	0.7%	0.7%
Grade 4	≥ 27.75 mmol/L	0%	0.4%
Pancreatic lipase			
Grade 2	> 1.5 to ≤ 3.0 x ULN	1.0%	1.8%
Grade 3	> 3.0 to ≤ 5.0 x ULN	0.3%	0%
Grade 4	> 5.0 x ULN	0%	0%
Pancreatic amylase			
Grade 2	> 1.5 to ≤ 2.0 x ULN	3.1%	2.5%
Grade 3	> 2.0 to ≤ 5.0 x ULN	2.4%	1.1%
Grade 4	> 5.0 x ULN	0.3%	0.4%

* Grade 4 data not applicable in Division of AIDS grading scale
# Optimised Background Regimen

Adverse drug reactions to PREZISTA/rtv (600/100 mg twice daily) identified in antiretroviral treatment-experienced lopinavir-naive adult patients

The safety assessment is based on all safety data from the Phase 3 trial TITAN comparing PREZISTA/rtv 600/100 mg b.i.d. versus lopinavir/ritonavir 400/100 mg b.i.d. in antiretroviral treatment-experienced HIV-1 infected adult patients. The total patient years of exposure in the PREZISTA/rtv arm and the lopinavir/rtv arm was 462.5 and 436.1, respectively.

The majority of the ADRs reported during treatment with PREZISTA/rtv were mild in severity. The most frequent (≥ 5%) ADRs of moderate to severe (grade 2-4) intensity were diarrhoea, hypertriglyceridaemia, hypercholesterolaemia, nausea, abdominal pain, vomiting, hepatic enzymes increased and rash. The most frequent (>1%) severe (grade 3 or 4) ADRs were related to laboratory abnormalities,. All other grade 3 or 4 ADRs were reported in less than 1% of the patients. 4.7 percent of the patients discontinued treatment due to ADRs.

Table 8: Adverse Drug Reactions to PREZISTA/rtv 600/100 mg b.i.d. of at least moderate intensity (grade 2-4) in antiretroviral treatment-experienced HIV-1 infected adult patients in the TITAN trial are mentioned in the table below*:

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

System Organ Class Adverse Drug Reaction	**PREZISTA/rtv 600/100 mg b.i.d. + OBR[#]** N=298	**lopinavir/rtv 400/100 mg b.i.d. + OBR[#]** N=297
Gastrointestinal disorders		
Abdominal distension	2.0%	0.3%
Abdominal pain	5.7%	2.7%
Acute pancreatitis	0.3%	0.3%
Diarrhoea	14.4%	19.9%
Dyspepsia	2.0%	1.0%
Flatulence	0.3%	1.0%
Nausea	7.0%	6.4%
Vomiting	5.4%	2.7%
Skin and subcutaneous tissue disorders		
Pruritus	1.0%	1.0%
Rash	5.0%	2.0%
Urticaria[†]	0.3%	0%
Musculoskeletal and connective tissue disorders		
Myalgia	1.0%	0.7%
Metabolism and nutrition disorders		
Anorexia	1.7%	2.0%
Diabetes mellitus	1.7%	0.3%
General disorders and administration site conditions		
Asthenia	3.4%	1.0%
Fatigue	2.0%	1.3%
Immune system disorders		
Immune reconstitution syndrome	0.3%	0%
Reproductive system and breast disorders		
Gynaecomastia	0.3%	0.3%
Psychiatric disorders		
Abnormal dreams	0.7%	0%

* Excluding laboratory abnormalities reported as ADRs
[#] Optimised Background Regimen
[†] Adverse drug reactions identified from post-marketing experience

Table 9: Laboratory abnormalities, grade 2-4, considered ADRs, in antiretroviral treatment-experienced HIV-1 infected adult patients in the TITAN trial are shown in the table below*:

Laboratory parameter	**Limit**	**PREZISTA/rtv 600/100 mg b.i.d. + OBR#** N=298	**lopinavir/rtv 400/100 mg b.i.d. + OBR#** N=297
ALT			
Grade 2	> 2.5 to ≤ 5.0 x ULN	6.9%	4.8%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.4%	2.4%
Grade 4	> 10.0 x ULN	1.0%	1.7%
AST			
Grade 2	> 2.5 to ≤ 5.0 x ULN	5.5%	6.2%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.4%	1.7%
Grade 4	> 10.0 x ULN	0.7%	1.7%
ALP			
Grade 2	> 2.5 to ≤ 5.0 x ULN	0.3%	0%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0.3%	0.3%
Grade 4	> 10.0 x ULN	0%	0%
Triglycerides			
Grade 2	5.64 to 8.47 mmol/L	10.4%	11.4%
Grade 3	> 8.47 to 13.55 mmol/L	6.9%	9.7%
Grade 4	> 13.55 mmol/L	3.1%	6.2%
Total cholesterol*			
Grade 2	6.19 to 7.77 mmol/L	24.9%	23.2%
Grade 3	> 7.77 mmol/L	9.7%	13.5%
LDL cholesterol*			
Grade 2	4.12 to 4.90 mmol/L	14.4%	13.5%
Grade 3	> 4.90 mmol/L	7.7%	9.3%
Elevated glucose levels			
Grade 2	6.95 to < 13.89 mmol/L	10.0%	11.4%
Grade 3	13.89 to < 27.75 mmol/L	1.4%	0.3%
Grade 4	≥ 27.75 mmol/L	0.3%	0%

Laboratory parameter	Limit	PREZISTA/rtv 600/100 mg b.i.d. + OBR[#] N=298	lopinavir/rtv 400/100 mg b.i.d. + OBR[#] N=297
Pancreatic lipase			
Grade 2	> 1.5 to ≤ 3.0 x ULN	2.8%	3.5%
Grade 3	> 3.0 to ≤ 5.0 x ULN	2.1%	0.3%
Grade 4	> 5.0 x ULN	0.3%	0%
Pancreatic amylase			
Grade 2	> 1.5 to ≤ 2.0 x ULN	6.2%	7.3%
Grade 3	> 2.0 to ≤ 5.0 x ULN	6.6%	2.8%
Grade 4	> 5.0 x ULN	0%	0%

* Grade 4 data not applicable in Division of AIDS grading scale
[#] Optimised Background Regimen

Adverse Drug Reactions to PREZISTA/rtv (600/100 mg twice daily) identified in treatment-experienced adult patients who failed more than one PI-containing regimen

In the pooled POWER trials, the total patient years of exposure was 812.4 in patients who immediately started treatment on PREZISTA/rtv 600/100 mg b.i.d. (See CLINICAL TRIALS)

The majority of the ADRs reported during treatment with PREZISTA/rtv were mild in severity. The most frequent (≥5%) moderate to severe (grade 2 – 4) ADRs were diarrhoea, headache, abdominal pain, nausea and vomiting. The most frequent grade 3 or 4 ADRs were increased hepatic and pancreatic enzymes, hypertriglyceridaemia, diarrhoea, hypercholesterolaemia, headache, abdominal pain and vomiting. All other grade 3 or 4 ADRs were reported in less than 1% of the patients.

2.1 percent of the patients discontinued treatment due to ADRs.

Table 10: Adverse Drug Reactions to PREZISTA/rtv 600/100 mg b.i.d. of at least moderate intensity (grade 2-4) in antiretroviral treatment-experienced HIV-1 infected adult patients in the pooled trials POWER 1, 2 and 3, are mentioned in the table below[1]:

System Organ Class Adverse Drug Reaction	**PREZISTA/rtv 600/100 mg b.i.d. + OBR[2]** (n=467)
Nervous system disorders	
Headache	8.8%
Gastrointestinal disorders	
Abdominal distension	1.9%
Abdominal pain	6.4%
Acute pancreatitis	0.4%
Diarrhoea	13.7%
Dyspepsia	1.5%
Flatulence	1.5%
Nausea	6.2%
Vomiting	5.6%
Skin and subcutaneous tissue disorders	
Pruritus	2.6%
Rash	3.4%
Urticaria†	0.6%
Musculoskeletal and connective tissue disorders	
Myalgia	3.2%
Osteonecrosis†	0.6%
Metabolism and nutrition disorders	
Anorexia	2.4%
Diabetes mellitus	1.3%
General disorders and administration site conditions	
Asthenia	3.6%
Fatigue	3.9%
Immune system disorders	
(Drug) hypersensitivity†	0.6%
Immune reconstitution syndrome	0.2%

System Organ Class Adverse Drug Reaction	PREZISTA/rtv 600/100 mg b.i.d. + OBR[2] (n=467)
Hepatobiliary disorders Hepatitis acute, cytolytic hepatitis, hepatotoxicity	0.4%
Reproductive system and breast disorders Gynaecomastia	0.9%
Psychiatric disorders Abnormal dreams	0.4%

[1] Excluding laboratory abnormalities reported as ADRs.
[2] Optimised Background Regimen.
† Adverse drug reactions identified from post-marketing experience

Table 11: Laboratory abnormalities, considered ADRs, in antiretroviral treatment-experienced HIV-1 infected adult patients in the pooled trials POWER 1, 2 and 3 are shown in the table below:

Laboratory parameter Preferred Term	Limit	PREZISTA/rtv 600/100 mg b.i.d. + OBR[1] N=467
ALT		
Grade 2	> 2.5 to ≤ 5.0 x ULN	6.1%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.4%
Grade 4	> 10.0 x ULN	0.9%
AST		
Grade 2	> 2.5 to ≤ 5.0 x ULN	6.9%
Grade 3	> 5.0 to ≤ 10.0 x ULN	3.0%
Grade 4	> 10.0 x ULN	0.6%
ALP		
Grade 2	> 2.5 to ≤ 5.0 x ULN	3.9%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0.9%
Grade 4	> 10.0 x ULN	0%
Triglycerides		
Grade 2	5.64 to 8.47 mmol/L	9.3%
Grade 3	> 8.47 to 13.55 mmol/L	8.2%
Grade 4	> 13.55 mmol/L	3.9%
Total cholesterol[2]		
Grade 2	6.19 to 7.77 mmol/L	17.7%
Grade 3	> 7.77 mmol/L	7.1%

Laboratory parameter Preferred Term	**Limit**	**PREZISTA/rtv 600/100 mg b.i.d. + OBR**[1] N=467
LDL cholesterol[2]		
Grade 2	4.12 to 4.90 mmol/L	13.2%
Grade 3	> 4.90 mmol/L	9.1%
Elevated glucose levels		
Grade 2	6.95 to < 13.89 mmol/L	15.4%
Grade 3	13.89 to < 27.75 mmol/L	1.7%
Grade 4	≥ 27.75 mmol/L	0.2%
Pancreatic lipase		
Grade 2	> 1.5 to ≤ 3.0 x ULN	5.2%
Grade 3	> 3.0 to ≤ 5.0 x ULN	2.6%
Grade 4	> 5.0 x ULN	0.9%
Pancreatic amylase		
Grade 2	> 1.5 to ≤ 2.0 x ULN	7.4%
Grade 3	> 2.0 to ≤ 5.0 x ULN	7.8%
Grade 4	> 5.0 x ULN	1.1%

[1] Optimised Background Regimen.
[2] Grade 4 data not applicable in Division of AIDS grading scale.

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

System Organ Class	**Adverse Drug Reaction**	**Incidence***
Musculoskeletal and connective tissue disorders	Osteonecrosis+	0.4%

* Incidence of at least grade 2 ADRs, calculated on pooled data of phase 2b and 3 trials (N=3,063)
+ Adverse drug reactions identified from post-marketing experience

Adverse drug reactions to PREZISTA/rtv identified in paediatric patients

The safety assessment in children and adolescents is based on the safety data from the Phase 2 trial DELPHI (TMC114-C212) in which 80 antiretroviral treatment-experienced HIV-1 infected paediatric patients aged from 6 to < 18 years and weighing at least 20 kg received PREZISTA/rtv in combination with other antiretroviral agents (see section 5.1 Pharmacodynamic Properties, Clinical Trials). Frequency, type and severity of adverse drug reactions in children and adolescents were comparable to those observed in adults.

Post-marketing experience

Adverse drug reactions identified during post-marketing experience.

System Organ Class	Adverse Drug Reaction	Frequency
Skin and subcutaneous tissue disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Very rare
	Toxic epidermal necrolysis	Very rare
	Acute generalised exanthematous pustulosis	Very rare
Renal and urinary disorders	Crystal nephropathy	Very rare

Rarely, events of rhabdomyolysis (associated with co-administration with HMG-CoA reductase inhibitors and PREZISTA) have been reported.

Effects of combination antiretroviral therapy

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

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (immune reactivation syndrome). Autoimmune disorders such as Graves' disease and autoimmune hepatitis have also been reported in the context of immune reactivation syndrome (see section 4.4 Special Warnings and Precautions for Use).

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

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

Special populations

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

In patients co-infected with hepatitis B or C virus receiving PREZISTA/rtv, the incidence of adverse events and clinical chemistry abnormalities was not higher than in patients receiving PREZISTA/rtv who were not co-infected, except for increased hepatic enzymes. The pharmacokinetic exposure in co-infected patients was comparable to that in patients without co-infection. Increased AST/ALT monitoring should be considered in patients with hepatitis co-infection, especially during the first months of PREZISTA/rtv therapy.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

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.

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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitors

ATC code: J05AE10.

5.1. PHARMACODYNAMIC PROPERTIES

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 binds to HIV-1 protease with a KD of 4.5 x 10-12 M.

Darunavir was not a significant inhibitor of any of 13 tested human cellular proteases.

Antiviral activity *in vitro*

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages and laboratory strains of HIV-2 in acutely infected T-cell lines, with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 4.7 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 increased by a median factor of 5.4 in the presence of 50% human serum *in vitro*.

Darunavir showed synergistic antiviral activity when studied in combination with the HIV protease inhibitors ritonavir, nelfinavir, or amprenavir and additive antiviral activity when studied in combination with the HIV protease inhibitors indinavir, saquinavir, lopinavir, atazanavir, or tipranavir, the nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs) zidovudine, lamivudine, zalcitabine, didanosine, stavudine, abacavir, emtricitabine, or tenofovir, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) etravirine, nevirapine, delavirdine, 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.

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 HIV PI Resistance-Associated Mutations (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.

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 (TMC114-C213) and POWER 2 (TMC114-C202) trials and in the POWER 3 analysis (TMC114-C215 + TMC114-C208), only the subgroups with > 10 HIV 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 many viruses resistant to most HIV PIs remain susceptible to darunavir.

Seven of the 9 darunavir-resistant viruses selected from HIV PI-resistant viruses had phenotypic data for tipranavir. Six of those showed a fold change in EC_{50} value < 3 for tipranavir, indicative of limited cross-resistance between these 2 HIV protease inhibitors.

Cross-resistance between darunavir and N(t)RTIs, NNRTIs, the entry inhibitors or the integrase inhibitors, is unlikely because the viral targets for those inhibitors are different.

Selection of viral resistance during PREZISTA/rtv therapy *in vivo*

Across all studied clinical trials the lowest rates of developing resistant HIV-1 virus are observed in antiretroviral treatment-naïve patients who are treated for the first time with darunavir in combination with other antiretroviral treatment. The Table below shows the development of mutations and loss of susceptibility to the HIV PIs in virologic failures at endpoint in the ARTEMIS, ODIN and TITAN trials.

Table 12: Development of mutations and loss of susceptibility to ARVs in virologic failures at endpoint in the ARTEMIS, ODIN and TITAN trials (see CLINICAL TRIALS for study design).

	ARTEMIS	ODIN		TITAN
	PREZISTA/rtv 800/100 mg once daily N=343	PREZISTA/rtv 800/100 mg once daily N=294	PREZISTA/rtv 600/100 mg twice daily N=296	PREZISTA/rtv 600/100 mg twice daily N=298
Total number of virologic failures*, n (%)	40 (11.7%)	65 (22.1%)	54 (18.2%)	41 (13.8%)
Rebounders	24 (7.0%)	11 (3.7%)	11 (3.7%)	27 (9.0%)
Never suppressed patients	16 (4.7%)	54 (18.4%)	43 (14.5%)	14 (4.7%)

Number of patients with virologic failure and paired baseline/endpoint genotypes, developing mutations[#] at endpoint, n/N				
Primary (major) HIV PI mutations	0/10	1[§]/60	0/42	7/39
HIV PI RAMs	3/10	7/60	4/42	15/39
NRTI RAMs	1/10	4/60	3/42	4/39
Number of patients with virologic failure and paired baseline/endpoint phenotypes, showing loss of susceptibility to ARVs at endpoint compared to baseline, n/N				
HIV PI				
amprenavir	0/10	1/58	0/40	0/31
atazanavir	0/10	2/56	0/40	1/30
darunavir	0/10	1/58	0/41	3/36
indinavir	0/10	2/57	0/40	1/32
lopinavir	0/10	1/58	0/40	0/33
nelfinavir	0/10	1/53	0/39	2/26
saquinavir	0/10	0/56	0/40	0/31
tipranavir	0/10	0/58	0/41	1/35
≥1 NRTIs in treatment regimen	2/9	7/59	4/41	4/35

TLOVR=Time to loss of virologic response; ARVs=Antiretroviral drugs; RAMs=Resistance-associated mutations; HIV PI=HIV Protease inhibitor; NRTI=Nucleoside reverse transcriptase inhibitor

[*] TLOVR non-VF censored algorithm based on HIV-1 RNA<50 copies/mL, except for TITAN (HIV-1 RNA<400 copies/mL)

[#] IAS-USA lists

[§] Primary (major) PI mutations: V32I, M46I, L76V, and I84V

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.

Cross-resistance with other HIV protease inhibitors *in vivo*

In the virologic failures of the ARTEMIS trial no cross-resistance with other HIV PIs was observed.

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

Of the viruses isolated from patients receiving PREZISTA/rtv 600/100 mg twice daily experiencing virologic failures in the TITAN trial, 8% (n=3) of those susceptible to darunavir at baseline developed decreased susceptibility to darunavir during treatment. Two of these 3 PREZISTA/rtv subjects were already resistant to all approved HIV PIs (fos)amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir at baseline. The third subject who was resistant to all other HIV approved PIs at baseline, remained susceptible to indinavir and tipranavir after PREZISTA failure. In the same group of patients experiencing virologic failure, 97% to 100% that were susceptible at baseline to amprenavir, atazanavir, indinavir, lopinavir, saquinavir or tipranavir remained susceptible after PREZISTA failure.

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 HIV PIs could not be studied in the POWER or DUET trials, since most of the baseline viruses were already resistant to these HIV PIs. Patients with no susceptible HIV 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 PREZISTA/rtv 600/100mg 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.

In early treatment-experienced patients (TITAN) three or more of these mutations were only found in 4% of the patients at baseline.

Table 13: 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 of the POWER and DUET trials

Number of mutations at baseline*	All % n/N	No/non-naïve use of enfuvirtide % n/N	Naive use of enfuvirtide % 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.

Table 14: 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 of the POWER and DUET trials

Baseline darunavir phenotype (fold change ranges)	All % n/N	No/non-naïve use of enfuvirtide % n/N	Naïve use of enfuvirtide % 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 treatment history of the individual patient and the patterns of mutations associated with different agents. When available, genotypic or phenotypic testing can be performed to guide the use of darunavir.

Clinical trials

Efficacy of PREZISTA/rtv in treatment naïve adult patients

The evidence of efficacy of PREZISTA/rtv 800/100 mg once daily is based on the analyses of 96 week data from the randomised, controlled, open-label Phase 3 trial ARTEMIS (TMC114-C211) in antiretroviral treatment naïve HIV-1 infected patients comparing PREZISTA/rtv 800/100 mg once daily 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 once daily. (TDF) and emtricitabine 200 mg once daily (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 once daily 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 x 10^6 cells/L (range 4 – 750 x 10^6 cells/L).

Table 15 shows the efficacy data of the 48 week and 96 week analyses from the ARTEMIS trial.

Table 15: Efficacy data from the ARTEMIS trial (48 week and 96 week analyses)

	At week 48[a]			At week 96 [b]		
Outcomes	PREZISTA/rtv 800/100 mg once daily N=343	lopinavir/rtv 800/200 mg per day N=346	Treatment difference (95% CI of difference)	PREZISTA/rtv 800/100 mg once daily 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)]	271 (79.0%)	245 (70.8%)	8.2 (1.7; 14.7)[d]
HIV-1 RNA < 400 copies/ mL[c)]	301 (87.8%)	295 (85.3%)	2.5 (-2.6; 7.6)[d)]	285 (83.1%)	268 (77.5%)	5.6 (-0.3; 11.6)
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]	–2.64	–2.45	-0.20[f] (-0.40; 0.01)[d]
median CD4+ cell count change from baseline (x 10^6/L)[e)]	137	141		171	188	

a) Data based on analysis at week 48
b) Data based on analysis at week 96
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

In the 48 week analysis, the virologic response (HIV-1 RNA < 50 copies/mL) for the PREZISTA/rtv arm was 83.7% and for the lopinavir/rtv arm 78.3% (Figure 2). Statistical comparisons between the treatment arms at week 48 confirmed non-inferiority of DRV/rtv versus lopinavir/rtv (p-value < 0.001) for both ITT (Intent-To-Treat) & OP (On Protocol) population.

Non-inferiority in virologic response to the PREZISTA/ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/mL, was demonstrated (at the pre-defined 12% non-inferioritv margin) for both Intent-To-Treat (ITT) and On Protocol (OP) populations in the 48 week analysis. These results were confirmed in the analyses of data at 96 weeks of treatment in the ARTEMIS trial. Furthermore, superiority of the PREZISTA/rtv arm over the lopinavir/rtv arm was demonstrated at Week 96 (p = 0.012 for the ITT population and p = 0.011 for the OP population).

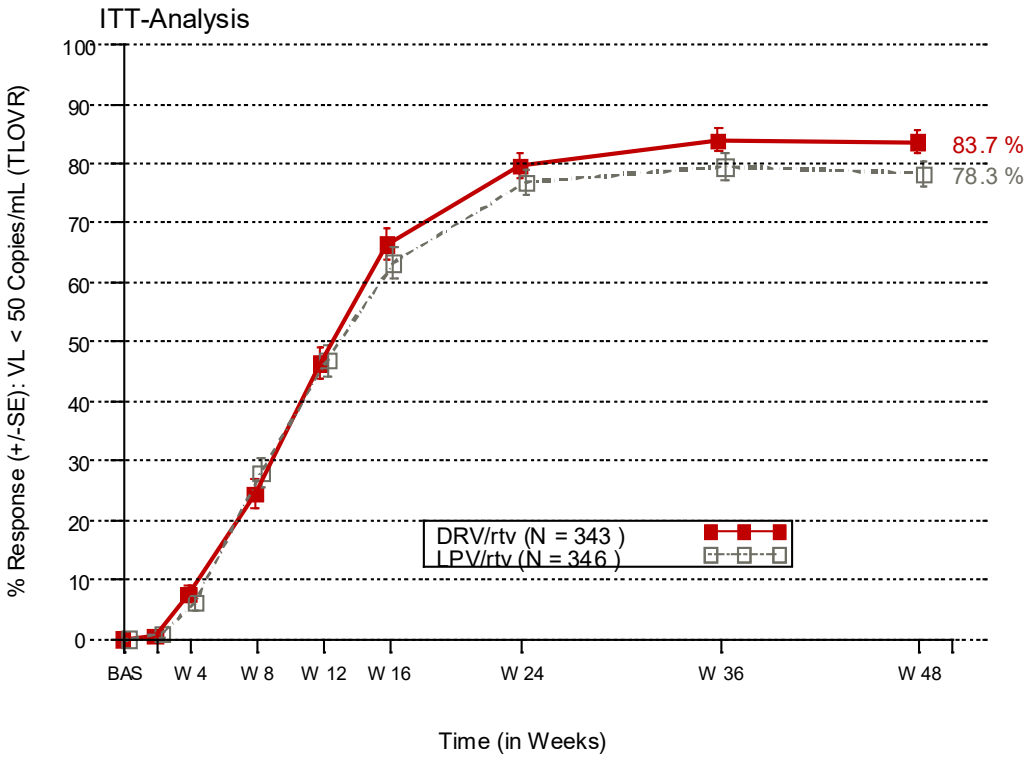


Figure 1. Virologic Response Over Time: Percentage of Patients With Viral Load < 50 Copies/mL (ITT – TLOVR) – ARTEMIS

The virological response (< 50 copies/mL) at 96 weeks by baseline viral load and baseline CD4+ cell count is presented in Table 16.

Table 16: Virological response (HIV-1 RNA < 50 copies/mL) by baseline viral load

	PREZISTA/rtv 800/100 mg once daily (Number of responders at week 96) n/N (%)	lopinavir/rtv 800/200 mg per day (Number of responders at week 96) n/N (%)	Treatment difference (95% CI of difference)[a)]
With baseline HIV-RNA < 100,000	182/226 (80.5%)	170 (75.2%)	5.3% (-2.3;13.0)
With baseline HIV-RNA ≥ 100,000	89/117 (76.1%)	75/120 (62.5%)	13.6%(1.9; 25.3)
With baseline CD4+ cell count <200	111/141 (78.7%)	96/148 (64.9%)	13.9% (3.5; 24.2)
With baseline CD4+ cell count ≥200	160/202 (79.2%)	149/198 (75.3%)	4.0% (-4.3; 12.2)

a) Based on normal approximation to the difference in % response

Efficacy of PREZISTA/rtv (800/100 mg once daily) in treatment-experienced adult patients with no darunavir resistance associated mutations

The evidence of comparable efficacy of PREZISTA/rtv 800/100 mg once daily and PREZISTA/rtv 600/100 mg twice daily 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 once daily to PREZISTA/rtv 600/100 mg twice daily 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 once daily arm and the PREZISTA/rtv twice daily 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 primary objective was to demonstrate non-inferiority of virologic response of the once daily regimen compared to the twice daily regimen. Virologic response was defined as a confirmed plasma viral load of < 50 HIV-1 RNA copies/mL at Week 48. Non-inferiority was confirmed if the lower limit of the 95% confidence interval (CI) for the difference in response (once daily minus twice daily) was greater than minus 12%. The analysis was to be performed on the Intention-to-treat population, which included all participants who took at least one dose of study medications.

In the 48 week analysis non-inferiority was demonstrated. The virological response was 72.1% for the PREZISTA/rtv once daily arm and 70.9% for the PREZISTA/rtv twice daily arm. The difference was 1.2% with 95% Confidence interval of -6.1 %; 8.5% (Table 17).

Table 17: Efficacy data from the ODIN trial (48 week analysis)

ODIN			
Outcomes	PREZISTA/rtv 800/100 mg once daily + OBR N=294	PREZISTA/rtv 600/100 mg twice daily + 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)]
With baseline HIV-1 RNA (copies/mL)			
≤50,000	174/222 (78.4%)	172/224 (76.8%)	1.6 (-6.2; 9.4)
>50,000	38/72 (52.8%)	38/72 (52.8%)	0.0 (-16.4; 16.4)
mean CD4+ cell count change from baseline (x 10^6/L)[c)]	108	112	-5 (-25; 16)[d)]

OBR=optimized background regimen

a) Imputations according to the TLOVR (time to loss of virologic response) algorithm
b) Based on a normal approximation of the difference in % response
c) Last Observation Carried Forward imputation
d) Difference in means

Limited data is available in patients with baseline HIV-1 RNA ≥100,000 copies/mL.

Efficacy of PREZISTA/rtv (600/100 mg twice daily) in treatment-experienced lopinavir-naïve adult patients

The evidence of efficacy of PREZISTA/rtv 600/100 mg b.i.d. in treatment-experienced patients is based on the 48 week analysis of the Phase 3 trial TITAN (TMC114-C214) 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 HIV 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 > 1000 copies/mL and were on a highly active antiretroviral therapy regimen (HAART) for at least 12 weeks.

Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 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).

Table 18 shows the efficacy data of the 48 week and 96 week analyses from the TITAN trial.

Table 18: Efficacy data from the TITAN trial (48 week and 96 week analyses)

	At Week 48[a]			At Week 96[b]		
Outcomes	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)[d]
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

In the 48 week analysis, virologic response, defined as the percentage of patients with plasma HIV-1 RNA level < 400 copies/mL, was 76.5% and 67.0% for the PREZISTA/rtv arm and lopinavir/rtv arm, respectively. Non-inferiority in virologic response was demonstrated ($p < 0.001$) for both the ITT (Figure 2) and OP population.

These results were confirmed in the analyses of data at 96 weeks of treatment in the TITAN trial (see Table 19). Furthermore, superiority of the PREZISTA/rtv arm over the lopinavir/rtv arm was demonstrated at 96 weeks ($p = 0.034$ for the ITT population and $p = 0.033$ for the OP population).

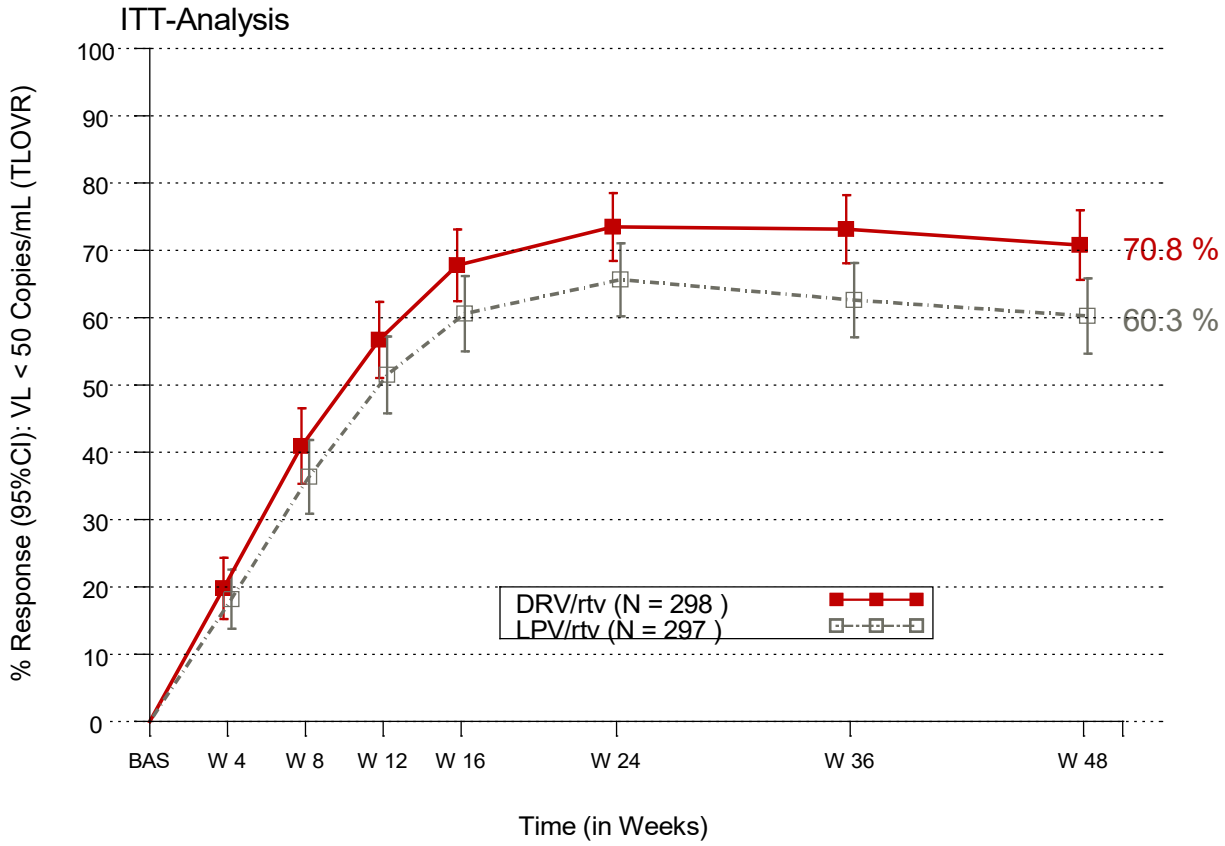


Figure 2. Virologic Response Over Time: Percentage of Patients With Viral Load < 50 Copies/mL (ITT – TLOVR) – TITAN

Efficacy of PREZISTA/rtv in treatment-experienced adult patients who failed more than one HIV PI-containing regimen

POWER 1 (TMC114-C213) and POWER 2 (TMC114-C202) are randomised, controlled Phase 2b trials in adult patients with a high level of HIV 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 ribonucleic acid (RNA) > 1000 copies/mL, had prior treatment with HIV PI(s), NNRTI(s) and NRTI(s), had at least 1 primary (i.e. major) 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 HIV PI arm. In both trials 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 x 10^6 cells/L (range 3 – 776 x 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.

Table 19 below shows the efficacy data of the 48 week and 96 week analyses from the pooled POWER 1 and POWER 2 trials.

Table 19: Efficacy Outcomes at Weeks 48 and 96 of the Studies POWER 1 and POWER 2 (Pooled Analysis)

	Randomized Studies POWER 1 and POWER 2		
	PREZISTA/rtv 600 mg b.i.d. + OBR N=131	Comparator PI + OBR N=124	Treatment difference (95% CI of difference)
Week 48 time point			
HIV-1 RNA $\log_{10}$ mean change from baseline ($\log_{10}$ copies/mL)[a)]	-1.69	-0.37	-1.32 (-1.58; -1.05)
HIV-1 RNA $\geq$ 1 $\log_{10}$ below baseline[d)]	81 (61.8%)	20 (16.1%)	45.7% (35.0%; 56.4%)[e)]
HIV-1 RNA < 400 copies/mL[d)]	72 (55.0%)	18 (14.5%)	40.4% (29.8%; 51.1%)[e)]
HIV-1 RNA < 50 copies/mL[d)]	59 (45.0%)	14 (11.3%)	33.7% (23.4%; 44.1%)[e)]
CD4+ cell count mean change from baseline (x 10^6/L)[c)]	103	17	86[b)] (57; 114)
Week 96 time point			
HIV-1 RNA $\log_{10}$ mean change from baseline ($\log_{10}$ copies/mL)[a)]	-1.58	-0.25	-1.33 (-1.59; -1.07)
HIV-1 RNA $\geq$ 1 $\log_{10}$ below baseline[d)]	74 (56.5%)	12 (9.7%)	46.8% (36.9%; 56.8%)[e)]
HIV-1 RNA < 400 copies/mL[d)]	65 (49.6%)	12 (9.7%)	39.9% (29.9%; 50.0%)[e)]
HIV-1 RNA < 50 copies/mL[d)]	51 (38.9%)	11 (8.9%)	30.1% (20.3%; 39.8%)[e)]
CD4+ cell count mean change from baseline (x 10^6/L)[c)]	133	15	118[b)] (84; 152)

a) Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0
b) P-values < 0.001, based on the ANOVA model
c) Last Observation Carried Forward imputation
d) Imputations according to the TLOVR algorithm

e) Confidence interval around observed differences of response rates; P-values < 0.001, based on the logistic regression model.

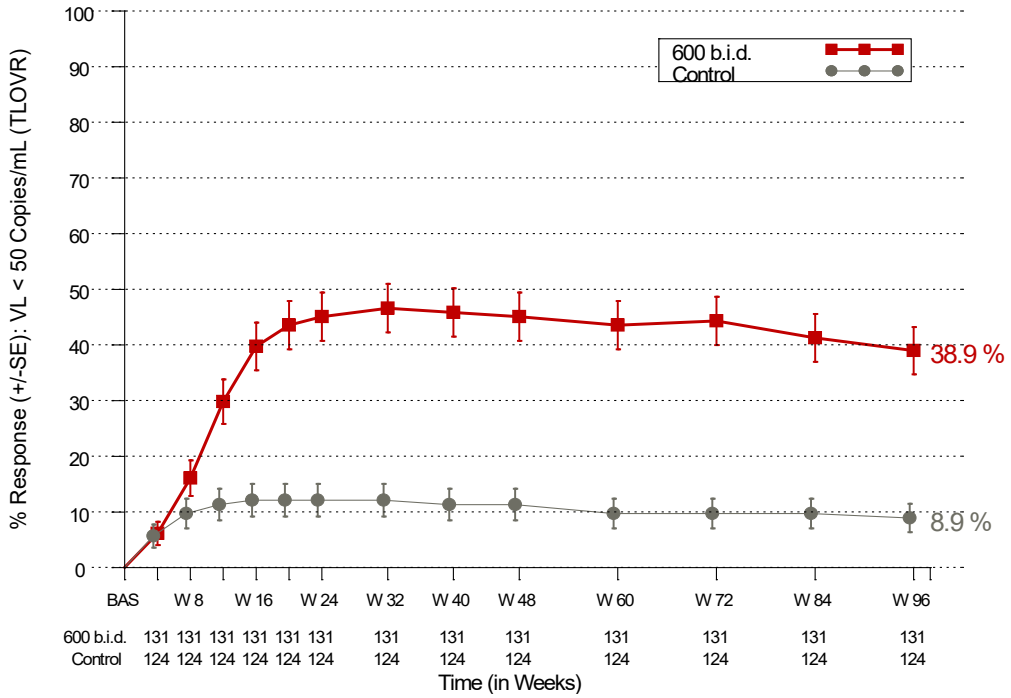


Figure 3: Virologic Response Over Time: Percentage of Patients With Plasma Viral Load < 50 Copies/mL (ITT – TLOVR) in the pooled POWER 1 and POWER 2 trials

POWER 3

Additional data on the efficacy of PREZISTA/rtv 600/100 mg b.i.d. have been obtained in treatment-experienced adult patients participating in the non-randomized trial TMC114-C215 (POWER 3). At week 48, 334 patients were included in the POWER 3 efficacy analysis who had initiated therapy with PREZISTA/rtv with the recommended dose of 600/100 mg b.i.d. The OBR consisted of at least two NRTIs with or without enfuvirtide. Entry criteria for the TMC114-C215 analysis were the same as those for studies POWER 1 and POWER 2.

Baseline characteristics of the patients included in the TMC114-C215/C208 analysis were comparable to those patients in Studies POWER 1 and POWER 2.

The POWER 3 48-week efficacy analysis supported the viral load reduction and CD4+ cell count increases observed in the Studies POWER 1 and POWER 2. Of the 334 patients at Week 48, 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 HIV-1 RNA copies/mL.

Analyses of data through 96 weeks of treatment with PREZISTA/rtv (600/100 mg b.i.d.) in the POWER 3 study supported the sustained antiretroviral efficacy and immunological benefit as demonstrated in the studies POWER 1 and POWER 2. Of the 336 patients at Week 96 in study POWER 3, 52.2% of patients had a virologic response defined as a decrease of at least 1 $\log_{10}$ in HIV-1 RNA from baseline. 42.1% of the patients reached an HIV-1 RNA level < 50 copies/mL and 50.0% of patients reached less than 400 HIV-1 RNA copies/mL. The mean decrease in HIV-1 RNA level compared to baseline was 1.43 $\log_{10}$ copies/mL and a mean increase in CD4+ cell count of 103 x 10^6 cells/L was observed. Out of the 206 patients who responded with complete viral suppression (< 50 copies/mL) at week 48 in Studies POWER 1, POWER 2 and POWER 3, 177 patients (86% of the responders at week 48) remained responders at week 96.

Description of the clinical study in paediatric patients

DELPHI (TMC114-C212) 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 paediatric patients aged 6 to < 18 years and weighing at least 20 kg. At baseline, the mean time since diagnosis was 10.7 years and 37.5% of patients had a baseline viral load ≥ 100,000 copies/mL. At week 24, the virologic response rate was evaluated in paediatric patients receiving PREZISTA/rtv in combination with other antiretroviral agents (see section 4.2 for dosage recommendations per body weight). 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 x 10^6 cells/L (range: 6 to 1505 x 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 paediatric patients had at least 1.0 $\log_{10}$ HIV-1 RNA decrease from baseline. The proportion of paediatric patients reaching undetectable viral load (< 50 HIV-1 RNA copies/mL) was 50.0%, and the proportion of paediatric 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 x 10^6 cells/L.

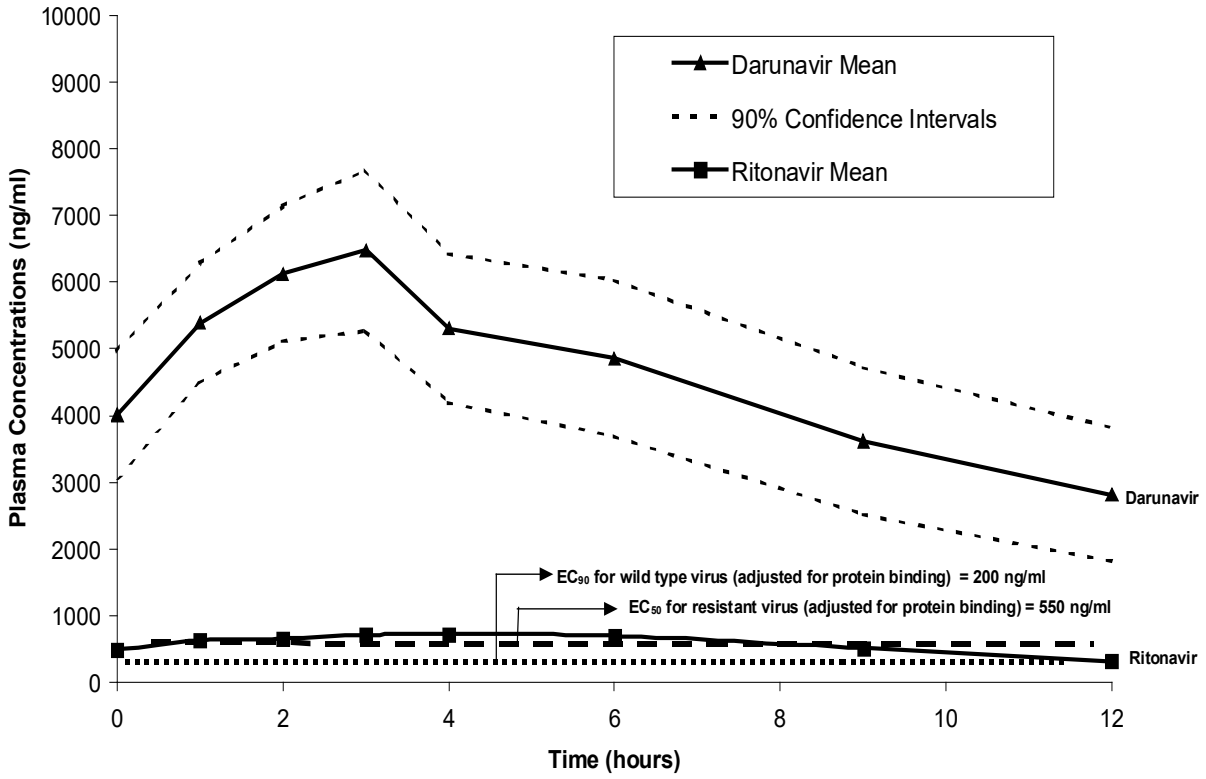
5.2. PHARMACOKINETIC PROPERTIES

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 participants.

For combination use with cobicistat and darunavir please refer to the PREZCOBIX (darunavir/ cobicistat) or TYBOST (cobicistat) Product Information.

Darunavir is primarily metabolized by cytochrome P_{450} 3A (CYP3A). Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

Figure 4: Mean Steady-State Plasma Concentration-Time Profiles of Darunavir and Ritonavir at 600/100 mg b.i.d. at Week 4 (Integrated data from POWER 1 and POWER 2, Primary 24-Week Analysis)



Mean plasma concentration-time profiles were derived from population pharmacokinetic analysis.

Absorption

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 section 4.4 Special Warnings and Precautions for Use).

When administered without food, the relative bioavailability of PREZISTA in the presence of low dose ritonavir is 30% lower, 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. The apparent volume of distribution of darunavir using population pharmacokinetic analysis was 122 L.

Metabolism

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

Excretion

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 faeces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in faeces 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

Paediatrics

The pharmacokinetics of darunavir in combination with ritonavir in 74 treatment-experienced paediatric 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 section 4.2 Dose and Method of Administration). Median (range) darunavir AUC_{12h} and C_{0h} values in this paediatric population were 63,670 (33,527; 115,360) ng.h/mL and 3,888 (1,836; 7,821) ng.h/mL, respectively.

Elderly

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 section 4.4 Special Warnings and Precautions for Use).

Gender

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

Pregnancy and Postpartum

Treatment with darunavir and ritonavir

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. Reduction in darunavir exposure was more pronounced in the once daily group as compared to the twice daily group across both 2nd and 3rd trimester of pregnancy. 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.

Twice daily dose regimen group

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.

Once daily dose regimen group

In women receiving darunavir/ritonavir 800/100 mg q.d during the 2nd trimester of pregnancy, mean intra-individual values for total darunavir C_{max}, AUC_{24h} and C_{min} were 33%, 31% and 30% lower, respectively, as compared with postpartum; during the 3rd trimester of pregnancy, total darunavir C_{max}, AUC_{24h} and C_{min} values were 29%, 32% and 50% lower, respectively, as compared with postpartum (see sections 4.4 Special Warnings and Precautions for Use and 4.2 Dose and Method of Administration).

Treatment with darunavir and cobicistat

The exposure to total darunavir and cobicistat after intake of darunavir/cobicistat 800/150 mg q.d. as part of an antiretroviral regimen was substantially lower during the second and third trimester of pregnancy compared with 6-12 weeks postpartum (see Table 20). The decrease in unbound (i.e. active) darunavir pharmacokinetic parameters (C_{max} and AUC_{24h}) during pregnancy compared to postpartum was less pronounced than for total darunavir.

Table 20: Pharmacokinetic Results of Total Darunavir after Administration of Darunavir/Cobicistat 800/150 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=7**	**3rd Trimester of pregnancy n=6**	**Postpartum n=6**
C_{max}, ng/mL	4340 ± 1616	4910 ± 970	7918 ± 2199
AUC_{24h}, ng.h/mL	47293 ± 19058	47991 ± 9879	99613 ± 34862
C_{min}, ng/mL	168 ± 149	184 ± 99	1538 ± 1344

In women receiving darunavir/cobicistat 800/150 mg q.d. during the 2nd trimester of pregnancy, mean intra-individual values for total darunavir C_{max}, AUC_{24h} and C_{min} were 49%, 56% and 92% lower, respectively, as compared with postpartum; during the 3rd trimester of pregnancy, total darunavir C_{max}, AUC_{24h} and C_{min} values were 37%, 50% and 89% lower, respectively, as compared with postpartum.

Renal impairment

No pharmacokinetic data are available in patients with severe renal impairment or end stage renal disease.

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. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis.

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 sections 4.2 Dose and Method of Administration and 4.4 Special Warnings and Precautions for Use).

For combination use with cobicistat and darunavir please refer to the PREZCOBIX (darunavir/ cobicistat) or TYBOST (cobicistat) Product Information.

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 patients with mild (Child-Pugh Class A, n=8) and moderate (Child-Pugh Class B, n=8) hepatic impairment were comparable with those in healthy patients. However, darunavir unbound concentrations were approximately 50% and 100% higher, respectively, in mild and moderate hepatic impairment, compared with those in healthy participants. The clinical relevance of this increase in unbound darunavir concentrations is unknown. Therefore, PREZISTA should be used with caution in mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see sections 4.2 Dose and Method of Administration and 4.4 Special Warnings and Precautions for Use).

Interactions with medicinal products

Darunavir and ritonavir are both inhibitors of the CYP3A and CYP2D6 isoforms, and inhibitors of P-gp. Co-administration of darunavir and ritonavir with medicinal products primarily metabolized by CYP3A, CYP2D6, or transported by P-gp may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see sections 4.3 Contraindications, 4.4 Special Warnings and Precautions for Use and 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Darunavir, ritonavir and cobicistat are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir, ritonavir and cobicistat, resulting in lowered plasma concentrations of darunavir, ritonavir and cobicistat. Darunavir boosted with cobicistat is more sensitive to CYP3A4 induction than darunavir boosted with ritonavir (see sections 4.2 Contraindications and 4.5 Interactions with Other Medicines and Other Forms of Interactions). Co-administration with other drugs that inhibit CYP3A may decrease the clearance of darunavir, ritonavir and cobicistat and may result in increased plasma concentrations of darunavir, ritonavir and cobicistat (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

For combination use with cobicistat and darunavir please refer to the PREZCOBIX (darunavir/ cobicistat) or TYBOST (cobicistat) Product Information.

Drug interaction studies were performed with darunavir and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of darunavir on the concentration of darunavir or drug are summarized in Table 3 (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

PREZISTA 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.

Carcinogenicity

PREZISTA 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. Systemic exposures at the highest

dose (based on plasma AUC) were approximately 0.5-fold (mice) and 0.75-fold (rats) relative to humans at the recommended therapeutic dose of darunavir/ritonavir (600/100 mg b.i.d).

The incidences of hepatocellular adenomas were statistically significantly increased at all doses in male mice; at the mid and high dose in female mice and male rats; and at the high dose in female rats. The incidence of hepatocellular carcinomas was significantly increased at the high dose in male mice; and male and female rats. The relevance of these findings for humans is limited. An increase in the incidence of thyroid follicular cell adenomas was noted in male rats. This is considered rodent specific and of no relevance to humans.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Microcrystalline cellulose

Colloidal anhydrous silica

Crospovidone

Magnesium stearate

Polyvinyl alcohol

Macrogol 3350

Titanium dioxide (E171)

Purified talc

Sunset yellow FCF aluminium lake (400 mg and 600 mg tablets only)

Hypromellose (800 mg tablets only)

Iron oxide red (E172) (800 mg tablets only).

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5. NATURE AND CONTENTS OF CONTAINER

PREZISTA 75 mg film-coated tablets* are provided in high density polyethylene (HDPE) plastic bottles containing 480 tablets, fitted with polypropylene (PP) child resistant closures.

PREZISTA 400* and 600 mg film-coated tablets are provided in high density polyethylene (HDPE) plastic bottles containing 60 tablets, fitted with polypropylene (PP) child resistant closures.

PREZISTA 800 mg film-coated tablets are provided in high density polyethylene (HDPE) plastic bottles containing 30 tablets, fitted with polypropylene (PP) child resistant closures.

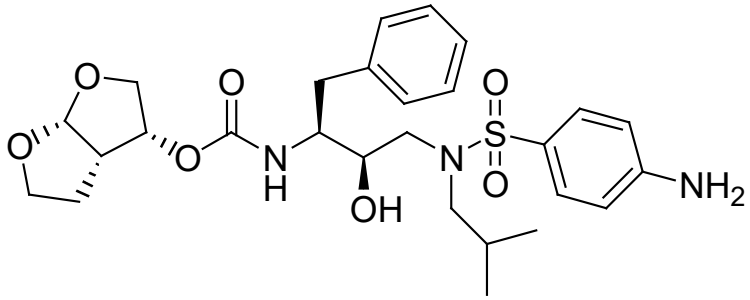
*Currently not marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure:



CAS No.: 206361-99-1

Molecular formula: $C_{27}H_{37}N_3O_7S$

Molecular weight: 547.66 daltons

The chemical name for darunavir is [(1*S,*2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R,*3a*S,*6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester.

Darunavir is isolated as darunavir ethanolate, a pseudo-polymorphic form of darunavir. Darunavir ethanolate is a white to off-white powder that is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol, and freely soluble in acetone and dichloromethane.

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113 Australia
Telephone: 1800 226 334

NZ Office: Auckland New Zealand

9. DATE OF FIRST APPROVAL

15 March 2007

10. DATE OF REVISION

27 March 2023

Summary table of changes

Section changed	Summary of new information
4.4 and 4.8	Removal of text regarding fat distribution and lipodystrophy
4.5	Revision to co-administration with dabigatran etexilate