1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

PREZISTA® 600 mg (film-coated tablet)

COMPOSITION

Each film-coated tablet contains 600 mg of darunavir as ethanolate salt.

Excipients:

Colloidal silicon dioxide, crospovidone, macrogol, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol (partially hydrolysed), talc and titanium dioxide (C.I. no. 77891)

Sugar free

CATEGORY AND CLASS

A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Mechanism of action

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

Antiviral activity in vitro

Darunavir exhibited activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages *in vitro* with median EC_{50} values ranging from 1,2 to 8,5 nM; (0,7 to 5,0 ng/ml). Darunavir demonstrated antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from < 0,1 to 4,3 nM. These EC_{50} values are well below the 50 % cellular toxicity concentration range of 87 µM to > 100 µM.

The EC_{50} value of darunavir increases by a median factor of 5,4 in the presence of human serum. Darunavir showed synergistic antiviral activity when studied in combination with the protease inhibitors ritonavir, nelfinavir or amprenavir and additive antiviral activity when studied in combination with the protease inhibitors indinavir, saquinavir, lopinavir, atazanavir or tipranavir, the N(t)RTIs zidovudine, lamivudine, zalcitabine, didanosine, stavudine, abacavir, emtricitabine or tenofovir, the NNRTIs nevirapine, delavirdine or efavirenz and the fusion inhibitor enfuvirtide. No antagonism was observed between darunavir and any of these antiretrovirals.

Resistance in vitro

In vitro darunavir-resistant virus isolates from wild type HIV-1 were selected. Viruses showing decreased susceptibility to darunavir (range: 6 to 21-fold) harboured 3 to 6 amino acid substitutions in the protease gene. Determinants of decreased susceptibility to darunavir in those viruses have not been identified.

In vitro selection of darunavir-resistant HIV-1 (range: 53 to 641-fold change in EC_{50} values) from nine HIV-1 strains harbouring multiple PI (protease inhibitor) resistance-associated mutations 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 nine darunavir-resistant isolates. A minimum of eight of these darunavir *in vitro* selected mutations, from which at least two were already present in the protease prior to selection, were required in the HIV-1 protease to render a virus resistant (multifold change [FC] > 10) to darunavir.

In 1 113 clinical isolates resistant to at least one protease inhibitor and in 886 baseline isolates from the patients enrolled in the clinical trials only the subgroups with > 10 PI resistance-associated mutations showed a median FC for darunavir > 10.

Cross-resistance in vitro

Cross-resistance has been observed among protease inhibitors. Darunavir has a < 10-fold decreased susceptibility to 90 % of 3 309 clinical isolates resistant to at least one protease inhibitor.

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

Pharmacokinetic properties

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

Darunavir is primarily metabolized by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

Absorption

Darunavir was rapidly absorbed following oral administration. Maximum plasma concentration of darunavir in the presence of low-dose ritonavir is generally achieved within 2,5 to 4,0 hours. The absolute oral bioavailability of a single 600 mg dose of darunavir alone was approximately 37 % and increased to approximately 82 % in the presence of 100 mg twice daily 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 darunavir was given orally in combination with ritonavir at 100 mg twice daily (see WARNINGS AND SPECIAL PRECAUTIONS).

When administered without food, the relative bioavailability of darunavir in the presence of low-dose ritonavir is 30 % lower as compared to intake with food. Therefore, darunavir tablets should be taken with ritonavir and with food. The type of food does not affect exposure to darunavir.

Distribution

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

Metabolism

In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolised by the hepatic CYP system and almost exclusively by isozyme CYP3A4. A ^{14}C-darunavir trial in healthy volunteers

showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir/rtv dose was due to the parent active substance. At least three 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 wild type human immunodeficiency virus (HIV).

Elimination

After a 400/100 mg ^{14}C-darunavir/rtv dose, approximately 79,5 % and 13,9 % of the administered dose of ^{14}C-darunavir could be retrieved in 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

There is no information on the pharmacokinetics of darunavir in combination with ritonavir in paediatric subjects.

Elderly

Population pharmacokinetic analysis in HIV-infected patients showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV infected patients (n=12, age ≥ 65) (see WARNINGS AND SPECIAL PRECAUTIONS).

Gender

Population pharmacokinetic analysis showed a slightly higher darunavir exposure (16,8 %) in HIV infected females compared to males. This difference is not clinically relevant.

Renal impairment

Results from a mass balance study with ^{14}C-darunavir/rtv showed that approximately 7,7 % of the administered dose of darunavir is excreted in the urine as unchanged active substance. Darunavir has not been studied in patients with renal impairment.

Hepatic impairment

Darunavir is primarily metabolised and eliminated by the liver. In a multiple-dose study with darunavir co-administered with ritonavir (600/100 mg) twice daily, it was demonstrated that the steady-state pharmacokinetic parameters of darunavir in subjects with mild (Child-Pugh Class A, n=8) hepatic impairment were comparable with those in healthy subjects. In moderate hepatic impairment (Child-Pugh Class B, n=8) the mean C_{max} was increased by 22 %, the AUC by 20 % and the C_{min} by 27 % after multiple doses. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS).

INDICATIONS

PREZISTA, in combination with 100 mg ritonavir (PREZISTA/rtv) and with other antiretroviral agents, is indicated for the treatment of HIV infection in antiretroviral treatment experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

This indication is based on week-24 analyses from 2 controlled clinical trials in treatment-experienced, HIV-1-infected patients, where PREZISTA/rtv showed a significantly greater reduction of plasma HIV RNA levels and greater increase in CD4+ cell counts when compared to a protease inhibitor (PI) regimen of choice, each given in combination with other antiretrovirals. (Additional data is available from open label studies (see Pharmacodynamic Properties)). There is no information on the use of PREZISTA/rtv in HIV-infected paediatric patients and in antiretroviral treatment-naïve adult patients. Treatment history and, when

available, genotypic or phenotypic testing should guide the use of PREZISTA/rtv.

CONTRAINDICATIONS

- Hypersensitivity to darunavir or to any of the excipients of PREZISTA.
- The presence of a contraindication to ritonavir.
- Darunavir and ritonavir are both inhibitors of the cytochrome P450 3A (CYP3A) isoforms. PREZISTA/rtv should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index).

These medicinal products are included in the table below:

Medicines that are contraindicated with PREZISTA/rtv	
Medicine Class: Medicine Name	Clinical Comment
Anticonvulsants: Carbamazepine, Phenobarbital, Phenytoin	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. PREZISTA/rtv should not be used in combination with phenobarbital, phenytoin or carbamazepine as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of the therapeutic effect of PREZISTA (see INTERACTIONS).
Antihistamines: Astemizole	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmia.
Antimycobacterial: Rifampicin	Rifampicin is a potent inducer of CYP450 metabolism. PREZISTA/rtv should not be used in combination with rifampicin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of the therapeutic effect of PREZISTA (see INTERACTIONS).

PDE5 inhibitors: Sildenafil - for treatment of pulmonary arterial hypertension.	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).
Alpha 1-adrenoreceptor antagonist: Alfuzosin	Potential for serious and/or life-threatening reactions such as hypotension.
Ergot Derivatives: Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues.
Herbal Products: St. John's Wort (*Hypericum perforatum*)	PREZISTA/rtv should not be used concomitantly with products containing St. John's Wort *(Hypericum perforatum)* because co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of the therapeutic effect of PREZISTA (see INTERACTIONS).
HMG-CoA Reductase Inhibitors: Lovastatin, Simvastatin	Potential for serious reactions such as risk of myopathy, including rhabdomyolysis.
Neuroleptic: Pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac dysrhythmia.
Sedative-Hypnotics: Midazolam, Triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Antifungals: Ketoconazole, itraconazole and voriconazole	CONTRAINDICATED because concomitant systemic use of ketoconazole, itraconazole or voriconazole and PREZISTA/rtv may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole or itraconazole may be increased by PREZISTA/rtv, while the plasma concentrations of voriconazole may be decreased in the presence of PREZISTA/rtv (see INTERACTIONS).
Buprenorphine/naloxone:	The results of an interaction trial with PREZISTA/rtv and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when administered with PREZISTA/rtv. Exposure of the active metabolite, norbuprenorphine, increased by 46 %. No dose adjustment for buprenorphine was required. Careful clinical monitoring is recommended if PREZISTA/rtv and buprenorphine are co-administered (see INTERACTIONS).

WARNINGS AND SPECIAL PRECAUTIONS

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV and that they may continue to develop opportunistic infections and other complications associated with HIV disease. Appropriate precautions should continue to be employed.

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

General

PREZISTA must be co-administered with ritonavir and food to exert its therapeutic effect (see DOSAGE AND DIRECTIONS FOR USE). Failure to correctly administer PREZISTA with ritonavir and food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired antiviral effect. The type of food does not affect exposure to PREZISTA. Patients should be instructed to swallow whole tablets with a drink such as water or milk. PREZISTA must always be used with 100 mg of ritonavir in combination with other antiretroviral medicines. Patients should not alter the dose of either PREZISTA or ritonavir, discontinue ritonavir, or discontinue therapy with PREZISTA without consulting their medical practitioner. If a patient misses a dose of PREZISTA or ritonavir by more than 6 hours, the patient should be told to wait and then take the next dose of PREZISTA and ritonavir at the regularly scheduled time. If the patient misses a dose of PREZISTA or ritonavir by less than 6 hours, the patient should be told to take PREZISTA and ritonavir immediately, and then take the next dose of PREZISTA and ritonavir at the regularly scheduled time. If a dose of PREZISTA or ritonavir is skipped, the patient should not double the next dose. Inform the patient that he or she should not take more or less than the prescribed dose of PREZISTA or ritonavir at any one time.

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

Skin rash

During the clinical development programme, severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported. Stevens-Johnson Syndrome has also been rarely reported and during post-marketing experience toxic epidermal necrolysis has been reported very rarely. 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. 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 %.

Sulpha allergy

Darunavir contains a sulphonamide moiety. PREZISTA should be used with caution in patients with a known sulphonamide allergy.

Interactions

PREZISTA and ritonavir are both inhibitors of CYP3A. Co-administration of PREZISTA/rtv with medicines primarily metabolised by CYP3A may result in increased plasma concentrations of such medicines, which could increase or prolong their therapeutic effect and adverse events (see CONTRAINDICATIONS and INTERACTIONS).

Diabetes mellitus/Hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycaemia have been reported during post-marketing surveillance in HIV-infected patients receiving PREZISTA. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued PREZISTA, hyperglycaemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between PREZISTA

and these events have not been established. 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.

Oestrogen-based contraceptives

Plasma concentrations of ethinylestradiol are decreased by induction of its metabolism by ritonavir and alternative methods of non-hormonal contraception are recommended (see "INTERACTIONS").

The phosphodiesterase type 5 (PDE5) inhibitors sildenafil, vardenafil and tadalafil are highly dependent on CYP3A for their metabolism. If concomitant use of PREZISTA/rtv with sildenafil, vardenafil or tadalafil is indicated, reduced doses of the PDE5 inhibitors are recommended (see INTERACTIONS).

There are insufficient data at this time to recommend a dose in antiretroviral treatment-naïve patients and in children.

Elderly:

As limited information is available on the use of PREZISTA/rtv in patients aged 65 and over, caution should be exercised in the administration of PREZISTA in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy (see Pharmacokinetic Properties).

The 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 twice daily. Therefore, PREZISTA should only be used in combination with 100 mg of ritonavir as a pharmacokinetic enhancer (see

Pharmacokinetic Properties). Increasing the dose of ritonavir did not significantly affect darunavir concentrations and is not recommended.

Patients with coexisting conditions

Hepatic impairment

There are no data regarding the use of PREZISTA/rtv when co-administered to patients with severe hepatic impairment; therefore, PREZISTA should not be used. No dose adjustment is required in patients with mild or moderate hepatic impairment (see DOSAGE AND DIRECTIONS FOR USE and Pharmacokinetic Properties).

Hepatotoxicity

Medicine-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/rtv. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities, including severe hepatic adverse events.

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

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

Renal impairment

Since the renal clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis (see DOSAGE AND DIRECTIONS FOR USE and Pharmacokinetic Properties).

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 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.

Fat redistribution and metabolic disorders

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

Immune reactivation 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 jeroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Resistance/Cross-resistance

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

Effects on ability to drive and use machines

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

INTERACTIONS

Darunavir and ritonavir are both inhibitors of the CYP3A isoform. Co-administration of PREZISTA and ritonavir and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect and adverse events.

PREZISTA/rtv should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are

associated with serious and/or life-threatening events (narrow therapeutic index). These medicinal products include alfuzosin, sildenafil (when used for treatment of pulmonary arterial hypertension), midazolam, triazolam, pimozide and the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine and methylergonovine) (see CONTRAINDICATIONS).

Rifampicin is a potent inducer of CYP450 metabolism. PREZISTA/rtv should not be used in combination with rifampicin, as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of the therapeutic effect of PREZISTA (see CONTRAINDICATIONS).

PREZISTA/rtv should not be used concomitantly with products containing St. John's Wort *(Hypericum perforatum)* because co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of the therapeutic effect of PREZISTA (see CONTRAINDICATIONS).

Antiretroviral medicinal products

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

Didanosine

PREZISTA/rtv (600/100 mg twice daily) did not significantly affect didanosine exposure. The combination of PREZISTA co-administered with 100 mg ritonavir and didanosine can be used without dose adjustments. As it is recommended that didanosine be administered on an empty stomach, didanosine should be administered 1 hour before or 2 hours after PREZISTA/rtv (which are administered with food).

Tenofovir

The results of an interaction trial with tenofovir (tenofovir disoproxil fumarate 300 mg once daily demonstrated that the systemic exposure of tenofovir was increased by 22 % when co-

administered with PREZISTA/rtv (300/100 mg twice daily). This finding is not considered to be clinically relevant. Tenofovir did not have a significant influence on darunavir exposure. No dose adjustments of PREZISTA, ritonavir or tenofovir disoproxil fumarate are required when these medicines are co-administered.

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 medicine interactions are expected for these medicinal compounds and PREZISTA/rtv.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Etravirine

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

Efavirenz

An interaction trial between PREZISTA/rtv (300/100 mg twice daily) and efavirenz (600 mg once daily) has been performed. In the presence of efavirenz, a decrease of 13 % for darunavir exposure and a decrease of darunavir C_{min} by 31 % were observed. Exposure to efavirenz was increased by 21 % when administered in combination with PREZISTA/rtv. The combination of PREZISTA/rtv and efavirenz should be used with caution.

Nevirapine

The results of an interaction trial with PREZISTA/rtv (400/100 mg twice daily) and nevirapine (200 mg twice daily) demonstrated that darunavir exposure was not affected when it was

administered concomitantly with nevirapine. Exposure to nevirapine increased by 27 % (compared to historical controls) when administered in combination with PREZISTA/rtv. Since this difference is not considered to be clinically relevant, the combination of PREZISTA/rtv and nevirapine can be used without dose adjustments.

Protease inhibitors (PIs)

Ritonavir

The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg PREZISTA was given orally in combination with ritonavir at 100 mg twice daily. Therefore, PREZISTA should only be used in combination with 100 mg of ritonavir as a pharmacokinetic enhancer (see WARNINGS AND SPECIAL PRECAUTIONS and Pharmacokinetic Properties).

Lopinavir/ritonavir

Results of interaction trials with PREZISTA with or without ritonavir and lopinavir/ritonavir (1 200 mg darunavir twice daily with or without 100 mg ritonavir twice daily and lopinavir/ritonavir 400/100 mg twice daily or 533/133,3 mg twice daily) demonstrated a decrease in the exposure (AUC) of darunavir by 40 %. The appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer PREZISTA/rtv with lopinavir/ritonavir.

Saquinavir

In an interaction study between PREZISTA (400 mg twice daily), saquinavir (1 000 mg twice daily) and ritonavir (100 mg twice daily), darunavir exposure was decreased by 26 % in the presence of saquinavir/rtv; saquinavir exposure was not affected by the presence of PREZISTA/rtv. It is not recommended to combine saquinavir and PREZISTA (with or without low-dose ritonavir).

Atazanavir

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

Indinavir

In an interaction study between PREZISTA/rtv (400/100 mg twice daily) and indinavir (800 mg twice daily), darunavir exposure was increased by 24 % in the presence of indinavir/rtv; indinavir exposure was increased by 23 % in the presence of PREZISTA/rtv. The appropriate dose of indinavir in combination with PREZISTA/rtv has not been established.

Other medicinal products

Antidysrhythmics (bepridil, systemic lidocaine, quinidine and amiodarone)

Exposure to bepridil, lidocaine, quinidine and amiodarone may be increased when co-administered with PREZISTA/rtv. This can lead to prolongation or an increase of their therapeutic effect and adverse events (see INTERACTIONS). Caution is warranted and therapeutic medicine monitoring of antidysrhythmics, if available, is recommended, when co-administered with PREZISTA/rtv.

Digoxin

An interaction trial with PREZISTA/rtv (600/100 mg twice daily) and a single dose of digoxin (0,4 mg) showed an increase of digoxin AUC_{last} of 77 % (ratio of least square means (LSM) was 1,77 with a 90 % CI of 0,90 to 3,50). It is recommended that the lowest dose of digoxin should initially be prescribed and digoxin dose should be titrated to obtain the desired clinical effect when co-administered with PREZISTA/rtv. Serum digoxin concentrations should be

monitored to assist in the titration.

Anticoagulants

Warfarin concentrations may be affected (decreased) when co-administered with PREZISTA/rtv. It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with PREZISTA/rtv.

Anticonvulsants (phenobarbital, phenytoin and carbamazepine)

Phenobarbital, phenytoin and carbamazepine 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 the therapeutic effect of PREZISTA (see CONTRAINDICATIONS).

Colchicine

Concomitant use of colchicine and PREZISTA/rtv may increase the exposure to colchicine. The following dose adjustments are recommended for colchicine. For the treatment of gout flares in patients on PREZISTA/rtv, the recommended dose of colchicine is 0,6 mg (1 tablet), followed by 0,3 mg (half tablet) 1 hour later. The treatment course is to be repeated no earlier than 3 days. For the prophylaxis of gout flares in patients on PREZISTA/rtv, the recommended dose of colchicine is 0,3 mg every day or every other day. For the treatment of familial Mediterranean fever in patients on PREZISTA/rtv, the maximum dose of colchicine is 0,6 mg every day (may be given as 0,3 mg twice daily). Patients with renal or hepatic impairment should not be given colchicine with PREZISTA/rtv.

Calcium channel blockers

The exposure to calcium channel blockers (e.g. felodipine, nifedipine, nicardipine) may increase when PREZISTA/rtv are used concomitantly. Caution is warranted and careful clinical

monitoring is recommended.

Clarithromycin

An interaction trial between PREZISTA/rtv (400/100 mg twice daily) and clarithromycin (500 mg twice daily) showed a 57 % increase in exposure to clarithromycin, while exposure to darunavir was not affected. For patients with renal impairment, a dose reduction of clarithromycin should be considered.

No dose adjustment of darunavir or clarithromycin is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered:

- For subjects with CL_{cr} of 30 to 60 ml/min, the dose of clarithromycin should be reduced by 50 %.
- For subjects with CL_{cr} of < 30 ml/min, the dose of clarithromycin should be reduced by 75 %.

Dexamethasone

Systemic dexamethasone induces CYP3A and thereby may decrease darunavir exposure. This may result in loss of therapeutic effect. Therefore, this combination should be used with caution.

Bosentan (endothelin receptor antagonist)

Concomitant use of bosentan and PREZISTA/rtv may increase plasma concentrations of bosentan. In patients who have been receiving PREZISTA/rtv for at least 10 days, bosentan should be started at 62,5 mg once daily or once daily on every alternate day, based upon individual tolerability. For patients on bosentan and initiating PREZISTA/rtv, the use of bosentan should be discontinued at least 36 hours prior to initiation of PREZISTA/rtv. After at

least 10 days following the initiation of PREZISTA/rtv, bosentan should be resumed at 62,5 mg once daily or once daily on every alternate day based upon individual tolerability.

Fluticasone

Concomitant use of inhaled fluticasone and PREZISTA/rtv may increase plasma concentrations of fluticasone. Alternatives should be considered, particularly for long-term use.

HMG-CoA reductase inhibitors

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. Increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of PREZISTA/rtv with lovastatin and simvastatin is therefore not recommended.

The results of an interaction trial with atorvastatin show that atorvastatin (10 mg once daily) in combination with PREZISTA/rtv (300/100 mg twice daily) provides an exposure to atorvastatin that is only 15 % lower than that obtained with atorvastatin (40 mg once daily) alone. When administration of atorvastatin and PREZISTA/rtv 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. PREZISTA/rtv (600/100 mg twice daily) increased exposure to a single dose of pravastatin (40 mg) by approximately 80 %. However, in a subset of subjects the pravastatin exposure was increased 5-fold. Until more information is available regarding this interaction and the underlying mechanism, it is not recommended that pravastatin be co-administered with PREZISTA/rtv.

H_2-Receptor antagonists and proton pump inhibitors

Co-administration of omeprazole (20 mg once daily) or ranitidine (150 mg twice daily) and

PREZISTA/rtv (400/100 mg twice daily) did not affect the exposure to darunavir. Based on these results, PREZISTA/rtv can be co-administered with H_2-receptor antagonists and proton pump inhibitors without dose adjustments.

Inhaled beta agonist (salmeterol)

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

Immunosuppressants (ciclosporin, tacrolimus, sirolimus)

Exposure to ciclosporin, tacrolimus, or sirolimus may be increased when co-administered with PREZISTA/rtv. Therapeutic medicine monitoring of the immunosuppressive agent is recommended when co-administered with PREZISTA/rtv.

Ketoconazole, itraconazole and voriconazole

Ketoconazole, itraconazole and voriconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole or voriconazole and PREZISTA/rtv may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole or itraconazole may be increased by PREZISTA/rtv. The concomitant administration of ketoconazole (200 mg twice daily) with PREZISTA/rtv (400/100 mg twice daily) increased exposure of ketoconazole and darunavir by 212 % and 42 %, respectively. Concomitant use of ketoconazole, itraconazole and voriconazole with PREZISTA is contraindicated (see CONTRAINDICATIONS).

Plasma concentrations of voriconazole may be decreased in the presence of darunavir/ritonavir. Voriconazole should not be administered to patients receiving PREZISTA/rtv (see CONTRAINDICATIONS).

Methadone

An interaction trial investigating the effect of PREZISTA/rtv (600/100 mg twice daily) on a stable methadone maintenance therapy showed an AUC decrease of 16 % for R-methadone. Based on pharmacokinetic and clinical findings, no adjustment of methadone dosage is required when initiating co-administration of PREZISTA/rtv. However, clinical monitoring is recommended as maintenance therapy may need to be adjusted in some patients (see WARNINGS AND SPECIAL PRECAUTIONS).

Buprenorphine/naloxone

The results of an interaction trial with PREZISTA/rtv and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when administered with PREZISTA/rtv. Exposure of the active metabolite, norbuprenorphine, increased by 46 %. No dose adjustment for buprenorphine was required. Careful clinical monitoring is recommended if PREZISTA/rtv and buprenorphine are co-administered (see CONTRAINDICATIONS).

Oestrogen-based contraceptives

The results of an interaction trial between PREZISTA/rtv (600/100 mg twice daily) and ethinylestradiol (35 mcg) and norethindrone (1 mg) demonstrated that at steady-state systemic exposures to ethinylestradiol and norethindrone are decreased by 44 % and 14 %, respectively. Therefore, alternative methods of non-hormonal contraception should be used (see WARNINGS AND SPECIAL PRECAUTIONS).

PDE5 inhibitors

Treatment of erectile dysfunction

In an interaction trial a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with

PREZISTA/rtv (400/100 mg twice daily). Concomitant use of PDE5 inhibitors for the treatment of erectile dysfunction with PREZISTA/rtv should be done with caution. If concomitant use of PREZISTA/rtv with sildenafil, vardenafil, or tadalafil is indicated, reduced doses of the PDE5 inhibitors are recommended (see INTERACTIONS).

If concomitant use of PREZISTA/rtv with sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2,5 mg in 72 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended (see WARNINGS AND SPECIAL PRECAUTIONS).

Treatment of pulmonary arterial hypertension

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

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

Rifabutin

Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and PREZISTA/rtv is expected to increase rifabutin exposure and decrease darunavir exposure.

When indicated, it is recommended that rifabutin be administered at a dosage of 150 mg once every other day when combined with PREZISTA/rtv.

Selective Serotonin Reuptake Inhibitors (SSRIs)

In an interaction trial between paroxetine (20 mg once daily) or sertraline (50 mg once daily) and PREZISTA/rtv (400/100 mg twice daily), the exposure to darunavir was not affected by the presence of sertraline or paroxetine. Exposure to sertraline and paroxetine was decreased by 49 % and 39 %, respectively, in the presence of PREZISTA/rtv. If SSRIs are co-administered with PREZISTA/rtv, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/rtv should be monitored for antidepressant response.

Antidepressants (Trazodone)

Concomitant use of trazodone and PREZISTA/rtv may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A inhibitor such as PREZISTA/rtv, the combination should be used with caution and a lower dose of trazodone should be considered.

HUMAN REPRODUCTION

Pregnancy

Safety and efficacy have not been demonstrated. In animal studies the exposure was lower than in human exposure, and no conclusions were possible.

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 the potential for serious adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving PREZISTA.

Fertility

There was no effect on mating or fertility with PREZISTA treatment in rats.

DOSAGE AND DIRECTIONS FOR USE

PREZISTA must always be given with 100 mg ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The prescribing information of ritonavir including the contraindications and warnings must therefore be consulted prior to initiation of therapy with PREZISTA/rtv.

Adults:

The recommended dosage of PREZISTA is one 600 mg tablet twice daily taken with ritonavir 100 mg twice daily and with food. The type of food does not affect the exposure to darunavir. Ritonavir (100 mg twice daily) is used as a pharmacokinetic enhancer of darunavir (see INTERACTIONSand Pharmacokinetic Properties). A further increase in the dose of PREZISTA or ritonavir has been shown not to result in any clinically relevant increase in antiviral activity.

Children (less than 12 years of age) and adolescents (12 to 17 years of age):

The safety and efficacy of PREZISTA/rtv in these populations are not known.

Hepatic impairment:

No dose adjustment is required in patients with mild or moderate hepatic impairment. There are no data regarding the use of PREZISTA/rtv when co-administered to patients with severe hepatic impairment; therefore, specific dosage recommendations cannot be made. PREZISTA/rtv should not be used in patients with severe hepatic impairment, as safety and efficacy have not been demonstrated (see WARNINGS AND SPECIAL PRECAUTIONS).

Renal impairment:

No dose adjustment is required in patients with renal impairment (see WARNINGS AND SPECIAL PRECAUTIONS and Pharmacokinetic Properties).

SIDE EFFECTS

Adverse drug reactions (ADR's) identified in the safety assessment

The safety assessment is based on all safety data from the Phase IIb clinical trials reported with the recommended dose of PREZISTA/rtv 600/100 mg twice daily in patients who immediately started treatment with the recommended dose (*de novo* patients).

In clinical trials, the most frequent (≥ 10 %) ADRs were diarrhoea, headache, abdominal pain, nausea and fatigue.

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.

Adverse drug reactions to PREZISTA/rtv 600/100 mg twice daily, all grades, in antiretroviral treatment-experienced HIV-1-infected adult patients in the pooled Phase IIb clinical trials are

mentioned in the table below*:

* excluding laboratory abnormalities reported as ADRs

Within each system organ class, the ADRs are ranked under CIOMS headings of frequency, using the following convention: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (≤ 1/10 000), including isolated reports.

Pooled analysis

Phase IIb clinical trials (PREZISTA/rtv 600/100 mg twice daily + OBR[#], n=467)

System Organ Class & Frequency Category	**Adverse Drug Reaction**
Immune system disorders	
uncommon:	Immune reconstitution syndrome
Metabolism and nutrition disorders	
common:	Diabetes mellitus, anorexia
Psychiatric disorders	
uncommon:	Abnormal dreams
Nervous system disorders	
very common:	Headache
Gastrointestinal disorders	
very common: common: uncommon:	Diarrhoea, nausea, abdominal pain Vomiting, dyspepsia, abdominal distension, flatulence Acute pancreatitis

Hepatobiliary disorders	
uncommon:	Hepatitis acute
Skin and subcutaneous tissue disorders	
common:	Lipodystrophy (lipohypertrophy, lipodystrophy, and lipoatrophy), rash, pruritus
Musculoskeletal and connective tissue disorders	
common:	Myalgia
Reproductive system and breast disorders	
common:	Gynaecomastia
General disorders and administration site conditions	
very common: common:	Fatigue Asthenia

[#] Optimised Background Regimen.

Laboratory abnormalities, considered ADRs, in antiretroviral treatment-experienced HIV-1-infected adult patients in the pooled Phase IIb clinical trials are shown in the table below:

Pooled analysis Phase IIb clinical trials		
Laboratory Parameter Preferred Term	**Limit**	**PREZISTA/rtv 600/100 mg twice daily + OBR[#]** N=467
ALT Grade 2 Grade 3 Grade 4	 > 2,5 to ≤ 5,0 x ULN > 5,0 to ≤ 10,0 x ULN > 10,0 x ULN	 6,1 % 2,4 % 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	5,65 to 8,47 mmol/l	9,3 %
Grade 3	8,48 to 13,56 mmol/l	8,2 %
Grade 4	> 13,56 mmol/l	3,9 %
Total cholesterol*		
Grade 2	6,22 to 7,77 mmol/l	17,7 %
Grade 3	> 7,77 mmol/l	7,1 %
LDL cholesterol*		
Grade 2	4,14 to 4,92 mmol/l	13,2 %
Grade 3	≥ 4,92 mmol/l	9,1 %
Elevated glucose levels		
Grade 2	6,99 to 13,87 mmol/l	15,4 %
Grade 3	13,93 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 %

[#] Optimised Background Regimen.

[*] Grade 4 data not applicable in division of AIDS grading scale.

Additional adverse reactions in other clinical trials

System Organ Class & Frequency Category	**Adverse Reaction**
Skin and subcutaneous tissue disorders	
uncommon:	Stevens-Johnson Syndrome

[*] Incidence of at least grade 2 ADRs, calculated on pooled data of phase IIb and III trials (N=3 063).

[+] Adverse drug reactions identified from post-marketing experience.

POST-MARKETING EXPERIENCE

Adverse drug reactions identified during post-marketing experience.

System Organ Class	**Adverse Drug Reaction**
Immune system disorders	Hypersensitivity
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis Angioedema, urticaria
Musculoskeletal and connective tissue disorders	Osteonecrosis[+]

Combination antiretroviral therapy has been associated with redistribution of body fat

(lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

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

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

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.

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 were not higher than in patients receiving PREZISTA/rtv who were not co-infected, except for increased hepatic enzymes (see WARNINGS AND SPECIAL PRECAUTIONS). The pharmacokinetic exposure in co-infected patients was comparable to that in patients without co-infection.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

Human experience of acute overdose with PREZISTA/rtv is limited.

Treatment

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

IDENTIFICATION

Film-coated tablet. White oval-shaped, debossed with 600 MG on one side and TMC on the other side.

PRESENTATION

PREZISTA film-coated tablets are provided in white, high-density polyethylene (HDPE) plastic bottles containing 60 tablets fitted with yellow, polypropylene (PP) child resistant closures, lined with a silver aluminium induction seal. Bottles are packed into an outer cardboard carton together with a leaflet.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Protect from light.

Keep in original packaging until required for use.

Keep the bottle tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

45/20.2.8/0616

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

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