## PROFESSIONAL INFORMATION INSERT

## SCHEDULING STATUS

**S4**

## PROPRIETARY NAME AND DOSAGE FORM

**PREZISTA® 400 mg** (film-coated tablet)

## COMPOSITION

Each film-coated tablet of PREZISTA 400 mg contains 400 mg of darunavir (as darunavir ethanolate).

*Excipients:*

Colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, FD&C Yellow #6 Aluminium Lake, talc, titanium dioxide

Sugar free

## CATERGORY AND CLASS

A.20.2.8 Antiviral agents.

## PHARMACOLOGICAL ACTION

### Pharmacodynamic Properties

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).

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

Resistance *in vitro*

*In vitro* darunavir-resistant virus isolates from wildtype HIV-1 selected viruses showing decreased susceptibility to darunavir (range: 6-21-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: 53 641 fold change in $EC_{50}$ values) from 9 HIV-1 strains harbouring multiple PI (protease inhibitor) 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. A minimum of 8 of these darunavir *in vitro* selected mutations, from

which at least 2 were already present in the protease prior to selection, were required in the HIV-1 protease to render a virus resistant (fold change [FC] > 10) to darunavir.

In 1 113 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir and in 886 baseline isolates from the patients enrolled in clinical trials, only the subgroups with > 10 PI RAMs showed a median FC for darunavir > 10.

Cross-resistance *in vitro*

Cross-resistance has been observed among HIV protease inhibitors. Darunavir has a < 10-fold decreased susceptibility against 90 % of 3 309 clinical isolates resistant to at least one protease inhibitor. Seven of the nine darunavir resistant viruses selected from PI resistant viruses had phenotypic data for tipranavir. Six of those showed a fold change (FC) < 3 for tipranavir, indicative of cross-resistance between these 2 protease inhibitors.

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

**Pharmacokinetic Properties**

The pharmacokinetic properties of 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 well absorbed following oral administration in the presence of low-dose ritonavir. 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 substance. 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 wild type 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 use of darunavir in combination with ritonavir in the paediatric population for the once daily dose.

*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 (see WARNINGS AND SPECIAL PRECAUTIONS).

*Gender*

Population pharmacokinetic analysis showed a slightly higher darunavir exposure 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 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) and moderate (Child Pugh Class B, n=8) hepatic impairment were comparable with those in healthy subjects. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS).

**INDICATIONS**

PREZISTA, in combination with low dose ritonavir (PREZISTA/rtv) and with other antiretroviral medicines, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment experienced adult patients who are protease-inhibitor-naïve patients or after exclusion of darunavir resistance associated mutations (DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V).

Genotypic or phenotypic testing should guide the use of PREZISTA/rtv.

Ritonavir is used as a pharmacokinetic enhancer of darunavir.

There is no information on the use of darunavir in combination with ritonavir in the paediatric population for the once daily dose.

## 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) isoform. PREZISTA/rtv should not be co-administered with medicines 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 medicines are included in the table below:

| **Medicines that are contraindicated with PREZISTA/rtv** | |
|---|---|
| **Medicine Class:**<br>Medicine Name | Clinical Comment |
| **Anticonvulsants:**<br>Phenobarbitone<br>Phenytoin | Phenobarbitone and phenytoin are inducers of CYP450 enzymes. PREZISTA/rtv should not be used in combination with phenobarbitone, or phenytoin, as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA (see INTERACTIONS). |
| **Antihistamines:**<br>Astemizole | CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmia. |

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| **Antimycobacterial:**<br>Rifampicin<br><br>Rifabutin | 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 therapeutic effect to PREZISTA (see INTERACTIONS).<br>The exposure to rifabutin and its active metabolite was increased 3-fold and the incidence of side effects was doubled when rifabutin was given at a dose of 150 mg every other day in combination with PREZISTA and ritonavir (see INTERACTIONS). |
| **Endothelin receptor antagonist:**<br>Bosentan | Concomitant use of bosentan and PREZISTA/rtv shoud be avoided (see INTERACTIONS). |
| **PDE-5 inhibitor:**<br>Sildenafil - when intended for the 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). |
| **Antigout:**<br>Colchicine in patients with hepatic or renal impairment | Co-administration of PREZISTA/rtv in patients with renal or hepatic impairment is contraindicated due to the potential risk of colchicine-induced toxic effects. |
| **Alpha 1-adreno-receptor antagonist:**<br>Alfuzosin | Potential for serious and/or life-threatening reactions such as hypotension. |

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| **Ergot Derivatives:**<br>Dihydroergotamine<br>Ergonovine<br>Ergotamine<br>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. |
| **GI Motility Agents:**<br>Cisapride | CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmia. |
| **Hepatitis C virus (HCV) direct-acting antivirals:**<br>**NS3-4A protease inhibitors**<br>Boceprevir<br>Telaprevir | It is not recommended to co-administer PREZISTA/rtv with boceprevir or telaprevir (see INTERATIONS). |
| **Herbal Products:**<br>St. John's wort (*Hypericum perforatum*) | PREZISTA/rtv should not be used concomitantly with products containing St. John's wort (*Hypericum perforatum*) because co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA (see INTERACTIONS). |
| **HMG-CoA reductase inhibitors:**<br>Lovastatin<br>Simvastatin | Potential for serious reactions such as risk of myopathy including rhabdomyolysis. |

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| **Neuroleptic:**<br>Pimozide | CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac dysrhythmia. |
| **Sedative/Hypnotics:**<br>Midazolam, Triazolam | CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. |
| **Antifungals:**<br>Ketoconazole<br>Itraconazole<br>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 buprenorphine/naloxone was 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, including PREZISTA, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

*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).

*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.

PREZISTA should 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.

*Severe skin reactions*

During the clinical development program, severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported. Stevens-Johnson Syndrome has been reported; and during post-marketing experience toxic epidermal necrolysis has also been reported. PREZISTA should be discontinued 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. The discontinuation rate due to rash in patients using PREZISTA/rtv was 0,5 %.
Rash occurred more commonly in treatment-experienced subjects receiving regimens containing PREZISTA/rtv + raltegravir compared to subjects receiving PREZISTA/rtv without raltegravir or raltegravir without PREZISTA/rtv. However, rash that was considered medicine related occurred at similar rates for all three groups.

*Sulpha allergy*

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

Patients with coexisting conditions

*Hepatic impairment*

PREZISTA should not be used in patients with severe hepatic impairment. 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, 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, 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 the elimination of PREZISTA 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).

*Haemophilia 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 such as PREZISTA. Haemophilia patients should therefore be made aware of the possibility of increased bleeding.

*Hyperglycaemia*

New onset diabetes mellitus, hyperglycaemia, or exacerbation of pre-existing diabetes mellitus has been reported in patients receiving PREZISTA.

*Lipodystrophy and metabolic abnormalities*

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral

wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

*Immune Reconstitution Inflammatory Syndrome*

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

*Osteonecrosis*

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term

exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

*Opportunistic infections*

Patients receiving PREZISTA should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

*Interactions with medicines*

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).

For medicines that are highly dependent on the metabolism by CYP3A and that have a narrow therapeutic index, such as amiodarone, bepridil, (systemic) lidocaine and quinidine, plasma concentrations of such medicines could increase when combined with PREZISTA/rtv. This can lead to prolongation or increase of their therapeutic effect and adverse events (see INTERACTIONS).

*HMG-CoA Reductase Inhibitors*

Concomitant use of PREZISTA/rtv with simvastatin, pravastatin or lovastatin is not recommended due to an increased risk of myopathy, including rhabdomyolysis, as a consequence of increased plasma concentrations of simvastatin, pravastatin or lovastatin.

*Methadone*

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 (see INTERACTIONS).

*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).

*PDE-5-Inhibitors*

If concomitant use of PREZISTA/rtv with sildenafil, vardenafil, or tadalafil is indicated, reduced doses of the PDE-5 inhibitors are recommended (see CONTRAINDICATIONS and INTERACTIONS).

**Effects on ability to drive and use machines**

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

**INTERACTIONS**

Darunavir and ritonavir are both inhibitors of the cytochrome CYP3A. Co-administration of PREZISTA and ritonavir 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.

PREZISTA/rtv should not be co-administered with medicines 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 medicines include astemizole, 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 CONTRAINDICATONS).

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 therapeutic effect to PREZISTA (see CONTRAINDICATONS and WARNINGS AND SPECIAL PRECAUTIONS).

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

**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 low dose 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. There was no change in the urinary excretion of tenofovir or darunavir during co-administration. Tenofovir did not have a clinically 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 other NRTIs such as 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 administered concomitantly with nevirapine. Exposure to nevirapine increased by 27 % (compared to historical controls) when administered in combination with PREZISTA/rtv. Since this difference is not considered to be clinically relevant, the combination of PREZISTA/rtv and nevirapine can be used without dose adjustments.

*Rilpivirine*

In an interaction trial between PREZISTA/rtv (800/100 mg once daily) and rilpivirine (150 mg once daily), no clinically relevant effect on darunavir exposure was observed. Exposure to rilpivirine increased by 130 % (2,3-fold) when administered in combination with PREZISTA/rtv. Since this difference is not considered to be clinically relevant, the combination of PREZISTA/rtv and rilpivirine can be used without dose adjustments.

HIV protease inhibitors (PIs)

*Ritonavir*

The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg PREZISTA was given orally in combination with ritonavir at 100 mg twice daily. Therefore, PREZISTA should only be used in combination with low dose 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 trial 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) demonstrated that systemic exposure to darunavir and atazanavir was not significantly affected when co-administered. Atazanavir can be co-administered with PREZISTA/rtv.

*Indinavir*

In an interaction trial between PREZISTA/rtv (400/100 mg 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.

*Other HIV protease inhibitors*

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

CCR5 antagonist

When used in combination with PREZISTA/rtv, the dose of maraviroc should be 150 mg twice daily.

An interaction trial between PREZISTA/rtv (600/100 mg twice daily) and maraviroc (150 mg twice daily) demonstrated that in the presence of PREZISTA/rtv the exposure of maraviroc was increased 4-fold. There was no apparent effect of maraviroc on darunavir/ritonavir exposure.

**Other medicines:**

*Alfuzosin*

Exposure to alfuzosin may be increased when co-administered with PREZISTA/rtv. Concomitant use of PREZISTA/rtv with alfuzosin is contraindicated (see CONTRAINDICATIONS).

Antidysrhythmics (*bepridil, systemic lidocaine, quinidine and amiodarone*)

Exposure to bepridil, lidocaine, quinidine and amiodarone may be increased when co-administered with PREZISTA/rtv. Caution is warranted and therapeutic medicine monitoring of antidysrhythmics is recommended when PREZISTA is administered with antidysrhythmic medicines.

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 normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/rtv.

Anticonvulsants (phenobarbitone, phenytoin and carbamazepine)

*Phenobarbitone and phenytoin*

Phenobarbitone 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 (see CONTRAINDICATIONS).

*Carbamazepine*

An interaction trial between PREZISTA/rtv (600/100 mg twice daily) and carbamazepine (200 mg twice daily) 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.

*Antimalarials*

An interaction trial between PREZISTA/rtv (600/100 mg twice daily) and artemether/lumefantrine (80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours) showed an increase in exposure to lumefantrine by 2,75-fold, while exposure to darunavir was not affected. The exposure to artemether and its active metabolite, dihydroartemisinin, decreased by 16 % and 18 %, respectively. The combination of PREZISTA and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.

*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 0,5 mg (1 tablet), followed by 0,25 mg 1 hour later. Treatment course to be repeated no earlier than 3 days. For the prophylaxis of gout flares in patients on PREZISTA/rtv, the recommended dose of colchicine is 0,25 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 0,5 mg every day (may be given as 0,25 mg twice daily). Patients with renal or hepatic impairment should not be given colchicine with PREZISTA/rtv.

*Antihistamines (Astemizole)*

Exposure to these antihistamines may be increased when co-administered with PREZISTA/rtv. Concomitant use of PREZISTA/rtv with astemizole is contraindicated (see CONTRAINDICATIONS).

*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 an increase in exposure to clarithromycin by 57 %, while exposure to darunavir was not affected. For patients with renal impairment, a dose reduction of clarithromycin should be considered.

For patients with renal impairment, the following dose adjustments should be considered:

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

*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*

Bosentan is metabolised by cytochrome CYP3A4 and CYP2C9. Concomitant use of bosentan and PREZISTA should be avoided (see CONTRAINDICATIONS).

*Fluticasone*

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

Hepatitis C virus (HCV) direct-acting antivirals:

NS3-4A protease inhibitors

Boceprevir

In an interaction trial between PREZISTA/rtv (600/100 mg twice daily) and boceprevir (800 mg three times daily), darunavir exposure was reduced by 44 % and boceprevir exposure was reduced by 32 %. It is not recommended to co-administer PREZISTA/rtv with boceprevir (see CONTRAINDICATIONS).

Telaprevir

In an interaction trial between PREZISTA/rtv (600/100 mg twice daily) and telaprevir (750 mg every 8 hours), darunavir exposure was reduced by 40 % and telaprevir exposure was reduced by 35 %. It is not recommended to co-administer PREZISTA/rtv with telaprevir (see CONTRAINDICATIONS).

HMG CoA reductase inhibitors

HMG CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A metabolism, are therefore expected to have markedly increased plasma concentrations when co-administered with PREZISTA/rtv. Increased concentrations of HMG CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of PREZISTA/rtv with lovastatin and simvastatin is therefore not recommended (see CONTRAINDICATIONS).

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, which 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 %, but only in a subset of subjects. When administration of pravastatin and PREZISTA/rtv is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effects while monitoring safety (see WARNINGS AND SPECIAL PRECAUTIONS).

An interaction study evaluating PREZISTA/rtv (600/100 mg twice daily) in combination with rosuvastatin (10 mg once daily) resulted in a 50 % increase in rosuvastatin exposure. It is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.

$H_2$ 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 once 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 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 drug 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. This was confirmed in an interaction trial where 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).

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.

Oestrogen based contraceptives

The results of an interaction trial between PREZISTA/rtv (600/100 mg twice daily) and ethinylestradiol and norethindrone 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).

PDE-5 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 PDE-5 inhibitors for the treatment of erectile dysfunction with PREZISTA/rtv should be done with caution. If concomitant use of PREZISTA/rtv with sildenafil, vardenafil, or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2,5 mg dose in 72 hours or tadalafil at a single dose not exceeding 10 mg dose in 72 hours is recommended (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, once daily and increase to 40 mg once daily 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 once daily and increase to 40 mg once daily based upon individual tolerability.

Rifabutin

Rifabutin is a substrate of CYP450 enzymes. In an interaction trial, an increase of systemic exposure to darunavir by 57 % was observed, when PREZISTA/rtv (600/100 mg twice daily) was administered with rifabutin (150 mg once every other day). 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 exposure to rifabutin (sum of main compound and its active metabolite) was increased 3-fold and the incidence of side effects was doubled when rifabutin was given at a dose of 150 mg every other day in combination with PREZISTA and ritonavir (see CONTRAINDICATIONS).

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.

## PREGNANCY AND LACTATION

### 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.

## DOSAGE AND DIRECTIONS FOR USE

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

*Adults:*

Genotypic or phenotypic testing should guide the use of PREZISTA/rtv. PREZISTA/ritonavir 800/100 mg once daily dosing regimen is recommended in HIV protease-inhibitor-naïve patients and in treatment-experienced patients with demonstrated absence of DRV-RAMs. PREZISTA should be given with food. The type of food does not affect the exposure to darunavir. Ritonavir

(100 mg) is used as a pharmacokinetic enhancer of darunavir (see INTERACTIONS and Pharmacokinetic Properties).

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

The safety and efficacy of the once daily dose of PREZISTA/rtv in paediatric patients has not been established.

*Missed Dose(s):*

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

*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 to PREZISTA/rtv identified in the ODIN trial**

Adverse Drug Reactions to PREZISTA/rtv 800/100 mg once daily (q.d.) of at least moderate intensity (grade 2 to 4) in antiretroviral treatment-experienced HIV-1 infected adult patients in the ODIN trial are mentioned in the table below.

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.

| ***Adverse Drug Reactions of at Least Grade 2 - ODIN trial*** (PREZISTA/rtv 800/100 mg daily + OBR#, n=[294]) | |
|---|---|
| **System Organ Class &** Frequency category | **Adverse Drug Reaction** |
| **Metabolism and nutrition disorders** | |
| Common: | Hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hypertriglyceridaemia |
| Uncommon: | Diabetes mellitus, anorexia, dyslipidaemia, lipodystrophy, low density lipoprotein increased |
| **Nervous system disorders** | |
| Common: | Headache |
| **Gastrointestinal disorders** | |
| Common: | Diarrhoea, vomiting, nausea, abdominal pain |
| Uncommon: | Abdominal distension, dyspepsia, flatulence, pancreatic enzymes increased |
| **Skin and subcutaneous tissue disorders** | |

| | |
|---|---|
| Common:<br><br>Uncommon: | Rash<br><br>Pruritus |
| **Musculoskeletal and connective tissue disorders** | |
| Uncommon: | Myalgia |
| **General disorders and administration site conditions** | |
| Uncommon: | Asthenia, fatigue |

* Excluding laboratory abnormalities reported as ADRs

# Optimised Background Regimen

Laboratory abnormalities, considered ADRs, in antiretroviral treatment-experienced HIV-1 infected adult patients of at least Grade 2 in the ODIN trial, are shown in the table below:

| **Laboratory Abnormalities of at least Grade 2 - ODIN trial**<br>(PREZISTA/rtv 800 mg daily + OBR#, n=[286])<br>**Worst Treatment Emergent Toxicity Grades*** | |
|---|---|
| | DRV/rtv 800/100 mg q.d<br>(N=286) |
| General Biochemistry | |
| Amylase | |
| Grade 2 | 3,1 % |
| Grade 3 | 2,4 % |
| Grade 4 | 0,3 % |
| Lipase | |
| Grade 2 | 1 % |
| Grade 3 | 0,3 % |

| **Laboratory Abnormalities of at least Grade 2 - ODIN trial**<br><br>(PREZISTA/rtv 800 mg daily + OBR#, n=[286])<br><br>**Worst Treatment Emergent Toxicity Grades*** | |
|---|---|
| | DRV/rtv 800/100 mg q.d<br><br>(N=286) |
| Lipids and Glucose | |
| Glucose | |
| Grade 2 | 6,3 % |
| Grade 3 | 0,7 % |
| Low Density Lipoprotein Calculated | |
| Grade 2 | 7 % |
| Grade 3 | 2,8 % |
| Total Cholesterol | |
| Grade 2 | 7,7 % |
| Grade 3 | 2,4 % |
| Triglycerides | |
| Grade 2 | 3,5 % |
| Grade 3 | 1,4 % |
| Grade 4 | 0,3 % |
| Liver Function | |
| Alanine Amino Transferase | |
| Grade 2 | 1,7 % |
| Alkaline Phosphatase | |
| Grade 2 | 0,7 % |
| Aspartate Amino Transferase | |

| **Laboratory Abnormalities of at least Grade 2 - ODIN trial**<br>(PREZISTA/rtv 800 mg daily + OBR#, n=[286])<br>**Worst Treatment Emergent Toxicity Grades*** | |
|---|---|
| | DRV/rtv 800/100 mg q.d<br>(N=286) |
| Grade 2 | 1,4 % |
| Grade 3 | 0,7 % |

# Optimised Background Regimen

* Only grading categories with observed laboratory values are listed

**Additional adverse drug reactions to PREZISTA/rtv identified in other clinical trials**

| **System Organ Class** | **Adverse Drug Reaction** | **Incidence*** |
|---|---|---|
| Immune System Disorders | Immune reconstitution syndrome | Uncommon |
| Psychiatric Disorders | Abnormal dreams | Uncommon |
| Gastrointestinal disorders | Acute pancreatitis | Uncommon |
| Hepato-biliary disorders | Hepatitis acute | Uncommon |
| Skin and subcutaneous tissue disorders | Angioedema<br>Stevens-Johnson Syndrome | Uncommon |

| | | |
|---|---|---|
| | Urticaria | |
| Reproductive System and Breast Disorders | Gynaecomastia | Uncommon |

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

**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, Acute Generalised Exanthematous Pustulosis |
| 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.

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.

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

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 TREATMENT**

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

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

Light orange oval-shaped, film-coated tablet, debossed with “TMC” and “400MG” on opposite sides.

## PRESENTATION

60 tablets are packed in a white, high-density polyethylene bottle and sealed with a white, polypropylene child resistant closure, lined with an aluminium induction seal.

## STORAGE INSTRUCTIONS

Store at or below 30 °C.

Keep the bottle tightly closed.

Keep in original container packaging until required for use.

**KEEP OUT OF REACH OF CHILDREN.**

## REGISTRATION NUMBER

47/20.2.8/1173

## 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**

Date of registration: 2 June 2017

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2 June 2017