Prezista™
darunavir

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of darunavir (corresponding to 325,23 mg of darunavir ethanolate).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacoterapeutic group: Antiviral for systemic use, ATC code: JO5A-E010.

Mechanism of action

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

Darunavir tightly binds to the HIV-1 protease with a K_D of 4.5×10^{-12} M.

Darunavir shows resilience to the effects of protease inhibitors resistance-associated mutations.
Darunavir is not an inhibitor of any of 13 tested human cellular proteases.

Antiviral activity *in vitro*

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/ml). Darunavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M(A,B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM. These EC50 values are well below the 50% cellular toxicity concentration range of 87 µM to > 100 µM.

The EC50 values 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, nelfinafir, or amprenavir and additive antiviral activity when studied in combination with the protease inhibitors indinavir, saquinavir, lopinavir, atanazanavir, or tipnavir, the N(t)RTIs zidovudin, lamivudine, zalcitabine, didanosine, stavudine, abacavir, emtricitabine, or tenofovir, the NNRTIs nevirapine, delavirdine, or efavirenz and the fusion inhitors enfuvirtide. No antagonism was observed between darunavir and any of those antiretrovirals.

Resistance *in vitro*

In vitro selection of PREZISTA-resistant virus from wildtype HIV-1 was lengthy (up to 2 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 220nM. viruses selected in these conditions and showing decreased suspectibility to darunavir (range: 6-12-fold) harboured 3 to 6 amino acid substitutions in the protease gene. Identification of determinants of decreased suspectibility to darunavir in those viruses is under investigation.

In vitro selection of PREZISTA resistant HIV-1 (range:53-641-fold change in EC50 value) from 9 HIV-1 strains harbouring multiple PI resitance associated mutations resulted in the overall emergence of 22 mutation in the protease, of wich L10F,V321, L33F, S37N,M461, 147V, 150V, L63P, A71V and 184v were presents in more than 50% of the 9 PREZISTA- 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 reguired in the HIV-1 protease to render a virus resistant (fold change [FC] > 10) to PRESTISTA.
In 1113 clinical isolates resistant to amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir, and in 886 baseline isolates from the patients enrolled in the POWER 1 and POWER 2 trials and in the POWER 3 analysis, only the subgroups with .10 PI resistance- associated mutations showed a median FC for PRESZISTA >10.

Cross- resistance *in vitro*
Cross-resistance has been observed among protease inhibitors. PREZISTA has a <10-fold decreased suspectibility against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lovinafir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to most Pls remain suspectible to PREZITA.
Seven of the 9 PREZISTA- resistant viruses selected from PI-resistant viruses had phenotypic data for tifranavir, Six of those showed a fold Change in EC 50 value, 3 for tipranavir, indicative of limited cross- resistance between these 2 protease inhibitors. Cross-resistance between PREZIZTA 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.

Clinical experience
The evidence of efficacy of PREZISTA/rtv is based on the analyses of 24-week data from 2 ongoing, randomised, controlled trials in antiretroviral treatment experience HIV-1 infected adult patients (POWER 1 and POWER 2). These efficacy results were confirmed by the 24-week pooled analysis of the label trials TMC 114-C215 and TMC114-c208 (POWER 3 analysis).

POWER 1 and POWER 2 are randomised, controlled Phase 2b trials consisting of 2 parts: an initial partially blinded, doses-finding part and a second long term part in which all patients randomised to PREZISTA/rtv received the recommended dose of 600/100 md b.i.d.
HIV-1 infected patients who were eligible for these trials had plasma HIV-1 RNA > 1000 copies/ml, had prior treatment with PI(s). NNRTI(s) and NRTI(s), had at least 1 primary PI mutation at screening and were on a stable PI-containing regimen at screening for at least 8 weeks. Randomisation was stratified by the number of PI mutations, screening viral load and the use of enfuvirtide.
This analysis included 318 patients in POWER 1 and 319 patients in POWER 2 who had completed 24 weeks of treatment or discontinued earlier.
Demographics and baseline characteristics were balanced between the PREZISTA/rtv and the comparator arm. in both studies combined, the 131 patients on PREZISTA/rtv 600/100 mg b.i.d. had a median age of 43.0 years (range 27-73), 89 % were male, 81 % white 10% black and 7% hispanic. The median baseline plasma HIV1 RNA was 4.52 $\log_{10}$ copies /ml (rangea02,99-6.44 $\log_{10}$ copies/ml) and the median baselin CD+ cell count was 153 x 106 cell (range 3-776 $x10^6$ cell/l). The median darunavir FC was 4.3 in the PREZISTA/rtv 600/100 mg b.i.d. arm patients had prior exposure to a mean of 4 Pls, 5 NRTIs versus 4 Pls, 6 NRTIs in the comparator arm. Nineteen percent of the patients in the prezista/rtv arm had prior use of a fusion inhibitor versus 16% in the comparator arm.
At 24 weeks the virologic response, defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 $\log_{1\,0}$ versus baseline, was evaluated in patients receiving PREZISTA/rtv plus an optimised back ground regimen (OBR) versus a control group receiving an investigator-selected PI (s) regimen plus an OBR. The OBR consisted of at least 2 NRTIs without enfuvirtide (ENF).

Based on resitance testing and prior medical history, selected PIs in the control arm included: lopinavir/ ritonavir in 36%, three percent of the control patients used dual-boosted PIs. Approximately 47% of all patients used enfuvirtide and 35% of the use was in patiens who were ENF-naive.

POWER 3: additional data on the efficacy of PREZISTA/rtv 600/100 mg b.i.d. have been obtained in treatment -experienced participating in the non randomised trials TMC114-C215 and TMC 114-208. The 246 patient from these trials included in the 24-weeks POWER 3 efficacy analysis iniated therapy with PREZISTA/rtv with the recommended dose of 600/100 mg b.i.d. The OBR consisted of at least two NRTIs with or without enfuvirtide. Entry criteria were the same as and baseline characteristics were comparable to those of POWER 1 and POWER 2. The median baseline plasma HIV-1 RNA was 4.60 $\log_{10}$ copies/ml (range 1.69 - 6.43 $\log_{10}$ copies/ml) and the median CD4+ cell count was 115 x 10^6 cells/l (range 0 - 831 x 10^6 cells/l). The median darunavir FC was 3.2. Patients had a prior exposure to 5 PIs, 6 NRTIs and 1 NRTI, 30% had prior use of enfuvirtide. Baseline characteristics are based on the total of 327 patients included in TMC 114-C215 and TMC 114-C208, whereas efficacy data are based on the available interim data 246 patients who had reached 24 weeks of treatment or discontinued earlier than the 24-week cut-off of the POWER 3 analysis.

The table below shows the efficacy data of the 24-week analyses on the recommended dose PREZISTA/rtv 600/100 mg b.i.d. from the pooled POWER 1 and POWER 2 trials as well as from the 24-week POWER 3 analysis.

	POWER 1 and POWER 2 pooled data			POWER 3
Outcomes	PREZISTA/rtv 600/100 mg b.i.d. N = 131	Control N = 124	Treatment difference	PREZISTA/rtv 600/100 mg b.i.d. N = 246
HIV-1 RNA Log change from baseline ($\log_{10}$ copies/ml) 1)	-1.89	-0.48	LSM 2) -1.41	-1,65
CD4+ cell count change from baseline (x 10^6/l) 3)	92	17	LSM 2) 75	80
HIV-1 RNA.>= 1 $\log_{10}$ below baseline 4)	92 (70%)	26 (21%)	Odds Ratio 5) 13.2	160 (65%)
HIV-1 RNA.< 400 copies/ml) 4)	82 (63%)	23 (19%)	Odds Ratio 5) 12.3	141 (57%)
HIV-1 RNA.< 50 copies/ml) 4)	59 (45%)	15 (12%)	Odds Ratio 5) 10.8	98 (40%)

1) Non-complementer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0.
2) Treatment differences are based on Least Square means from an ANOVA model including the stratification factors. P-values < 0.001.
3) Last Observation Carried Forward imputation.
4) Imputation according to the TLOVR algorithm.
5) Odds ratios are derived from logistic regression models including the stratification factors.

Response rates and changes in the treatment arms are observed data. P-values <0.001.

In the pooled POWER 1 and POWER 2 analysis, the proportion of patients in the PREZISTA/rtv (600/100 mg b.i.d.) arm provided superior decreases in $\log_{10}$ viral load from baseline compared to the comparator arm. At week 24, the proportion of patients in the PREZISTA/rtv arm resulted in 70% of patients with a decrease of at least 1.0 $\log_{10}$ in viral load, compared to 21% in the comparator arm. The proportion of patients with HIV-1 RNA < 50 copies/ml was 45% in the PREZISTA/rtv arm compared to 12% for the comparator arm.
The 24-week efficacy POWER 3 analysis confirmed the viral load reduction and CD4+ increase observed in the POWER 1 and POWER 2 trials. Of the 246 patients included in the week-24 analysis, 65% had a virologic response defined as a decrease of at least 1.0 $\log_{10}$ in plasma viral load versus baseline and 40% of the patients reached less than 50 HIV RNA copies/ml.

Additionally, suportive long-term efficacy data of PREZISTA/rtv 600/100 mg b.i.d. in treatment-experienced patients up to 48 weeks is available from the pooled analysis of POWER 1 and POWER 2. For patients reaching week-48 or discontinued earlier the 48-week analysis suggest that responses were sustained, the same percentage of patients were undetectable (< 50 HIV RNA copies/ml) at week-24 and week-48 (45% and 45% respectively).

<u>Antiviral activity of PREZISTA/rtv in treatment-experienced patients</u>
in the phase 2 trials POWER 1 and 2 and the POWER 3 analysis,458 highly treatment experienced patients received PRESZISTA/rtv in their initial regimen at the selected 600/100mg b.i.d. dose.

In vivo selection of viral resistance during PREZISTA/rtv therapy
In the phase 2 trials POWER 1 and POWER 2 in the POWER 3 analysis, multiple protease inhibitor-resistant HIV-1 isolates from highly treatment experinced patients who received PREZISTA/rtv and experienced virologic failure,either by rebound (data available for 50 patients), or by never being suppressed (data avaiblable for 70 patients), developed amino acid substitutions that were associated with a decrease insuspectibility to darunavir. The amino acid subsitutions that developed on PREZISTA/rtv 600/100 mg b.i.d. In greather than 20% of FREZISTA/rtv virologic failure isolates were V321 and 154L. Other subsitutions that developmed in 10 to 20% of PREZISTA/rtv virologic failure isolates were L33F, 147V and L89V.

In vivo cross-resistance with other protease inhibitors
Currently, little information is available on cross-resistance of viruses selected during therapy with PREZISTA/rtv. In viruses isolated from patients experiencing virologic failure by rebound from the PREZISTA/rtv 600/100 mg b.i.d group, a median PREZISTA FC increase of 8.14 at endpoint compared to baseline was found. In the same group of patients, no FC incrase (median increase of 0.82) at endpoint compared to baseline was found for tipranavir, suggesting limited cross-resistance between these 2 pls. Patients with resistence to tipranavir (FC>3) at baseline showed a mean change in viral load at week-24 of-1.38 $\log_{10}$. The FC increase could not be studied for the other pls, since the baseline isolates were already resistant to these Pls. Patients with no susceptible commercially available PI at baseline (thus excluding tipranavir) showed a mean change in viral load at week-24 of -1.57 $\log_{10}$.

Baseline genotype and virologic outcome

Analysis were conducted to evaluated the impact of spesific baseline protease inhibitor resistance-associated mutations at baseline on virologic response. The presence at baseline of the mutations V321,147V,or 154L or M, was associated with a decreased virologic response to darunavir and decreased susceptibility to darunavir in the POWER 1 and POWER 2 studies.
In addition, a diminished virologic response was observed in patients with≥ 7 PI resistance-associated mutations (any change at position 30,32,36,46,47,48,50,53,54,73,82,84,88 or 90) at baseline. Nevertheless, the response rate in all subgroups (by type and number of mutation at baseline) was generally higher in the darunavir/rtv groups compared to the response rate in the control groups. In a supportive analysis of the POWER 1 and POWER 2 studies and the POWER 3 analysis, the presence at baseline of three or more of the mutations V11I, V321, L33F, 147V, 150V, 154L,or M, G73S, L76V, 184V or L89V was associated with a decreased virologic response to PREZISTA/rtv.

Response to PREZISTA/rtv 600/100 mg b.i.d. by baseline genotype*:
As-treated analysis of studies POWER1,POWER2 and POWER3

Number s at baseline of mutation*	Change in log_{10} viral load at week 24	Proportion of subjects with ≥ 1 log_{10} decrease at week 24	Proportion of subjects with < 50 copies/ml at week 24
0-2	-2.1	78% 213/274	50% 138/274
3	-1.12	45% 26/58	22% 13/58
≥ 4	-0.46	27% 11/41	10% 4/41

Number of mutation from the list of mutations associated with a diminished response to PREZISTA/rtv (321, L33F, 147V,150V 154L or M, G73s, L76V, 184V or L89V)
Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.
Baseline darunavir phenotype (shift in suspectibility relative to reference) was shown to be a predictive factor virologic out come.
Response rates assessed by baseline darunavir phenotype are shown in the table below. These baseline phenotype groups are based on the select patient populations in the power 1 and POWER 2 studies and the POWER 3 analysis and are not meant to represent definitive clinical suspectibility breakpoints. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment suspectibility to darunavir in PI-experienced patients.

Response to PREZISTA/rtv 600/100 mg b.i.d. by baseline darunavir phenotype. As-treated analysis of studies POWER 1, POWER 2 and POWER 3

Baseline darunavir phenotype N=349	Proportion of subjects with ≥ 1 log_{10} decrease at week 24	Proportion of subjects with < 50 log_{10} copies/ml at week 24
< 10	82% 201/244	53% 129/244
10 – 40	44% 27/62	26% 16/62
> 4	40% 17/43	14% 6/43

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

Phamacokinetic properties

The pharmacokinetic properties of PREZISTA, co-administered with ritonavir, have been evaluated in health adult volunteers and 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 concentration.

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

Absorption

Darunavir was rapidly absorbed following oral administration. Maximum plasma consentration of darunavir in the presence of low-dose ritonavir is generally achieved within 2.5-4.0 hours.

The absolute oral bioavaibility of a single 600mg dose of PREZISTA alone was approximately 37% and increased to approximately 82% in the presence of 100 mg b.i.d. ritonavir. The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg PREZISTA was given orally in combination with ritonavir at 100 mg b.i.d (see Special warning and Precaution for Use).

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

Distribition

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 health volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg PREZISTA/rtv dose was due to the parent drug. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 10-fold less than the activity of darunavir against wildtype HIV.

Elimination

After a 400/100mg ^{14}C-darunavir/rtv dose, appoximately 79,5% and 13.9% of the administered dose of ^{14}C-darunavir could be retrived in faeces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feaces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir.The intravenous clearance of darunavir alone (150mg) and in the

presence of low-dose ritonavir was 32.8 i/h and 5.9l/h,respectively.

Special population

Paediatrics

The pharmacokinetic of PREZISTA in combination with ritonavir in paediatric subjects are under investigation. There are insufficient data at this time to recommend a dose.

Elderly

Population pharmacokinetic analysis in HIV-infecfected showed that PREZISTA pharmacokinetics are not considerably different in the age range (18 to75 years) evaluated in HIV infected patients (n=12, age≥65)see special warning and precautions for use).

Gender

Population pharmacokinetic analysis showed a slightly higher darunavir exposure (16.8) in HIV infected female compared to males. This difference is not clinically relevant.

Renal impairment

Result 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 urin as uchanged drug.

Although PREZIZTA has not been studied in patients with renal imparment, population pharmacokinetic analysis showed that the pharmacokinetics of PREZISTA were not signicicantly affected in HIV infected patients with moderate renal imparment (CrCl beetwen 30-60 ml/min, n=20) (see Posology and Method of Administration ; and special warnings and precaution for use).

Hepatic impairment

Darunavir is primarily metabolised and eliminated by the liver. PREZISTA has not yet been studied in patients with hepatic impairment (see Posolgy and Method of Administration; and Special Warnings and Precautions for Use)

Preclinical Safety Data

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

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

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

and postnatal development assessment in rats, darunavir with and without ritonavir, caused a transient reduction in body weight of the offspring during lactation. This was attributed to drug exposure via the milk. No post weaning function were affected with darunavir alone or in combination with ritonavir.
Long term carcinogenicity studies of darunavir in rodents have not been completed. Darunavir, however , was tested negative in the *in vitro* Ames reverse mutation assay and *in vitro* chromosonal aberration assay in human lymphocyte, both tested in the absence and presence of metabolic activation system. Darunavir did not induce chromosomal damage in the *in vivo* micronucleous test in mice.

CLINICAL PARTICULARS

Therapeutic Indications

PREZISTA, in combination with 100 mg ritonavir (PREZISTA/rtv) and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment experienced adult patients.
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 antiretroviral drugs. Additional data is available from open label studies (see Pharmacodynamic properties).
Clinical studies on the use of PREZISTA/rtv in HIV infected paediatric patients and in antiretroviral treatment naive adult patients are ongoing.

Posology and Method of Administration

PREZISTA mustalways be given with 100 mg ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The prescribing information of ritonavir must therefore be consulted prior to initation of therapy with PREZISTA/rtv.

Adults: The recommended dosage of PREZISTA is 600 mg twice daily (b.i.d) taken with ritonavir 100 mg b.i.d and with food. The type of food does not affect the exposure to darunavir. Ritonavir (100 mg b.i.d) is used as a pharmacokinetic enhancer of darunavir (see interaction with Other Medicinal Products and Other Forms of Interactions ; and Pharmacokinetic properties). A futher increase in the dose of PREZISTA or ritonavir is not likely to result in any clinically relevant increase in antiviral activity.

Chlidren (*less than 12 years of age) and adolescent* (12 to 17 years of age): the safety and efficacy of FREZISTA/rtv in these populations are under investigation. there are insufficient data at this time to recommend a dose (see pharmacokinetic properties).

Hepatic impairment : There are currently no data regarding the use of PREZISTA/rtv when co-administered to patients with hepatic impairment; therefore specific dosage rcommendation cannot be made. PREZISTA/rtv should be used with caution in patients with hepatic impairment (see Special Warning and Precaution for Use; and Pharmacokinetics properties).

Renal impairment: no dose adjusment is required in patients with renal impairment (see special warnings and precautions for use; and pharmacokinetic properties).

Missed dose : The missed dose should be taken as soon as possible, if the dose was missed by

less than 6 hours. The next dose of PREZISTA and ritonavir should be taken at the regulary scheduled time. if the dose of PREZISTA or ritonavir was missed by more than 6 hours, the next dose of PREZISTA or ritonavir should be taken at regulary scheduled time. Doses should not be doubled.

method of administration : oral administration

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

There are insufficient data at this time to recommed a dose in antiretrovial treatment naive 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, reclecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy (see pharmacokinetic properties).

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

Darunavir countains a sulfonamide moiety.
PREZISTA should be used with caution in patients with a known sulfonamide allergy.
During the clinical development program, severe skin rash, including erythema multiforme and stevens-johsons Syndrome, has been reported. In some cases,fever and elevations of transaminases have also been reported. In clinical (n=924), rash (all grades, regardless of causality) occurred in 7 % of subjects treated with PREZISTA; the discontinuation rate due to rash was 0.3%. Rashes were generally mild-to-moderate, self-limited maculopapular skin eruptions. Treatment with PREZISTA should be discontinue if severse rash develops.

<u>Patients with coexisting condition</u>
Liver disease
Darunavir and ritonavir are primaly metabolised and eliminated by the liver and increased plasma concentration are expected in patients with hepatic impairment. There arecurrently no data regarding the use of PREZISTA/rtv when co-administered to patients with hepatic impairment; therefore, specific dosage recomendations cannot in patients with hepatic impairment (see posology and metod of administration ; and pharmacokinetic).

Patients with pre-extisting liver disfuction, including cronic active hepatitis, can have an

increased frequency of liver function abnormalities during combination antiretrovinal therapy and should be monitored according to standard practise. If there is evidence of worsening of liver disease in such patients, interruption or discontinuation of treatment must be considered

Renal disease
Since the renal clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis (see Posology and Method of Administration; 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 of these patients editional factor VIII was given. In more than half of the repoted cases, treatment with PIs was continued or reintroduced if treatement have been discontinued. A causal relationship has been sugested, although the mechanism of action has not been elucidated. Haemophilia patients should therefore be made aware of the possibility of increased bleeding.

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

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

Osteonecrosis
Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol comsumption, severe immunosupression, 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.

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 month of initiation of

CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis carinii* pneumonia. any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Interactions with medicinal products

Darunavir and ritonavir are both inhibitors of the CYP3A4 isoform. Co-administration of PREZISTA and ritonavir with medicinal products primarily metabolised by CYP3A4 may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect and adverse events (see Contraindications and Interaction with Other Medicinal Products and Other Forms of Interaction).

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 Interaction with Other Medicinal Products and Other Forms of Interaction).

PREZISTA/rtv should not be used concomitantly with products containing St. John's worth (*Hypericum perforatum*) because co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA (see Interaction with Other Medicinal Products and Other Forms of Interaction).

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism. Concomitant use of PREZISTA/rtv with simvastatin or lovastatin is not recommended due to an increased risk of myopathy, including rhabdomyolysis, as a consequence of increased plasma concentrations of simvastatin and lovastatin. PREZISTA/rtv increased exposure to pravastatin by approximately 80%, but only in a subset of subject. The clinical relevance of this interaction is currently unknown. Until more information is available regarding this interaction and the underlying mechanism, it is not recommended to co-administer pravastatin with PREZISTA/rtv.
If treatment with an HMG-CoA reductase inhibitor is dedicated, reduced starting doses of atorvastatin are recommended (see Interaction with Other Medicinal Products and Other Forms of Interaction).

When methadone is co-administered with PREZISTA/rtv, patients should be monitored for opiate abstinence syndrome, as ritonavir is known to induce the metabolism of methadone, leading to a decrease of methadone plasma concentrations (see Interaction with Other Medicinal Products and Other Forms of Interaction).
The phosphodiesterase type 5 (PDE5) inhibitors sildenafil, vardenafil and tadalafil are highly dependent on CYP3A4 for thir metabolism. If concomitant use of PREZISTA/rtv with sildenafil, vardenafil, or tadalafil is indicated, reduced doses of the PDE5 inhibitors are recommended (see Interaction with Other Medicinal Products and Other Forms of Interaction).

For medicinal products that are highly dependent on the metabolism by CYP3A4 and that have a narrow therapeutic index, such as amiodarone, bepridil, (systemic) lidocaine and quinidine, plasma concentrations of such medicinal products could increase when combined with PREZISTA/rtv. This can lead to prolongation or increase of their therapeutic effect and adverse events (see Interaction with Other Medicinal Products and Other Forms of Interaction).

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 therapeutic effect to PREZISTA (see Interaction with Other Medicinal Products and Other Forms of Interaction).

UNDESIRABLE EFFECTS

The safety assessment is based on all safety data from the POWER 1 and POWER 2 trials and the POWER 3 analysis (see pharmacodynamic properties) reported with the recommended dose PREZISTA/rtv 600/100 mg b.i.d. in the 458 patients who immediately started treatment with the recommended dose (*de novo* patients).

In the *de novo* patients, the most frequently (≥ 2%) reported adverse reactions that were at least grade 2 in severity and considered possibly related to PREZISTA /rtv were diarrhea (2.6%), vomiting (2.2%) and hypertriglyceridaemia (2.0%).
Forty percent of these patients experienced at least one adverse event that was drug related.
The majority of the AEs reportedduring treatmnet with PREZISTA/rtv 600/100 mg b.i.d were grade 1 and 2 in severity. The most commonly reported grade 3 or 4 events were increased blood amylase (3.3%) and increased GGT (2.2%). All other grade 3 or 4 AEs were reported in less than 2% of the patients.
Four percent of the patients discontinued treatment due to AEs.

The most frequent clinical adverse reactions reporrted in the *de novo* patients are summarized below. The adverse reactions are listed by system organ class and frequency. Frequencies are defined as very common (≥ 1/10), common (≥1/100, < 1/10) and uncommon (≥ 1/1000 and <1/100). The frequency was calculated using adverse reactions that were of at least moderate intensity (grade 2 or more) and reported by the investigators as being attributable (at least possible causal relationship) to PREZISTA/rtv.

<u>The most frequent clinical adverse reactions were* :</u>

Body system	Adverse reaction	Frequency
Metabolism and nutritional disorders	hypertriglyceridaemia	Common
Nervous System disorders	headache	Common
Gastrointestinal disorders	Diarrhea, vomiting, nausea, abdominal pain, constipation	Common

<u>Uncommon adverse reactions of at least moderate intensity were* :</u>

- Infections and infestations: folliculitis
- Metabolism and nutrition disorders: anorexia, hypercholesterolaemia, hyperlipidaemia, diabetes mellitus, decreased appetite, obesity, fat redistribution, hyponatraemia, polydipsia
- Psychiatric disorders: confusional state, disorientation, irritability, altered mood, nightmares, anxiety.
- Nervous system disorders: peripheral neuropathy, hypoaesthesia, memory impairment, paraesthesia, somnolence, transient ischaemic attack.
- Ear and labyrinth disorders: vertigo
- Cardiac disorders: myocardial infarction, tachycardia
- Vascular disorders: hypertension
- Respiratory, thoracic and mediastinal disorders: dyspnoea, cough, hiccups

- Gastrointestinal disorders: flatulence, abdominal distension, dry mouth,dyspepsia
- Skin and subcutaneous disorders: lipoatrophy, night sweats, allergic dermatitis, eczema, toxic skin eruption, alopecia, dermatitis medicamentosa, hyperhidrosis, skin inflammation, maculopapular rash
- Musculoskeletal, connective tissue and bone disorders: arthalgia, pain in extremity, myalgia, osteopenia,
  osteoporosis
- Renal and urinary disorders: acute renal failure, renal insufficiency, nephrolithiasis, polyuria
- Reproductive system and breast disorders: gynaecomastia
- General disorders: asthenia, pyrexia, fatigue, rigors, hyperthermia, peripheral oedema

* Adverse reactions reported in the SOC "Investigations" and "Blood and Limphatic disorder" are addressed under laboratory abnormalities.

Laboratory abnormalities
Treatment emergent clinical laboratory abnormalities (grade 3 or 4) observed in the *de novo* patients and reported in greater than or equal to 2% of subjects were increases in triglycerides (8.6%), pancreatic amylase (6.6%), total cholesterol (4.9%), gamma glutamyltransferase (GGT) (3.8%), partial thromboplastine time (PTT) (3.6%), pancreatic lipase (3.5%), alanine aminotransferse (ALT) (2.4%), aspartate aminotransferase (AST) (2.2%) and decreases in white blood cell count (6.4%), neutrophils (4,7%), total absolute neutrophils count (4.2%), lymphocytes (3.8%). All other abnormal laboratory parameters were observed in less than 2% of the subjects.

Severe cases of skin rash, including erythema multiforme and Stevens-Johnson Syndrome have been reported in ongoing clinical trials withPREZISTA/rtv.

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 hyperthropy and dorsocervical fat accumulation (buffalo hump).

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

Increased CPK, myalgia, myositis and rarely, rhaabdomyolysis 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 infection may arise.

Patients co-infected with hepatitis B and/or hepatitis C virus
Patients co-infected with hepatitis B and/or hepatitis C virus receiving PREZISTA/rtv did not experience higher incidence of adverse event and clinical chemistry abnormalities than patients receiving PREZISTA/rtv who were not co-infected. The pharmacokinetics exposure is co-infected patients was comparable to that in patients without co-infection. Standard clinical monitoring of hepatitis patients is considered adequate.

CONTRAINDICATION
Hypersensitivity to darunavir or to any of the excipients.

Darunavir and ritonavir are both inhibitors of the cytochrome P450 3A4 (CYP3A4) isoform. PREZISTA/rtv should not be co-administered with medicinal product that are highly dependent on CYP3A4 for clearance and for which increased plasma concentration are associated with serious and/or life-threatning events (narrow therapeutic index). These medicinal products include astemizole, terfenadine, midazolam, triazolam, cisapride, pimozide, and the ergots alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (see interactions with Other Medicinal Products and Other Forms of Interaction).

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Darunavir and ritonavir are both inhibitors of the CYP3A4 isoform. Coadministration of PREZISTA and ritonavir and medicine products primarily metabolized by CYP3A4 may result in increaswd plasma concentrations of such medicine 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 CYP3A4 for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These medicinal products include astemizole, terfenadine, midazolam, triazolam, cisapride, pimozide and 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 therapeutic effect to PREZISTA (see Special Warnings and Precautions for Use).

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 Special Warnings and Precautions for Use).

Antiretroviral medicine products

<u>Nucleoside/nucleotide reverse transcriptase inhibitor (N(t)RTIs)</u>
Didanosine
It is recommended that didanosine be administered on an empty stomach. Therefore, 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 q.d.) demonstrated that the systemic exposure of tenofavir was increased by 22% when co-administered with PREZISTA/rtv (300/100 mg b.i.d.). This finding is not considered to be clinically relevant. There was no change in the urinary excreation of tenofovir or darunavir during

co-administration. Tenofovir did not have a significant influence on darunavir exposure. No dose adjustments of PREZISTA, ritonavir, or tenofovir disoproxil fumarate are required when these drugs are co-administered.

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

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

Nevirapine
The result of an interaction trial with PREZISTA/rtv (400/100 mg b.i.d.) and nevirapine (200 mg b.i.d.) demonstrated that darunavir exposure was not affected when administered concominantly 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 single dose of 600 mg PREZISTA was given orally in combination with ritonavir at 100 mg b.i.d. Therefore, PREZISTA should only be used in combination with 100 mg of ritonavir as a pharmacokinetic enhancer (see Special Warnings and Precautions for Use ; and Pharmacokinetic properties).

Lopinavir/ritonavir

The results of an interaction trial with PREZISTA/rtv (300/100 mg b.i.d.) and lopinavir/ritonavir (400/100 mg b.i.d.) demostrated that exposure to is decreased by 53% in the presence of lopinavir/ritonavir (with or without an additional dose of 100 mg ritonavir). The exposure to lopinavir decreased by 19% when co-administered with PREZISTA alone and increased by 37% when co-administered with PREZISTA/rtv. It is not recommended to combine lopinavir/ritonavir and PREZISTA, with or without an additional low-dose ritonavir.

Saquinavir

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

Atazanavir

An interaction trial between PREZISTA/rtv (400/100 mg b.i.d.) and atazanavir (300 mg q.d) demonstrated that systemic exposured to darunavir and atazavir was not 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 b.i.d) and indinavir (800 mg b.i.d) and indinavir (800 mg b.i.d),darunavir exposure was increased by 24% in the presence of indinavir/rtv; indinavir exposure was increased by 23% in the presence of PREZISTA/rtv. When used in combination with PREZISTA/rtv, dose adjustment of indinavir from 800 mg b.i.d. to 600 mg b.i.d. may be warranted in case of intolerance.

Other protease inhibitors

The co-administration of PREZISTA/rtv and pis other than lopinavir/ritonavir, atazanaavir and indinavir have not beeb studied. Therefore, such so-administration is not recommended**.**

Other medical products

Antiarrythmics (bepridil,systemiclidocaine, quinidine and amiodarone)
Exposure to bepridil,lidocaie, quinidine and amiodarone may be increased whe co-administered with PREZISTA/rtv. CAution is warranted and therapic drug monitoring of antiarrhythmics is recommended when available.

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

Anticonvulsants (phenobarbital,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 cause significant decreases in darunavir plasma concentrations. this may result in loss of therapeutic effect to PREZISTA (see Special Warnings and Precautions for Use).

Calcium channel blockers
The exposure to calcium channel blockers (e.g., felopine, 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 b.i.d.) and clarithromycin (500 mg b.i.d.) showed an increase in exposure to by 57%, while exposure to darunavir was not affected. For patients with renal impairment, a dose reduction of clarithromycin should be considered.

Dexamethasone
Systemic dexamethasone induced CYP3A4 and thereby may decrease darunavir exposure. This may result in loss of therapeutic effect. Therefore this combination should be used with caution.

Fluticasone propionate
Concomitant use of inhaled fluticasone propionate and PREZISTA/rtv may increase plasma concentrations of fluticasone propionate. 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 CYP3A4 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 myophaty, including rhabdomyolysis. Concomitant use of PREZISTA/rtv with lovastatin and simvastatin is therefore not recommended.
The result of an interaction trial with atorvastatin show that atorvastatin (10 mg q.d.) in combination with PREZISTA/rtv (300/100 mg b.i.d.) provides an exposure to atorvastatin, which is only 15% lower than that obtained with atorvastatin (40 mg q.d.) alone. When administration of atorvastatin and PERZISTA/rtv is desired, it is recommended to start with an atorvastatin dose of 10 ng q.d. A gradual dose increase of atorvastatin may be tailored to the clinical response.
PERZISTA/rtv (600/100 mg b.i.d.) increased exposure to a single dose of pravastatin (40 mg) by approximately 80%, but only in a subset of subjects. The clinical relevance of this interaction is currently unknown. Until more information is available regarding this interaction and the underlying mechanism, it is not recommended to co-administer pravastatin with PREZISTA/rtv (see Special Warnings and Precautions for Use).

H_2-Receptor antagonists and proton pump inhibitors
Co-administration of omeprazole (20 mg q.d.) or ranitidine (150 mg b.i.d.) and PREZISTA/rtv (400/100 mg b.i.d.) 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 adjusments.

Immunosuppressant (cyclosporine, tacrolimus, sirolimus)
Exposure to cyclosporine, tacrolimus, 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 CYP3A4. Concomitant systemic use of ketoconazole, itraconazole and voriconazole and PREZISTA/rtv may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole, itraconazole and voriconazole may be increased by PREZISTA/rtv. This was confirmed in an interaction trial where the concomitant administration of ketoconazole (200 mg b.i.d.) with PREZISTA/rtv (400/100 mg b.i.d.) increased exposure of ketoconazole and darunavir by 212% and 42%, respectively. When co-administration is required the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Although enzymes other than CYP3A are also involved with voriconazole metabolism, an increase in voriconazole

exposure may be anticipated when co-administered with PREZISTA/rtv.

Methadone
When methadone is co-administered with PREZISTA/rtv, patients should be monitored for opiate abstinence syndrome, as ritonavir is known to induce the metabolism of methadone, leading to a decrease in its plasma concentrations. An increase in methadone dosage may be considered based on clinical response (see Special Warnings and Precautions for Use).

Estrogen-based contraceptives
Exposure to ethinylestradiol may be decreased by induction of its metabolism by ritonavir. Alternative or additional contraceptive measures should be used when estrogen-based contraceptives are co-administered with PREZISTA/rtv (see Special Warnings and Precautions for Use).

PDE-5 inhibitors
In an interaction trial a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with PREZISTA/rtv (400/100 mg b.i.d.).
Concomitant use of PDE-5 inhibitors 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, vardenavil at a single dose not exceeding 2.5 mg dose in 72 hours or tadafil at single dose not exceeding 10 mg dose in 72 hours is recommended (see Special Warnings and Precautions for Use).

Rifabutin
Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and PREZISTAN/rtv is expected to increase rifabutin exposure and decrease darunavir exposure. When indicated, it is recommended to administer rifabutin 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 q.d.) or sertaline (50 mg q.d.) and PREZISTA/rtv (400/100 mg b.i.d.), the exposure to darunavir was not affected by the presence of sertaline or paroxetine. Exposure to sertaline 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 sertaline or paroxetine who start treatment with PREZISTA/rtv should be monitored for antidepressant response.

Pregnancy and Lactation

Pregnancy
There are no adequate and well controlled studies with darunavir in pregnant women. Studies in animals have not shown evidance off developmental toxicity or effect on reproductive function and fertility (see Preclinical Safety Data).
PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk.
Lactation

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

Fertility
There was no effect on mating or fertility with PREZISTA treatment in rats (see Preclinical Safety Data).

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

Overdose

Human experience of acute overdose with PREZISTA/rtv is limited. Single doses up to 3200 mg of the oral solution of PREZISTA alone and up to 1600 mg of the tablet formulation of PREZISTA i n combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects
There is no specific antidote for overdose with PREZISTA. Treatment of overdose with PREZISTA consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. 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.

SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30^{o}C.

Shelf life
2 years.

HARUS DENGAN RESEP DOKTER

Manufactured by Jassen Ortho LLC, Gurabo, Puerto Rica
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