

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

PREZISTA 300 mg film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of darunavir (as ethanolate).

Excipient: Each tablet contains 1.375 mg sunset yellow FCF (E110). For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange oval shaped tablet, debossed with “300MG” on one side and “TMC114” on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

PREZISTA, co-administered with 100 mg ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adult patients who failed more than one regimen containing a protease inhibitor (PI).

This indication is based on week-24 analyses of virological and immunological response from 2 controlled dose range finding Phase II trials and additional data from uncontrolled studies (see section 5.1).

In deciding to initiate treatment with PREZISTA co-administered with 100 mg ritonavir careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of PREZISTA.

### 4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

PREZISTA must always be given orally with 100 mg ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of ritonavir must therefore be consulted prior to initiation of therapy with PREZISTA.

*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 (see sections 4.4, 4.5 and 5.2).

*Children and adolescents:* PREZISTA is not recommended for use in children and adolescents because there are no data on safety, efficacy and pharmacokinetics.

*Elderly:* Limited information is available in this population (see sections 4.4 and 5.2).

*Hepatic impairment:* Darunavir is metabolised by the hepatic system. Severe liver impairment could therefore result in an increase of darunavir exposure and a worsening of its safety profile. Therefore, PREZISTA should be used with caution in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment and should not be used in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3, 4.4 and 5.2).

*Renal impairment:* No dose adjustment is required in patients with renal impairment (see sections 4.4 and 5.2).

In case a dose of PREZISTA and/or ritonavir was missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of PREZISTA and ritonavir with food as soon as possible. If this was noticed later than 6 hours of the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

This guidance is based on the 15 hour half-life of darunavir in the presence of ritonavir and the recommended dosing interval of approximately 12 hours.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Patients with severe (Child-Pugh Class C) hepatic impairment.

Rifampicin must not be used with PREZISTA because co-administration may cause large decreases in darunavir concentrations which may in turn significantly decrease the darunavir therapeutic effect (see section 4.5).

Herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking PREZISTA due to the risk of decreased plasma concentrations and reduced clinical effects of darunavir (see section 4.5).

Co-administration of PREZISTA with 100 mg ritonavir, with active substances that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. These active substances include e.g. antiarrhythmics (amiodarone, bepridil, quinidine, systemic lidocaine), antihistamines (astemizole, terfenadine), ergot derivatives (e.g. dihydroergotamine, ergonovine, ergotamine, methylergonovine), gastrointestinal motility agents (cisapride), neuroleptics (pimozide, sertindole), sedatives/hypnotics (triazolam, orally administered midazolam) and HMG-CoA reductase inhibitors (simvastatin and lovastatin) (see section 4.5).

### **4.4 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 transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be employed.

PREZISTA should only be used in combination with 100 mg of ritonavir as a pharmacokinetic enhancer (see section 5.2).

Increasing the dose of ritonavir from that recommended in section 4.2 did not significantly affect darunavir concentrations and is not recommended.

*Elderly:* As limited information is available on the use of PREZISTA 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 sections 4.2 and 5.2).

Darunavir binds predominantly to  $\alpha$ 1-acid glycoprotein. This protein binding is concentration dependent indicative for saturation of binding. Therefore, protein displacement of medicinal products highly bound to  $\alpha$ 1-acid glycoprotein cannot be ruled out.

Darunavir contains a sulphonamide moiety. PREZISTA should be used with caution in patients with a known sulphonamide allergy. During the clinical development program, severe skin rash, including erythema multiforme and Stevens-Johnson Syndrome, has been reported. Treatment with PREZISTA should be discontinued if severe rash develops.

## Patients with coexisting conditions

### *Liver disease*

The safety and efficacy of PREZISTA have not been established in patients with severe underlying liver disorders and PREZISTA is therefore contraindicated in patients with severe liver impairment. PREZISTA should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment should be considered.

### *Renal disease*

No special precautions or dose adjustments are required 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. Therefore, no special precautions or dose adjustments are required in these patients (see sections 4.2 and 5.2).

### *Haemophiliac patients*

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis in patients with haemophilia type A and B treated with PIs. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued or reintroduced if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

### Diabetes mellitus/Hyperglycaemia

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

### Fat redistribution and metabolic disorders

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age and with 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 section 4.8).

### Osteonecrosis

Although the etiology 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.

### Immune reactivation syndrome

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia caused by *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. In addition, reactivation of herpes simplex and herpes zoster has been observed in clinical studies with PREZISTA co-administered with 100 mg ritonavir.

#### Interactions with medicinal products

Several of the interaction studies have been performed at lower than recommended doses of darunavir. The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated. For full information on interactions with other medicinal products see section 4.5.

PREZISTA tablets contain sunset yellow FCF (E110) which may cause an allergic reaction.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Darunavir and ritonavir are both inhibitors of the CYP3A4 isoform. Co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP3A4 may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions.

PREZISTA co-administered with 100 mg ritonavir must not be combined with medicinal products that are highly dependent on CYP3A4 for clearance and for which increased systemic exposure is associated with serious and/or life-threatening events (narrow therapeutic index). These medicinal products include amiodarone, bepridil, quinidine, systemic lidocaine, astemizole, terfenadine, midazolam, triazolam, cisapride, pimozone, sertindole, simvastatin, lovastatin and the ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine and methylergonovine) (see section 4.3).

The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg b.i.d. Therefore, PREZISTA must only be used in combination with 100 mg of ritonavir as a pharmacokinetic enhancer (see sections 4.4 and 5.2).

Several of the interaction studies (see tables below) have been performed at lower than recommended doses of darunavir. The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated.

#### *Medicinal products that affect darunavir/ritonavir exposure*

Darunavir and ritonavir are metabolised by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir (e.g. rifampicin, rifabutin, St John's wort, lopinavir). Co-administration of darunavir and ritonavir and other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (e.g. indinavir, systemic azoles like ketoconazole and clotrimazole). These interactions are described in the interaction tables below.

#### ***Interaction table***

Interactions between darunavir/ritonavir and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in the tables below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”, twice daily as “b.i.d.” and once daily as “q.d.”).

### Interactions – Darunavir/ritonavir with Protease Inhibitors

The efficacy and safety of the use of PREZISTA with 100 mg ritonavir and any other PI (e.g. (fos)amprenavir, nelfinavir and tipranavir) has not been established in HIV patients. Generally, dual therapy with protease inhibitors is not recommended.

Co-administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Dose of darunavir/ritonavir (mg)	Medicinal Product Assessed	AUC	C <sub>min</sub>
Lopinavir/ritonavir	400/100 b.i.d.	300/100 b.i.d.	Lopinavir Darunavir	↑ 37% ↓ 53%	↑ 72% ↓ 65%
It is not recommended to combine PREZISTA co-administered with 100 mg ritonavir with lopinavir/ritonavir.					
Saquinavir	1000 b.i.d.	400/100 b.i.d.	Darunavir	↓ 26%	↓ 42%
The study with boosted saquinavir showed no significant effect of darunavir on saquinavir. It is not recommended to combine PREZISTA co-administered with 100 mg ritonavir with saquinavir.					
Indinavir	800 b.i.d.	400/100 b.i.d.	Indinavir Darunavir	↑ 23% ↑ 24%	↑ 125% ↑ 44%
When used in combination with PREZISTA co-administered with 100 mg ritonavir, dose adjustment of indinavir from 800 mg b.i.d. to 600 mg b.i.d. may be warranted in case of intolerance.					
Atazanavir	300 q.d.	400/100 b.i.d.	Atazanavir Darunavir	↔ ↔	↔ ↔
Darunavir/ritonavir did not significantly affect atazanavir exposure, however 90% CI for C <sub>min</sub> were 99 – 234%. Atazanavir can be used with PREZISTA co-administered with 100 mg ritonavir.					

### Interactions – Darunavir/ritonavir with Antiretroviral Agents other than Protease Inhibitors

Co-administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Dose of darunavir/ritonavir (mg)	Medicinal Product Assessed	AUC	C <sub>min</sub>
Efavirenz	600 q.d.	300/100 b.i.d.	Efavirenz Darunavir	↑ 21% ↓ 13%	↑ 17% ↓ 31%
Efavirenz decreases the plasma concentrations of darunavir as a result of CYP3A4 induction. Darunavir/ritonavir increases the plasma concentrations of efavirenz as a result of CYP3A4 inhibition. Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when PREZISTA co-administered with 100 mg ritonavir is given in combination with efavirenz.					
Nevirapine	200 b.i.d.	400/100 b.i.d.	Nevirapine Darunavir	↑ 27% ↔	↑ 47% ↔
Darunavir/ritonavir increases the plasma concentrations of nevirapine as a result of CYP3A4 inhibition. Since this difference is not considered to be clinically relevant, the combination of PREZISTA co-administered with 100 mg ritonavir and nevirapine can be used without dose adjustments.					
Tenofovir	300 q.d.	300/100 b.i.d.	Tenofovir Darunavir	↑ 22% ↔	↑ 37% ↔

Ritonavir effect on MDR-1 transport in renal tubuli has been a proposed mechanism for increased plasma concentrations of tenofovir. Monitoring of renal function may be indicated when PREZISTA co-administered with 100 mg ritonavir is given in combination with tenofovir, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.

Zidovudine Didanosine Zalcitabine Emtricitabine Stavudine Lamivudine Abacavir	Based on the different elimination pathways of the other NRTIs zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine, that are primarily renally excreted, and didanosine and abacavir for which metabolism is not mediated by CYP450, no interactions are expected for these medicinal compounds and PREZISTA co-administered with 100 mg ritonavir.
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### Interactions – Darunavir/ritonavir with Non-antiretroviral co-administered Medicinal Products

Co-administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Dose of darunavir/ritonavir (mg)	Medicinal Product Assessed	AUC	C <sub>min</sub>
<b>Antiarrhythmics</b>					
Digoxin	0.4 mg single dose	600/100 b.i.d.	Digoxin	↑ 60%	ND
Darunavir/ritonavir increases the plasma concentrations of digoxin. Inhibition of Pgp may be a likely explanation. Given that digoxin has a narrow therapeutic index, it is recommended that the lowest possible dose of digoxin should initially be prescribed in case digoxin is given to patients on darunavir/ritonavir therapy. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject.					
<b>Antibiotics</b>					
Clarithromycin	500 b.i.d.	400/100 b.i.d.	Clarithromycin Darunavir	↑ 57% ↔	↑ 174% ↔
Darunavir/ritonavir increases the plasma concentrations of clarithromycin as a result of CYP3A4 inhibition and possible Pgp inhibition. Concentrations of the metabolite 14-OH-clarithromycin were not detectable. Caution is warranted and clinical monitoring is recommended. For patients with renal impairment, a dose reduction of clarithromycin should be considered.					
<b>Anticoagulant</b>					
Warfarin	Warfarin concentrations may be affected when co-administered with darunavir with ritonavir. The international normalised ratio (INR) should be monitored when warfarin is combined with PREZISTA co-administered with 100 mg ritonavir.				
<b>Anticonvulsants</b>					
Phenobarbital Phenytoin Carbamazepine	Phenobarbital, phenytoin and carbamazepine are inducers of CYP450 enzymes. PREZISTA co-administered with 100 mg ritonavir should not be used in combination with these medicines, as co-administration may cause significant decreases in darunavir plasma concentrations.				
<b>Antifungals</b>					

Voriconazole	The combined use of voriconazole with darunavir co-administered with 100 mg ritonavir has not been studied. Voriconazole is metabolised by cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Ritonavir, which can induce some of these isoenzymes, may decrease voriconazole plasma concentrations. Voriconazole should not be co-administered with PREZISTA with 100 mg ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.				
Ketoconazole	200 b.i.d.	400/100 b.i.d.	Ketoconazole	↑ 212%	↑ 868%
			Darunavir	↑ 42%	↑ 73%
	Ketoconazole is a potent inhibitor as well as substrate of CYP3A4. Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of ketoconazole should not exceed 200 mg.				
Itraconazole	Itraconazole, like ketoconazole, is a potent inhibitor as well as substrate of CYP3A4. Concomitant systemic use of itraconazole and darunavir co-administered with 100 mg ritonavir may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of itraconazole may be increased by darunavir co-administered with 100 mg ritonavir. Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of itraconazole should not exceed 200 mg.				
Clotrimazole	Concomitant systemic use of clotrimazole and darunavir co-administered with 100 mg ritonavir may increase plasma concentrations of darunavir. This was confirmed using a population pharmacokinetic model. The increase in the median darunavir AUC <sub>24h</sub> value for the patients taking clotrimazole from the overall median was 33%. Caution is warranted and clinical monitoring is recommended, when co-administration of clotrimazole is required.				

#### Calcium channel blockers

Felodipine Nifedipine Nicardipine	Darunavir and ritonavir inhibit CYP3A4 and as a result can be expected to increase the plasma concentrations of calcium channel antagonists, which are CYP3A4 substrates. Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with PREZISTA with 100 mg ritonavir.				
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#### HMG Co-A Reductase Inhibitors

Lovastatin Simvastatin	Lovastatin and simvastatin, which are highly dependent on CYP3A4 metabolism are expected to have markedly increased plasma concentrations when co-administered with darunavir co-administered with 100 mg ritonavir. This may cause myopathy, including rhabdomyolysis. Concomitant use of PREZISTA co-administered with 100 mg ritonavir with lovastatin and simvastatin is therefore contraindicated (see section 4.3).				
Atorvastatin	10 q.d.	300/100 b.i.d.	Atorvastatin	3 – 4 times ↑	3 – 4 times ↑
			Darunavir	ND	ND
	The results of this interaction trial show that atorvastatin (10 mg q.d.) in combination with darunavir/ritonavir (300/100 mg b.i.d.) provides an exposure to atorvastatin, which is only 15% lower than that obtained with (40 mg q.d.) atorvastatin alone. When administration of atorvastatin and PREZISTA co-administered with 100 mg ritonavir is desired, it is recommended to start with an atorvastatin dose of 10 mg q.d. A gradual dose increase of atorvastatin may be tailored to the clinical response.				
Pravastatin	40 mg single dose	600/100 b.i.d.	Pravastatin	0 – 5 times ↑	ND



Darunavir/ritonavir did not increase exposure to a single dose of pravastatin in most subjects but up to 5-fold in a limited subset of subjects. When administration of pravastatin and PREZISTA co-administered with 100 mg ritonavir is required, it is recommended to start with the lowest possible dose of pravastatin and titrate it up to the desired clinical effect while monitoring for safety.

<b>Hormonal contraceptive</b>					
Ethinylestradiol	35 µg/1 mg q.d.	600/100 b.i.d.	Ethinylestradiol	↓ 44%	↓ 62%
Norethindrone			Norethindrone	↓ 14%	↓ 30%
Alternative or additional contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with PREZISTA and 100 mg ritonavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.					
<b>Immunosuppressants</b>					
Cyclosporine	Exposure to cyclosporine, tacrolimus, or sirolimus will be increased when co-administered with PREZISTA co-administered with 100 mg ritonavir.				
Tacrolimus					
Sirolimus	Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs.				
<b>H2-receptor antagonists and proton pump inhibitors</b>					
Ranitidine	150 b.i.d.	400/100 b.i.d.	Darunavir	↔	↔
Based on these results, PREZISTA co-administered with 100 mg ritonavir can be co-administered with H <sub>2</sub> -receptor antagonists without dose adjustments.					
Omeprazole	20 q.d.	400/100 b.i.d.	Darunavir	↔	↔
Based on these results, PREZISTA co-administered with 100 mg ritonavir can be co-administered with proton pump inhibitors without dose adjustments					
<b>Opioids</b>					
Methadone	When methadone is co-administered with PREZISTA co-administered with 100 mg ritonavir, 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.				
<b>PDE-5 inhibitors</b>					
Sildenafil	In an interaction study 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 darunavir/ritonavir (400/100 mg b.i.d.). Concomitant use of PDE-5 inhibitors with PREZISTA co-administered with 100 mg ritonavir should be done with caution. If concomitant use of PREZISTA co-administered with 100 mg ritonavir 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.				
Vardenafil					
Tadalafil					
<b>Rifamycines</b>					
Rifabutin	Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and darunavir with ritonavir is expected to increase rifabutin exposure and decrease darunavir exposure; co-administration of a standard dose of rifabutin is not recommended as this may be associated with rifabutin intolerance. Therefore, whenever indicated, it is recommended to administer rifabutin at a dosage of 150 mg once every other day when combined with PREZISTA co-administered with 100 mg ritonavir. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients.				

Rifampicin Rifampicin is a potent inducer of CYP450 metabolism. PREZISTA co-administered with 100 mg ritonavir must not be used in combination with rifampicin, as co-administration may cause significant decreases in darunavir plasma concentrations (see section 4.3).

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**Selective Serotonin Reuptake Inhibitors (SSRIs)**

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Paroxetine	20 q.d.	400/100 b.i.d.	Paroxetine	↓ 39%	↓ 37%
			Darunavir	↔	↔
Sertraline	50 q.d.	400/100 b.i.d.	Sertraline	↓ 49%	↓ 49%
			Darunavir	↔	↔

If SSRIs are co-administered with PREZISTA and ritonavir, the recommended approach is a 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 co-administered with 100 mg ritonavir should be monitored for antidepressant response.

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**Steroids**

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Fluticasone propionate In a clinical study where ritonavir 100 mg capsules b.i.d were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, fluticasone propionate plasma concentrations increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% confidence interval 82 - 89%). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide. Consequently, concomitant administration of PREZISTA, co-administered with 100 mg ritonavir and these glucocorticoids, is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period. The effects of high fluticasone systemic exposure on ritonavir plasma levels are as yet unknown.

Dexamethasone Systemic dexamethasone induces CYP3A4 and thereby may decrease darunavir exposure. Therefore this combination should be used with caution.

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**Others**

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St. John's wort PREZISTA co-administered with 100 mg ritonavir must not be used concomitantly with products containing St John's wort (*Hypericum perforatum*) because co-administration may cause significant decreases in darunavir plasma concentrations and also in ritonavir concentrations. This is due to the induction of metabolising enzymes by St John's wort. If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Darunavir exposure (and also ritonavir exposure) may increase on stopping St John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort (see section 4.3).

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**4.6 Pregnancy and lactation**

Pregnancy

There are no adequate and well controlled studies with darunavir in pregnant women. Studies in animals do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

PREZISTA co-administered with 100 mg ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk.

#### Lactation

It is recommended that HIV infected women must not breast-feed their infants under any circumstances in order to avoid transmission of HIV. It is not known whether darunavir is excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk and at high levels (1000 mg/kg/day) resulted in toxicity. Mothers should be instructed not to breast-feed if they are receiving PREZISTA.

#### Fertility

No human data on the effect of darunavir on fertility are available. There was no effect on mating or fertility with darunavir treatment in rats (see section 5.3).

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

No studies on the effects of PREZISTA in combination with ritonavir on the ability to drive and use machines have been performed. However, dizziness has been reported in some patients during treatment with regimens containing PREZISTA co-administered with 100 mg ritonavir and should be borne in mind when considering a patient's ability to drive or operate machinery (see section 4.8).

### **4.8 Undesirable effects**

The safety data are based on studies that used experimental and commercial formulations of darunavir. The bioavailability of darunavir was approximately 20% higher with the commercial formulation as compared to the experimental formulations. The safety of darunavir has been assessed in a limited number of patients who were taking potentially interacting medicinal products during the clinical studies. The safety of darunavir has not been assessed in patients who are taking NNRTIs. Therefore, the data obtained may not be wholly applicable to the more general use of darunavir.

The data on safety of PREZISTA 600 mg with ritonavir 100 mg twice daily are derived from 2 ongoing Phase IIb trials, complemented by data from 2 open-label trials, in which a total of 458 patients who initiated therapy with the recommended dose (*de novo* patients). Forty percent of these patients experienced at least one adverse reaction that was drug related.

In the *de novo* patients, the most frequently ( $\geq 2\%$ ) reported adverse reactions that were at least grade 2 in severity and considered possibly related to PREZISTA co-administered with 100 mg ritonavir were diarrhoea (2.6%), vomiting (2.2%) and hypertriglyceridaemia (2.0%).

The majority of the adverse reactions reported during treatment with PREZISTA co-administered with 100 mg ritonavir twice daily were grade 1 to 2 in severity. The most commonly reported adverse reactions of any grade were nausea (7.2%), diarrhoea (6.6%) and headache (3.3%). All other adverse reactions were reported in less than 3% of the patients.

One percent of the patients discontinued treatment due to adverse reactions.

The adverse reactions are listed by system organ class (SOC) and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common ( $\geq 1/100$  to  $< 1/10$ ), and uncommon ( $\geq 1/1000$  to  $< 1/100$ ).

Adverse reactions reported in the *de novo* patients (grade 1 – 4) are summarised below.

The frequency was calculated using adverse reactions reported by the investigators as being attributable (at least possible causal relationship) to PREZISTA co-administered with 100 mg ritonavir.

SOC	Adverse reaction	Frequency
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Investigations	increased alanine aminotransferase, increased blood creatinine, increased blood amylase, increased aspartate aminotransferase, increased gamma-glutamyltransferase, increased lipase, increased blood glucose, increased blood alkaline phosphatase, increased blood urea	uncommon
Cardiac disorders	myocardial infarction, abnormal electrocardiogram, tachycardia, atrial dilatation	uncommon
Blood and lymphatic system disorders	neutropenia, thrombocytopenia	uncommon
Nervous system disorders	headache, dizziness  peripheral neuropathy, paraesthesia, hypoaesthesia, memory impairment, somnolence, transient ischaemic attack, attention disturbance, abnormal coordination, syncope	common  uncommon
Eye disorders	keratoconjunctivitis sicca	uncommon
Ear and labyrinth disorders	vertigo	uncommon
Respiratory, thoracic and mediastinal disorders	dyspnoea, cough, hiccups	uncommon
Gastrointestinal disorders	vomiting, diarrhoea, nausea, abdominal pain, constipation, flatulence, abdominal distension, dyspepsia  dry mouth, salivary hypersecretion, tongue ulceration	common  uncommon
Renal and urinary disorders	acute renal failure, polyuria, renal insufficiency, nephrolithiasis, dysuria, nocturia, proteinuria	uncommon
Skin and subcutaneous tissue disorders	lipoatrophy, erythema multiforme*, dermatitis medicamentosa, skin inflammation, night sweats, hyperhidrosis, alopecia, maculopapular rash, allergic dermatitis, eczema, toxic skin eruption, dry skin, pruritus, face oedema, urticaria	uncommon
Musculoskeletal and connective tissue disorders	arthralgia, pain in extremity, myalgia, osteopenia, osteoporosis, muscle cramp	uncommon
Endocrine disorders	hypothyroidism	uncommon
Metabolism and nutrition disorders	hypertriglyceridaemia, anorexia  diabetes mellitus, hypercholesterolaemia, polydipsia, hyperlipidaemia, fat redistribution, decreased appetite, increased weight, hyponatraemia, obesity	common  uncommon
Infections and infestations	folliculitis	uncommon
Vascular disorders	hypertension, flushing	uncommon
General disorders and administration site conditions	asthenia, fatigue  pyrexia, hyperthermia, peripheral oedema, rigors	common  uncommon
Reproductive system and breast disorders	gynaecomastia, erectile dysfunction	uncommon
Psychiatric disorders	insomnia  anxiety, confusional state, disorientation, irritability, altered mood, nightmare	common  uncommon

\* Reported with another dosage.

### 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 thromboplastin time (PTT) (3.6%), pancreatic lipase (3.5%), alanine aminotransferase (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 Stevens-Johnson Syndrome (rare) have been reported in ongoing clinical trials with PREZISTA with 100 mg ritonavir.

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) (see section 4.4).

Combination antiretroviral therapy has also been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

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

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

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 (see section 4.4).

There have been reports of increased spontaneous bleeding in haemophiliac patients receiving antiretroviral protease inhibitors (see section 4.4).

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

Among 458 patients receiving PREZISTA co-administered with ritonavir 600/100 mg b.i.d., 59 patients were co-infected with chronic hepatitis B or C. Co-infected patients were more likely to have baseline and treatment emergent hepatic transaminase elevations than those without chronic viral hepatitis (see section 4.4).

## **4.9 Overdose**

Human experience of acute overdose with PREZISTA co-administered with 100 mg ritonavir is limited. Single doses up to 3200 mg of darunavir as oral solution alone and up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

There is no specific antidote for overdose with PREZISTA. Treatment of overdose with PREZISTA consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. 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.

## **5. PHARMACOLOGICAL PROPERTIES**

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, ATC code: J05AE10.

### Mechanism of action

Darunavir is an inhibitor of the HIV-1 protease ( $K_D$  of  $4.5 \times 10^{-12}$  M). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.

### Antiviral activity *in vitro*

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

The  $EC_{50}$  value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir showed synergistic antiviral activity when studied in combination with the protease inhibitors ritonavir, nelfinavir, or amprenavir and additive antiviral activity when studied in combination with the protease inhibitors indinavir, saquinavir, lopinavir, atazanavir, or tipranavir, the N(t)RTIs zidovudine, lamivudine, zalcitabine, didanosine, stavudine, abacavir, emtricitabine, or tenofovir, the NNRTIs nevirapine, delavirdine, or efavirenz and the fusion inhibitor enfuvirtide. No antagonism was observed between darunavir and any of those antiretrovirals.

### Resistance

*In vitro* selection of darunavir-resistant virus from wild type HIV-1 was lengthy (up to 2 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 220 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 6 - 21-fold) harboured 3 to 6 amino acid substitutions in the protease gene. Identification of determinants of decreased susceptibility to darunavir in those viruses is under investigation.

*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 resistance-associated mutations showed that a minimum of 8 darunavir *in vitro* selected mutations were required in the HIV-1 protease to render a virus resistant (fold change [FC] > 10) to darunavir.

In POWER 1, 2 and 3 (see Clinical experience subsection) the amino acid substitutions that developed on PREZISTA co-administered with ritonavir (600/100 mg b.i.d.) in greater than 20% of the isolates were V32I and I54L. Amino acid substitutions that developed in 10 to 20% of the isolates were L33F, I47V and L89V.

### Cross-resistance

Darunavir has a < 10-fold decreased susceptibility against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to most PIs remain susceptible to darunavir.

### Clinical experience

#### *Efficacy of PREZISTA co-administered with 100 mg ritonavir in treatment-naïve patients*

There are no data on the efficacy of darunavir co-administered with 100 mg ritonavir in treatment-naïve HIV-1 infected patients.

#### *Efficacy of PREZISTA co-administered with 100 mg ritonavir in treatment-experienced patients*

The evidence of efficacy of PREZISTA co-administered with 100 mg ritonavir in treatment-experienced patients is based on the following:

**POWER 1 and POWER 2** are randomised, controlled trials consisting of an initial dose-finding part and a second long-term part in which all patients randomised to PREZISTA co-administered with 100 mg ritonavir received the recommended dose of 600/100 mg b.i.d.

HIV-1 infected patients who were eligible for these trials had previously failed more than 1 PI containing regimen.

PREZISTA co-administered with 100 mg ritonavir plus an optimised background regimen (OBR) was compared to a control group receiving an investigator-selected PI(s) regimen plus an OBR. The OBR consisted of at least 2 NRTIs with or without enfuvirtide (ENF).

**POWER 3:** additional data on the efficacy of PREZISTA co-administered with ritonavir 600/100 mg b.i.d. with OBR have been obtained in similar treatment-experienced patients participating in the non randomised trials TMC114-C215 and TMC114-C208. Entry criteria were the same as and baseline characteristics were comparable to those of POWER 1 and POWER 2.

### Results 24-week analyses

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

	POWER 1 and POWER 2 pooled data			POWER 3
<i>Baseline characteristics</i>				
Median plasma HIV-1 RNA	4.52 log <sub>10</sub> copies/ml			4.60 log <sub>10</sub> copies/ml
Median CD4+ cell count	153 x 10 <sup>6</sup> cells/l			115 x 10 <sup>6</sup> cells/l
<i>Outcomes</i>	PREZISTA/ritonavir 600/100 mg b.i.d. n=131	Control n=124	Treatment difference	PREZISTA/ritonavir 600/100 mg b.i.d. n=327
HIV-1 RNA log <sub>10</sub> change from baseline (log <sub>10</sub> copies/ml) <sup>a</sup>	-1.89 (-2.11; -1.68) <sup>f</sup>	-0.48 (-0.65; -0.31) <sup>f</sup>	-1.41 (LSM <sup>b</sup> ) (-1.67; -1.14) <sup>f</sup>	-1.73 (-1.87; -1.58) <sup>f</sup>
CD4+ cell count change from baseline (x 10 <sup>6</sup> /l) <sup>c</sup>	92 (73; 112) <sup>f</sup>	17 (0; 35) <sup>f</sup>	75 (LSM <sup>b</sup> ) (49; 101) <sup>f</sup>	80 (69; 90) <sup>f</sup>
HIV RNA ≥ 1 log <sub>10</sub> below baseline <sup>d</sup>	92 (70%) (62%; 78%) <sup>f</sup>	26 (21%) (14%; 28%) <sup>f</sup>	49% (39%; 60%) <sup>e, f</sup>	217 (66%) (61%; 71%) <sup>f</sup>
HIV RNA < 400 copies/ml <sup>d</sup>	82 (63%) (54%; 71%) <sup>f</sup>	23 (19%) (12%; 25%) <sup>f</sup>	44% (33%; 55%) <sup>e, f</sup>	193 (59%) (54%; 64%) <sup>f</sup>
HIV RNA < 50 copies/ml <sup>d</sup>	59 (45%) (37%; 54%) <sup>f</sup>	15 (12%) (7%; 18%) <sup>f</sup>	33% (23%; 43%) <sup>e, f</sup>	141 (43%) (38%; 48%) <sup>f</sup>

<sup>a</sup> Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0

<sup>b</sup> Treatment differences are based on Least Square Means (LSM) from an ANOVA model including the stratification factors. P-values < 0.001

<sup>c</sup> Last Observation Carried Forward imputation

<sup>d</sup> Imputations according to the TLOVR algorithm

<sup>e</sup> Confidence interval around observed difference of response rates; P-values < 0.001

<sup>f</sup> 95% confidence intervals.

### Baseline genotype or phenotype and virologic outcome

In POWER 1, 2 and 3 the presence at baseline of 3 or more of mutations V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V or L89V was associated with a decreased virologic response to PREZISTA co-administered with 100 mg ritonavir. The presence of these individual mutations was associated with a median of 10 PI resistance associated mutations of the IAS-USA list of mutations.

*Response to PREZISTA co-administered with ritonavir (600/100 mg b.i.d.) by baseline genotype\*: As treated analysis of POWER 1, 2 and 3.*

Number of mutations at baseline*	Change in log <sub>10</sub> viral load at week 24	Proportion of subjects with ≥ 1 log <sub>10</sub> 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 mutations from the list of mutations associated with a diminished response to PREZISTA/ritonavir (V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V or L89V)

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

*Response to PREZISTA co-administered with ritonavir (600/100 mg b.i.d.) by baseline darunavir phenotype: As treated analysis of POWER 1, 2 and 3.*

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

### **Long-term results**

Additionally, supportive long-term efficacy data of PREZISTA co-administered with ritonavir 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 indicates that proportions of patients with at least 1 log drop in viral load decrease over time (from 69% to 61%); however, the same percentage of patients were undetectable (< 50 HIV RNA copies/ml) at week-24 and week-48 respectively (45%).

This medicinal product has been authorised under a so-called “conditional approval” scheme.

This means that further evidence on this medicinal product is awaited.

The European Medicines Agency (EMA) will review new information on the product every year and this SPC will be updated as necessary.

## **5.2 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 metabolised by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

### Absorption

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

The absolute oral bioavailability of a single 600 mg dose of darunavir 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 darunavir was given orally in combination with ritonavir at 100 mg b.i.d. (see section 4.4).

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



### Distribution

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

Following intravenous administration, the volume of distribution of darunavir alone was  $88.1 \pm 59.0$  l (Mean  $\pm$  SD) and increased to  $131 \pm 49.9$  l (Mean  $\pm$  SD) in the presence of 100 mg twice-daily ritonavir.

### 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  $^{14}\text{C}$ -darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir with ritonavir dose was due to the parent active 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  $^{14}\text{C}$ -darunavir with ritonavir dose, approximately 79.5% and 13.9% of the administered dose of  $^{14}\text{C}$ -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 are no pharmacokinetic data available in children and adolescents.

#### *Elderly*

Population pharmacokinetic analysis in HIV infected patients showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV infected patients (n=12, age  $\geq$  65) (see section 4.4). However, only limited data were available in patients above the age of 65 year.

#### *Gender*

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

#### *Renal impairment*

Results from a mass balance study with  $^{14}\text{C}$ -darunavir with ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine unchanged.

Although darunavir has not been studied in patients with renal impairment, population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected patients with moderate renal impairment (CrCl between 30 - 60 ml/min, n=20) (see sections 4.2 and 4.4).

#### *Hepatic impairment*

Darunavir is primarily metabolised and eliminated by the liver. In a multiple dose study with PREZISTA co-administered with ritonavir (600/100 mg) twice daily, it was demonstrated that the steady state pharmacokinetic parameters of darunavir in patients with mild (Child-Pugh Class A, n=8) and moderate (Child-Pugh Class B, n=3) hepatic impairment were comparable with that in healthy subjects. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not yet been studied (see sections 4.2, 4.3 and 4.4).

## **5.3 Preclinical safety data**

Animal toxicology studies have been conducted at exposures up to clinical exposure levels with darunavir alone, in mice, rats and dogs and in combination with ritonavir in rats and dogs. In repeated-dose toxicology studies in mice, rats and dogs, there were only limited effects of treatment with darunavir. In rodents the target organs identified were the haematopoietic system, the blood coagulation system, liver and thyroid. A variable but limited decrease in red blood cell-related parameters was observed, together with increases in activated partial thromboplastin time. Changes were observed in liver (hepatocyte hypertrophy, vacuolation, increased liver enzymes) and thyroid (follicular hypertrophy). In the rat, the combination of darunavir with ritonavir lead to a small increase in effect on RBC parameters, liver and thyroid and increased incidence of islet fibrosis in the pancreas (in male rats only) compared to treatment with darunavir alone. In the dog, no major toxicity findings or target organs were identified up to exposures equivalent to clinical exposure at the recommended dose.

In a study conducted in rats, the number of corpora lutea and implantations were decreased in the presence of maternal toxicity. Otherwise, there were no effects on mating or fertility with darunavir 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 gain of the offspring pre-weaning and there was a slight delay in the opening of eyes and ears. Darunavir in combination with ritonavir caused a reduction in the number of pups that exhibited the startle response on day 15 of lactation and a reduced pup survival during lactation. These effects may be secondary to pup exposure to the active substance via the milk and/or maternal toxicity. No post weaning functions were affected with darunavir alone or in combination with ritonavir. In juvenile rats that were directly dosed on days 12 - 25 of their life, increased mortality was observed and, in some of the animals, convulsions.

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* chromosomal 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* micronucleus test in mice up to exposure levels that were maximally similar to the human therapeutic exposure.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose  
Colloidal anhydrous silica  
Crospovidone  
Magnesium stearate

#### Tablet film-coat

Poly(vinyl alcohol) – partially hydrolyzed  
Macrogol 3350  
Titanium dioxide (E171)  
Talc  
Sunset yellow FCF (E110)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

High density polyethylene (HDPE) plastic bottle containing 120 tablets, fitted with polypropylene (PP) child resistant closure.

One bottle

### **6.6 Special precautions for disposal**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV  
Turnhoutseweg 30  
B-2340 Beerse  
Belgium

## **8. MARKETING AUTHORISATION NUMBER(S)**

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>.

## **ANNEX II**

- A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**
- C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER**

**A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

Janssen-Cilag SpA  
Via C. Janssen  
IT-04010 Borgo San Michele  
Latina  
Italy

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

*Pharmacovigilance system*

The MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

*Risk Management plan*

The MAH commits to performing additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

**C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER**

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame. The results of which shall be taken into account in the risk benefit balance during the assessment of the application for a renewal.

<b>Area</b>	<b>Description</b>	<b>Due date</b>
Clinical	1 The final study report from the interaction study TMC114-C163 (A Phase I, open-label, randomized, crossover trial in healthy subjects to investigate the pharmacokinetic interaction between rifabutin and TMC114, coadministered with low-dose ritonavir, at steady-state) should be submitted.	31 October 2007

Clinical	2	The final study report from the interaction study TMC114-C123 (A Phase I, open label, randomized, crossover trial in healthy subjects to investigate the pharmacokinetic interaction between didanosine and TMC114, coadministered with low-dose ritonavir, at steady-state) should be submitted.	30 April 2007
Clinical	3	The 48 week (primary analysis) final study report from study TMC114-C214 (A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of TMC114/RTV versus LPV/RTV in treatment-experienced HIV-1 infected subjects) should be provided and should contain an analysis assessing the effect of coadministered nevirapine and efavirenz on darunavir; in addition estimation of intra-subject variability. The week 96 final study report from study TMC114-C214 should be provided.	31 July 2007  Q3 2008
Clinical	4	The week 96 final study report from study TMC114-C202 (A Phase II randomized, controlled, partially blinded trial to investigate dose response of TMC114/RTV in 3-class-experienced HIV-1 infected subjects, followed by an open-label period on the recommended dose of TMC114/RTV) should be submitted. The week 144 final study report from study TMC114-C202 should be submitted.	31 July 2007  Q3 2008
Clinical	5	The week 96 final study report from study TMC114-C213 (A Phase II randomized, controlled, partially blinded trial to investigate dose-response of TMC114/RTV in 3-class-experienced HIV-1 infected subjects, followed by an open-label period on the recommended dose of TMC114/RTV) should be submitted. The week 144 final study report from study TMC114-C213 should be submitted.	30 April 2007  Q1 2008
Clinical	6	The week 96 final study report from study TMC114-C215 (An open label trial of TMC114/RTV in HIV-1 infected, treatment experienced subjects) should be submitted. The week 144 final study report TMC114-C215 should be submitted.	31 December 2007  Q3 2008
Clinical	7	The cut-off Q2 2007 study report from study TMC114-C208 (An open label trial of TMC114/RTV in HIV-1 infected subjects who were randomized in the trials TMC114-C201, TMC114-C207 or in sponsor selected Phase I trials) should be submitted.	31 December 2007
Clinical	8	The cut-off Q2 2007 study report from study TMC114-C209 (Open-label safety study of TMC114 in combination with low dose RTV and other ARVs in highly experienced HIV-1 infected patients with limited or no treatment options) should be submitted.	31 December 2007

Clinical	<p>9 The data from the darunavir treatment arm that do not receive the candidate NNRTI (TMC125) for the two following studies should be provided:</p> <ul style="list-style-type: none"> <li>- week 24 (primary analysis) final study report from study TMC125-C206 (A Phase III randomized, double-blinded, placebo-controlled trial to investigate the efficacy, tolerability and safety of TMC125 as part of an ART including TMC114/RTV and an investigator-selected OBR in HIV-1 infected subjects with limited to no treatment options)</li> <li>- week 24 (primary analysis) final study report from study TMC125-C216 (A Phase III randomized, double-blinded, placebo-controlled trial to investigate the efficacy, tolerability and safety of TMC125 as part of an ART including TMC114/RTV and an investigator-selected OBR in HIV-1 infected subjects with limited to no treatment options) should be submitted.</li> </ul>	31 October 2007
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**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**



## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON / BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

PREZISTA 300 mg film-coated tablets  
darunavir

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 300 mg darunavir (as ethanolate).

**3. LIST OF EXCIPIENTS**

Contains sunset yellow FCF (E110).

**4. PHARMACEUTICAL FORM AND CONTENTS**

120 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV  
Turnhoutseweg 30  
B-2340 Beerse  
Belgium

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/0/00/000/000

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE (this is only applicable to the outer pack)**

prezista 300 mg

**B. PACKAGE LEAFLET**

## PACKAGE LEAFLET: INFORMATION FOR THE USER

### PREZISTA 300 mg film-coated tablets darunavir

#### **Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If a side effect gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

1. What PREZISTA is and what it is used for
2. Before you take PREZISTA
3. How to take PREZISTA
4. Possible side effects
5. How to store PREZISTA
6. Further information

## **1. WHAT PREZISTA IS AND WHAT IT IS USED FOR**

### **What is PREZISTA?**

PREZISTA is an antiretroviral medicine used in the treatment of Human Immunodeficiency Virus (HIV) infection. It belongs to a group of medicines called protease inhibitors. PREZISTA works by reducing the amount of HIV in your body. This will improve your immune system and reduces the risk of developing illnesses linked to HIV infection.

### **What it is used for?**

PREZISTA is used to treat adults who are infected by HIV and who have not responded (sufficiently) to other antiretroviral medicines.

PREZISTA must be taken in combination with a low dose of ritonavir and other anti-HIV medicines. Your doctor will discuss with you which combination of medicines is best for you.

## **2. BEFORE YOU TAKE PREZISTA**

PREZISTA is to be taken in combination with a low dose of ritonavir and other antiretroviral medicines. It is therefore important that you carefully read the package leaflet that is provided with these medicines. If you have any further questions about the medicines prescribed, please ask your doctor or pharmacist.

### **Do not take PREZISTA:**

- if you are **allergic** (hypersensitive) to darunavir, other ingredients of PREZISTA or to ritonavir.
- if you have **severe liver problems**. Ask your doctor if you are unsure about the severity of your liver disease. Some additional tests might be necessary.

### **Do not combine PREZISTA with any of the following medicines:**

- *astemizole* or *terfenadine* (to treat allergy symptoms)
- *midazolam* or *triazolam* (to treat trouble with sleeping and/or anxiety)
- *cisapride* (to treat some stomach conditions)
- *pimozide* or *sertindole* (to treat psychiatric conditions)
- *ergot alkaloids* (like ergotamine, dihydroergotamine, ergonovine and methylergonovine used to treat migraine and headaches)

- *amiodarone, bepridil, quinidine and systemic lidocaine* (to treat certain heart disorders e.g. abnormal heart beat)
- *lovastatin and simvastatin* (medicines to lower cholesterol levels)
- *rifampicin* (medicines to treat some infections such as tuberculosis)
- *products that contain St John's wort (Hypericum perforatum)*

If you are taking any of these, ask your doctor about switching to another medicine.

### Take special care with PREZISTA

PREZISTA is not a cure for HIV infection. PREZISTA does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Therefore, you must continue to use appropriate precautions.

People taking PREZISTA may still develop infections or other illnesses associated with HIV infection. You must keep in regular contact with your doctor.

PREZISTA has only been used in limited numbers of patients 65 years or older. If you belong to this age group, please discuss with your doctor if you can use PREZISTA.

### Tell your doctor about your situation

Make sure that you check the following seven points and tell your doctor if any of these apply to you.

- Tell your doctor if you have had **problems with your liver** before, including hepatitis B or C. Your doctor may evaluate how severe your liver disease is before deciding if you can take PREZISTA.
- Tell your doctor if you have **diabetes**. PREZISTA might increase sugar levels in the blood.
- Tell your doctor immediately if you notice any **symptoms of infection**. In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.
- Tell your doctor if you **notice changes in body fat**. Redistribution, accumulation or loss of body fat may occur in patients receiving a combination of antiretroviral medicines.
- Tell your doctor if you have **haemophilia**. PREZISTA, might increase the risk of bleeding.
- Tell your doctor if you are **allergic to sulphonamides** (e.g. used to treat certain infections).
- Tell your doctor if you notice any **musculoskeletal problems**. Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

### Taking other medicines

PREZISTA might interact with other medicines. Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

There are some medicines that **you must not combine** with PREZISTA. These are mentioned above under the heading 'Do not combine PREZISTA with any of the following:'

In most cases, PREZISTA can be combined with anti-HIV medicines belonging to another class (e.g. NRTIs (nucleoside reverse transcriptase inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors) and FIs (fusion inhibitors)). PREZISTA with ritonavir has not been tested with all PIs (protease inhibitors). Therefore always tell your doctor if you take other anti-HIV medicines and follow your doctor's instruction carefully on which medicines can be combined.

The effects of PREZISTA might be reduced if you take any of the following products. Tell your doctor if you take:

- *phenobarbital, phenytoin, carbamazepine* (medicines to prevent seizures)
- *dexamethasone* (steroids).

The effects of other medicines might be influenced if you take PREZISTA. Tell your doctor if you take:

- *felodipine, nifedipine, nicardipine* (medicines for heart disease) as the therapeutic effect or unwanted side effects of these medicines may be increased.
- *warfarin* (medicines used to reduce clotting of the blood) as their therapeutic effect or unwanted side effects may be altered; your doctor may have to check your blood.
- hormonal contraceptives and hormonal replacement therapy. PREZISTA might reduce its effectiveness. When used for birth control, you must combine hormonal contraceptives with other birth control methods such as a condom.
- *pravastatin, atorvastatin* (medicines to lower cholesterol levels). The risk of muscle tissue disorder might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *cyclosporin, tacrolimus, sirolimus* (medicines for your immune system) as the therapeutic effect or unwanted side effects of these medicines might be increased. Your doctor might want to do some additional tests.
- *fluticasone propionate* (medicines to control asthma). Its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.

The dosage of other medicines might need to be changed since either their own or PREZISTA's therapeutic effect or unwanted side effects may be influenced when combined.

Tell your doctor if you take:

- *digoxin* (medicines to treat certain heart disorders)
- *ketconazole, itraconazole, clotrimazole* (medicines against fungal infections). Voriconazole should only be taken after medical evaluation.
- *rifabutin* (medicines against bacterial infections)
- *sildenafil, vardenafil, tadalafil* (medicines for erectile dysfunction)
- *clarithromycin* (antibiotics)
- *paroxetine, sertraline* (medicines to treat depression and anxiety)
- *methadone*

### **Taking PREZISTA with food and drink**

See section 3 'How to take PREZISTA with food and drink.'

### **Pregnancy and breast-feeding**

Tell your doctor immediately if you are pregnant or if you are breast-feeding. Pregnant or breast-feeding mothers should not take PREZISTA unless specifically directed by the doctor. It is recommended that HIV infected women should not breast-feed their infants because of the possibility of your baby becoming infected with HIV through your breast milk.

### **Driving and using machines**

Do not operate machines or drive if you feel dizzy after taking PREZISTA.

### **Important information about some of the ingredients of PREZISTA**

PREZISTA tablets contain sunset yellow FCF (E110) which may cause allergic reactions.

## **3. HOW TO TAKE PREZISTA**

Always use PREZISTA exactly as your doctor has told you. You must check with your doctor if you are not sure.

Even if you feel better, do not stop taking PREZISTA without talking to your doctor.

PREZISTA is not for use in children and adolescents, as it has not been studied in patients under 18 years.

## Instructions

- The usual dose of PREZISTA is two tablets twice daily.
- Take PREZISTA always together with ritonavir. PREZISTA cannot work properly without ritonavir.
- In the morning, take two 300 milligram PREZISTA tablets together with 100 milligram ritonavir.
- In the evening, take two 300 milligram PREZISTA tablets together with 100 milligram ritonavir.
- Take PREZISTA with food. PREZISTA cannot work properly without food. The type of food is not important.
- Swallow the tablets with a drink such as water or milk.

## Removing the child resistant cap



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

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

## If you take more PREZISTA than you should

Contact your doctor or pharmacist immediately.

## If you forget to take PREZISTA

If you notice **within 6 hours**, you must take the tablets immediately. Always take with ritonavir and food. If you notice **after 6 hours**, then skip the intake and take the next doses as usual. Do not take a double dose to make up for a forgotten dose.

## Do not stop using PREZISTA without talking to your doctor first

HIV therapy may increase your sense of well-being. Even when you feel better, do not stop taking PREZISTA. Talk to your doctor first.

If you have any further questions on the use of this product, ask your doctor.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, PREZISTA can cause side effects, although not everybody gets them. When treating HIV infection, it is not always easy to identify what side effects are caused by PREZISTA, which are caused by other medicines you are taking, or which are caused by the HIV infection itself.

Common side effects (This means that less than 1 in 10 patients, but more than 1 in 100 patients might experience these.)

- vomiting, diarrhoea, nausea, abdominal pain, constipation, flatulence, distension of the abdomen, indigestion, loss of appetite
- headache, dizziness, lack or loss of strength, fatigue, sleeplessness
- increases in a type of blood fat
- skin rash. The rash is usually mild to moderate. A skin rash might also be a symptom of a rare severe situation. It is therefore important to contact your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether PREZISTA must be stopped.

Uncommon side effects (This means that less than 1 in 100 patients, but more than 1 in 1000 patients might experience these.)

- heart attack, abnormal electrocardiogram, racing heart, enlargement of the heart chamber



- numbness, tingling or pain in hands or feet, loss of skin sensibility, memory impairment, pins and needles, drowsiness, minor stroke, attention disturbance, fainting
- problems with your balance
- difficulty breathing, cough, hiccups
- dry mouth, excessive saliva, ulcers on the tongue
- kidney failure, painful, frequent or excessive passage of urine, sometimes with excess of proteins, kidney stones, decreased kidney function
- loss of fat beneath the skin, skin inflammation, night sweats, hair loss, eczema, excessive sweating, hair follicle inflammation, dry skin, itching, dry eyes, swelling of the face, urticaria
- joint pain, pain in extremity, muscle pain or cramps, osteoporosis
- diabetes, decrease of appetite, abnormal thirst, body changes associated with fat redistribution, increased weight, obesity, decreased activity of the thyroid
- high blood pressure, flushing
- fever, swelling of lower limbs due to fluids, chills
- excessive development of the breast glands in men, erectile dysfunction
- anxiety, a feeling of confusion or disorientation, irritability, altered mood, nightmare
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood tests. Your doctor will explain these to you. Examples are: low white blood cell count, low blood platelet count, high levels of cholesterol, high blood fat levels, low sodium level.

Some side effects are typical for anti-HIV medicines in the same family as PREZISTA. These are:

- raised blood sugar and worsening of diabetes.
- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.
- changes in body shape due to fat redistribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (buffalo hump). The cause and long-term health effects of these conditions are not known at this time.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

## **5. HOW TO STORE PREZISTA**

Keep out of the reach and sight of children.

Do not use PREZISTA after the expiry date which is stated on the box and on the bottle after the letters EXP. The expiry date refers to the last day of that month.

PREZISTA does not require any special storage conditions.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## **6. FURTHER INFORMATION**

### **What PREZISTA contains**

- The active substance is darunavir. Each tablet contains 300 mg of darunavir as ethanolate.
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate. The film-coating contains poly(vinyl alcohol) - partially hydrolyzed, macrogol 3350, titanium dioxide (E171), talc, sunset yellow FCF (E110).

### **What PREZISTA looks like and contents of the pack**

Film-coated, orange, oval shaped tablet, mentioning TMC114 on one side, 300MG on the other side. 120 tablets in a plastic bottle.

**Marketing Authorisation Holder**

Janssen-Cilag International NV, Turnhoutseweg 30, 2340 Beerse, Belgium

**Manufacturer**

Janssen-Cilag SpA, Via C. Janssen, 04010 Borgo San Michele, Latina, Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**

TIBOTEC, een divisie van, une division de, eine Division der JANSSEN-CILAG NV/SA  
Roderveldlaan 1  
B-2600 Berchem  
Tél/Tel: +32 3 280 54 11

**Luxembourg/Luxemburg**

TIBOTEC, une division de, eine Division der JANSSEN-CILAG NV/SA  
Roderveldlaan 1  
B-2600 Berchem  
Belgique/Belgien  
Tél: +32 3 280 54 11

**България**

Представителство на TIBOTEC, дивизия на Johnson & Johnson, d.o.o.  
ж.к. Младост 4  
Бизнес Парк София, сграда 4  
София 1715  
Тел.: +359 2 976 94 00

**Magyarország**

TIBOTEC, a JANSSEN-CILAG Kft. divíziója  
H-2045 Törökbálint, Tó Park  
Tel: +36 23 513 800

**Česká republika**

TIBOTEC, divize JANSSEN-CILAG s.r.o.  
Karla Engliše 3201/06  
CZ-150 00 Praha 5 - Smíchov  
Tel: +420 227 012 222

**Malta**

AM MANGION LTD.  
Mangion Building, New Street off Valetta Road  
MT-Luqa LQA 06  
Tel: +356 25402600 - 10

**Danmark**

TIBOTEC, en division af JANSSEN-CILAG A/S  
Hammerbakken 19  
DK-3460 Birkerød  
Tlf: +45 45 94 82 82

**Nederland**

TIBOTEC, een divisie van JANSSEN-CILAG B.V.  
Postbus 90240  
NL-5000 LT Tilburg  
Tel: +31 13 583 73 73

**Deutschland**

JANSSEN-CILAG GmbH  
Raiffeisenstr. 8  
D-41470 Neuss  
Tel: +49 2137 955-0

**Norge**

TIBOTEC, en divisjon av JANSSEN-CILAG AS  
Hoffsveien 1D  
N-0275 Oslo  
Tlf: +47 24 12 65 00

**Eesti**

TIBOTEC, JANSSEN-CILAG Polska Sp z o.o.  
Eesti filiaal  
Weizenbergi 20b  
EE-10150 Tallinn  
Tel: +372 626 6500

**Österreich**

TIBOTEC, eine Division von JANSSEN-CILAG Pharma GmbH  
Pfarrgasse 75  
A-1232 Wien  
Tel: +43 1 610 300

**Ελλάδα**

TIBOTEC, τμήμα της JANSSEN-CILAG  
Φαρμακευτική Α.Ε.Β.Ε.  
Λεωφόρος Ειρήνης 56  
GR-151 21 Πεύκη, Αθήνα  
Τηλ: +30 210 61 40 061

**España**

JANSSEN-CILAG, S.A. división TIBOTEC  
Paseo de las Doce Estrellas, 5-7  
Campo de las Naciones  
E-28042 Madrid  
Tel: +34 91 722 81 00

**France**

TIBOTEC, une division de JANSSEN-CILAG  
1, rue Camille Desmoulins, TSA 91003  
F-92787 Issy Les Moulineaux, Cedex 9  
Tél: 0 800 25 50 75 / +33 1 55 00 44 44

**Ireland**

TIBOTEC, a division of JANSSEN-CILAG Ltd.  
Saunderton High Wycombe  
Buckinghamshire HP14 4HJ - UK  
Tel: +44 1494 567 444

**Ísland**

TIBOTEC, deild hjá JANSSEN-CILAG  
c/o Vistor hf.  
Hörgatún 2  
IS-210 Garðabær  
Sími: +354 535 7000

**Italia**

TIBOTEC, una divisione di JANSSEN-CILAG  
SpA  
Via M.Buonarroti, 23  
I-20093 Cologno Monzese MI  
Tel: +39 02 2510 1

**Κύπρος**

Βαρνάβας Χατζηπαναγής Λτδ,  
7 Ανδροκλέους  
CY-1060 Λευκωσία  
Τηλ: +357 22 755 214

**Latvija**

TIBOTEC, JANSSEN-CILAG Polska Sp. z o.o.  
filiale Latvija  
Baznīcas iela 20/22  
Rīga, LV-1010  
Tel: +371 7039805

**Polska**

TIBOTEC, oddział JANSSEN-CILAG Polska  
Sp. z o.o. ul. Szyszkowa 20  
PL-02-285 Warszawa  
Tel: +48 22 668 01 50

**Portugal**

TIBOTEC, uma divisão da JANSSEN-CILAG  
FARMACÊUTICA, LDA.  
Estrada Consiglieri Pedroso, 69 A  
Queluz de Baixo  
PT-2734-503 Barcarena  
Tel: +351 21 43 68 835

**România**

TIBOTEC, subsidiară a Janssen-Cilag, Johnson &  
Johnson d.o.o.  
Sipotul Fantanilor no. 8, Sect. 1  
010 157 București  
Tel: +40 21 312 1169

**Slovenija**

TIBOTEC za Janssen-Cilag, del  
Johnson&Johnson d.o.o.  
Šmartinska cesta 53  
SI-1000 Ljubljana  
Tel: +386 1 401 18 30

**Slovenská republika**

TIBOTEC, divízia Johnson & Johnson s.r.o.  
Plynárska 7/B  
SK-824 78 Bratislava  
Tel: +421 233 552 600

**Suomi/Finland**

TIBOTEC  
JANSSEN-CILAG OY  
Metsänneidonkuja/Skogsjungfrugränden 8  
FI-02130 Espoo/Esbo  
Puh/Tel: +358 9 4155 5300

**Sverige**

TIBOTEC, en division inom JANSSEN-CILAG  
AB  
Box 7073  
S-192 07 Sollentuna  
Tel: +46 8 626 50 00

**United Kingdom**

TIBOTEC, a division of JANSSEN-CILAG Ltd.  
Saunderton High Wycombe  
Buckinghamshire HP14 4HJ - UK  
Tel: +44 1494 567 444

**Lietuva**

UAB "Johnson & Johnson"

Šeimyniškių g. 1A

LT-09312 Vilnius

Tel: +370 5 278 68 88

**This leaflet was last approved in xxx 2006.**

This medicine has been given "conditional approval".

This means that there is more evidence to come about this medicine.

The European Medicines Agency (EMA) will review new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site:**Error! Hyperlink reference not valid.** <http://www.emea.europa.eu/>.