

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

PREZISTA 100 mg/ml oral suspension

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ml of oral suspension contains 100 mg of darunavir (as ethanolate).

Excipient with known effect: sodium methyl parahydroxybenzoate (E219) 3.43 mg/ml.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Oral suspension

White to off-white opaque suspension

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

PREZISTA, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult and paediatric patients from the age of 3 years and at least 15 kg body weight (see section 4.2).

PREZISTA, co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients (see section 4.2).

In deciding to initiate treatment with PREZISTA co-administered with cobicistat or low dose 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 (see sections 4.2, 4.4 and 5.1).

### **4.2 Posology and method of administration**

Therapy should be initiated by a health care provider experienced in the management of HIV infection. After therapy with PREZISTA has been initiated, patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their health care provider.

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer. Darunavir may therefore have different contraindications and recommendations for concomitant medications depending on whether the compound is boosted with ritonavir or cobicistat (see sections 4.3, 4.4 and 4.5).

#### Posology

PREZISTA must always be given orally with cobicistat or low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of cobicistat or ritonavir as appropriate, must therefore be consulted prior to initiation of therapy with PREZISTA. Cobicistat is not indicated for use in twice daily regimens or for use in the paediatric population.

### *ART-naïve adult patients*

The recommended dose regimen is 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food.

### *ART-experienced adult patients*

The recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food.

A dose regimen of 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without darunavir resistance associated mutations (DRV-RAMs)\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100$  cells  $\times 10^6/l$ .

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

If HIV-1 genotype testing is not available, the recommended dose regimen is PREZISTA 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food.

### *ART-naïve paediatric patients (3 to 17 years of age and weighing at least 15 kg)*

The weight-based dose of PREZISTA and ritonavir in paediatric patients is provided in the table below. The dose of cobicistat to be used with PREZISTA in children less than 18 years of age has not been established.

| <b>Recommended dose for treatment-naïve paediatric patients (3 to 17 years) with PREZISTA and ritonavir<sup>a</sup></b> |  |
|---|--|
| <b>Body weight (kg)</b>   | <b>Dose (once daily with food)</b>   |
| $\geq 15$ kg to < 30 kg   | 600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily                |
| $\geq 30$ kg to < 40 kg   | 675 mg (6.8 ml) <sup>b</sup> PREZISTA/100 mg (1.2 ml) ritonavir once daily |
| $\geq 40$ kg  | 800 mg (8 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily                |

<sup>a</sup> ritonavir oral solution: 80 mg/ml

<sup>b</sup> rounded up for suspension dosing convenience

### *ART-experienced paediatric patients (3 to 17 years of age and weighing at least 15 kg)*

PREZISTA twice daily taken with ritonavir taken with food is usually recommended.

A once daily dose regimen of PREZISTA taken with ritonavir taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without darunavir resistance associated mutations (DRV-RAMs)\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100$  cells  $\times 10^6/l$ .

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The weight-based dose of PREZISTA and ritonavir in paediatric patients is provided in the table below. The recommended dose of PREZISTA with low dose ritonavir should not exceed the recommended adult dose (600/100 mg twice daily or 800/100 mg once daily). The dose of cobicistat to be used with PREZISTA in children less than 18 years of age has not been established.

| <b>Recommended dose for treatment-experienced paediatric patients (3 to 17 years) with PREZISTA and ritonavir<sup>a</sup></b> |  |   |
|---|--|---|
| <b>Body weight (kg)</b>   | <b>Dose (once daily with food)</b>   | <b>Dose (twice daily with food)</b>                           |
| $\geq 15$ kg to < 30 kg   | 600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily                | 380 mg (3.8 ml) PREZISTA/50 mg (0.6 ml) ritonavir twice daily |
| $\geq 30$ kg to < 40 kg   | 675 mg (6.8 ml) <sup>b</sup> PREZISTA/100 mg (1.2 ml) ritonavir once daily | 460 mg (4.6 ml) PREZISTA/60 mg (0.8 ml) ritonavir twice daily |
| $\geq 40$ kg  | 800 mg (8 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily                | 600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir twice daily  |

<sup>a</sup> ritonavir oral solution: 80 mg/ml

<sup>b</sup> rounded up for suspension dosing convenience

For ART-experienced paediatric patients HIV genotypic testing is recommended. However, when HIV genotypic testing is not feasible, the PREZISTA/ritonavir once daily dosing regimen is recommended in HIV protease inhibitor-naïve paediatric patients and the twice daily dosing regimen is recommended in HIV protease inhibitor-experienced patients.

PREZISTA oral suspension can be used in patients unable to swallow PREZISTA tablets. PREZISTA is also available as 75 mg, 150 mg, 300 mg, 400 mg, 600 mg and 800 mg film-coated tablets.

#### *Advice on missed doses*

The following guidance is based on the half-life of darunavir in the presence of cobicistat or ritonavir and the recommended dosing interval of approximately 12 hours (twice daily regimen) or approximately 24 hours (once daily regimen).

- If using the twice daily regimen: in case a dose of PREZISTA and/or ritonavir is 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 is noticed later than 6 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.
- If using the once daily regimen: in case a dose of PREZISTA and/or cobicistat or ritonavir is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of PREZISTA and cobicistat or ritonavir with food as soon as possible. If this is noticed later than 12 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

#### Special populations

##### *Elderly*

Limited information is available in this population, and therefore, PREZISTA should be used with caution in this age group (see sections 4.4 and 5.2).

##### *Hepatic impairment*

Darunavir is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, PREZISTA should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its safety profile. Therefore, PREZISTA must 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 for darunavir/ritonavir in patients with renal impairment (see sections 4.4 and 5.2). Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients.

Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance. Hence, the use of creatinine clearance as an estimate of renal elimination capacity may be misleading. Cobicistat as a pharmacokinetic enhancer of darunavir should, therefore, not be initiated in patients with creatine clearance less than 70 ml/min if any co-administered agent requires dose adjustment based on creatinine clearance: e.g. emtricitabine, lamivudine, tenofovir disoproxil (as fumarate, phosphate or succinate) or adefovir dipovoxil.

For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

##### *Paediatric population*

PREZISTA should not be used in children

- below 3 years of age, because of safety concerns (see sections 4.4 and 5.3), or,
- less than 15 kg body weight, as the dose for this population has not been established in a sufficient number of patients (see section 5.1).

The weight-based dose regimen for PREZISTA and ritonavir is provided in the tables above. The dose of cobicistat to be used with PREZISTA has not been established in this patient population.

#### *Pregnancy and postpartum*

No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. PREZISTA/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk (see sections 4.4, 4.6 and 5.2).

Treatment with darunavir/cobicistat 800/150 mg during pregnancy results in low darunavir exposure (see sections 4.4 and 5.2). Therefore, therapy with PREZISTA/cobicistat should not be initiated during pregnancy, and women who become pregnant during therapy with PREZISTA/cobicistat should be switched to an alternative regimen, (see sections 4.4 and 4.6). PREZISTA/ritonavir may be considered as an alternative.

#### Method of administration

Patients should be instructed to take PREZISTA with cobicistat or low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir (see sections 4.4, 4.5 and 5.2).

PREZISTA suspension is administered orally. Shake the bottle vigorously prior to each dose. The supplied oral dosing pipette should not be used for any other medicinal products.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Concomitant treatment with any of the following medicinal products given the expected decrease in plasma concentrations of darunavir, ritonavir and cobicistat and the potential for loss of therapeutic effect (see sections 4.4 and 4.5).

Applicable to darunavir boosted with either ritonavir or cobicistat:

- The combination product lopinavir/ritonavir (see section 4.5).
- The strong CYP3A inducers rifampicin and herbal preparations containing St John's wort (*Hypericum perforatum*). Co-administration is expected to reduce plasma concentrations of darunavir, ritonavir and cobicistat, which could lead to loss of therapeutic effect and possible development of resistance (see sections 4.4 and 4.5).

Applicable to darunavir boosted with cobicistat, not when boosted with ritonavir:

- Darunavir boosted with cobicistat is more sensitive for CYP3A induction than darunavir boosted with ritonavir. Concomitant use with strong CYP3A inducers is contraindicated, since these may reduce the exposure to cobicistat and darunavir leading to loss of therapeutic effect. Strong CYP3A inducers include e.g. carbamazepine, phenobarbital and phenytoin (see sections 4.4 and 4.5).

Darunavir boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the co-administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat). These active substances include e.g.:

- alfuzosin
- amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine
- astemizole, terfenadine
- colchicine when used in patients with renal and/or hepatic impairment (see section 4.5)

- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- elbasvir/grazoprevir
- cisapride
- dapoxetine
- domperidone
- naloxegol
- lurasidone, pimozide, quetiapine, sertindole (see section 4.5)
- triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5)
- sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil
- simvastatin, lovastatin, lomitapide (see section 4.5)
- dabigatran, ticagrelor (see section 4.5).

#### **4.4 Special warnings and precautions for use**

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Regular assessment of virological response is advised. In the setting of lack or loss of virological response, resistance testing should be performed.

PREZISTA must always be given orally with cobicistat or low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products (see section 5.2). The Summary of Product Characteristics of cobicistat or ritonavir as appropriate, must therefore be consulted prior to initiation of therapy with PREZISTA.

Increasing the dose of ritonavir from that recommended in section 4.2 did not significantly affect darunavir concentrations. It is not recommended to alter the dose of cobicistat or ritonavir.

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 (see section 4.5).

##### ART-experienced patients – once daily dosing

PREZISTA used in combination with cobicistat or low dose ritonavir once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA  $\geq 100,000$  copies/ml or CD4+ cell count  $< 100$  cells  $\times 10^6/l$  (see section 4.2). Combinations with optimised background regimen (OBRs) other than  $\geq 2$  NRTIs have not been studied in this population. Limited data are available in patients with HIV-1 clades other than B (see section 5.1).

##### Paediatric population

PREZISTA is not recommended for use in paediatric patients below 3 years of age or less than 15 kg body weight (see sections 4.2 and 5.3).

##### Pregnancy

PREZISTA/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk. Caution should be used in pregnant women with concomitant medications which may further decrease darunavir exposure (see sections 4.5 and 5.2).

Treatment with darunavir/cobicistat 800/150 mg once daily during the second and third trimester has been shown to result in low darunavir exposure, with a reduction of around 90% in  $C_{min}$  levels (see section 5.2). Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in darunavir exposure may result in virological failure and an increased risk of mother to child transmission of HIV infection. Therefore, therapy with PREZISTA/cobicistat should not be initiated during pregnancy, and women who become pregnant during therapy with

PREZISTA/cobicistat should be switched to an alternative regimen (see sections 4.2 and 4.6).  
PREZISTA given with low dose ritonavir may be considered as an alternative.

#### 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).

#### Severe skin reactions

During the darunavir/ritonavir clinical development program (N=3,063), severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens-Johnson Syndrome has been rarely (< 0.1%) reported, and during post-marketing experience toxic epidermal necrolysis and acute generalised exanthematous pustulosis have been reported. PREZISTA should be discontinued immediately if signs or symptoms of severe skin reactions develop. These can include, but are not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash occurred more commonly in treatment-experienced patients receiving regimens containing PREZISTA/ritonavir + raltegravir compared to patients receiving PREZISTA/ritonavir without raltegravir or raltegravir without PREZISTA (see section 4.8).

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

#### Hepatotoxicity

Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA. During the darunavir/ritonavir clinical development program (N=3,063), hepatitis was reported in 0.5% of patients receiving combination antiretroviral therapy with PREZISTA/ritonavir. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

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

If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients using PREZISTA used in combination with cobicistat or low dose ritonavir, interruption or discontinuation of treatment should be considered promptly.

#### Patients with coexisting conditions

##### *Hepatic impairment*

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 hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, PREZISTA should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

##### *Renal impairment*

No special precautions or dose adjustments for darunavir/ritonavir 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). Cobicistat has not been studied in patients receiving dialysis, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients (see section 4.2).

Cobicistat decreases the estimated creatinine clearance due to inhibition of tubular secretion of creatinine. This should be taken into consideration if darunavir with cobicistat is administered to patients in whom the estimated creatinine clearance is used to adjust doses of co-administered medicinal products (see section 4.2 and cobicistat SmPC).

There are currently inadequate data to determine whether co-administration of tenofovir disoproxil and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil without cobicistat.

#### *Haemophilic 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. Haemophilic patients should, therefore, be made aware of the possibility of increased bleeding.

#### *Weight and metabolic parameters*

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

#### Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

#### Immune reconstitution inflammatory syndrome

In HIV infected patients with severe immune deficiency at the time of initiation 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 jirovecii* (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 low dose ritonavir.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.8).

#### Interactions with medicinal products

Several of the interaction studies have been performed with darunavir at lower than recommended doses. 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.



#### *Pharmacokinetic enhancer and concomitant medications*

Darunavir has different interaction profiles depending on whether the compound is boosted with ritonavir or cobicistat:

- Darunavir boosted with cobicistat is more sensitive for CYP3A induction: concomitant use of darunavir/cobicistat and strong CYP3A inducers is therefore contraindicated (see section 4.3), and concomitant use with weak to moderate CYP3A inducers is not recommended (see section 4.5). Concomitant use of darunavir/ritonavir and darunavir/cobicistat with lopinavir/ritonavir, rifampicin and herbal products containing St John's wort, *Hypericum perforatum*, is contraindicated (see section 4.5).
- Unlike ritonavir, cobicistat does not have inducing effects on enzymes or transport proteins (see section 4.5). If switching the pharmacoenhancer from ritonavir to cobicistat, caution is required during the first two weeks of treatment with darunavir/cobicistat, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of ritonavir as a pharmacoenhancer. A dose reduction of the co-administered drug may be needed in these cases.

Efavirenz in combination with boosted PREZISTA may result in sub-optimal darunavir  $C_{min}$ . If efavirenz is to be used in combination with PREZISTA, the PREZISTA/ritonavir 600/100 mg twice daily regimen should be used. See the Summary of Product Characteristics for PREZISTA 75 mg, 150 mg, 300 mg and 600 mg tablets (see section 4.5).

Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A and P-glycoprotein (P-gp; see sections 4.3 and 4.5).

PREZISTA oral suspension contains sodium methyl parahydroxybenzoate (E219) which may cause allergic reactions (possibly delayed).

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

The interaction profile of darunavir may differ depending on whether ritonavir or cobicistat is used as pharmacoenhancer. The recommendations given for concomitant use of darunavir and other medicinal products may therefore differ depending on whether darunavir is boosted with ritonavir or cobicistat (see sections 4.3 and 4.4), and caution is also required during the first time of treatment if switching the pharmacoenhancer from ritonavir to cobicistat (see section 4.4).

##### **Medicinal products that affect darunavir exposure (ritonavir as pharmacoenhancer)**

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 these compounds and consequently that of darunavir, leading to loss of therapeutic effect and possible development of resistance (see sections 4.3 and 4.4). CYP3A inducers that are contraindicated include rifampicin, St John's wort and lopinavir.

Co-administration of darunavir and ritonavir with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir, which may result in increased plasma concentrations of darunavir and ritonavir. Co-administration with strong CYP3A4 inhibitors is not recommended and caution is warranted, these interactions are described in the interaction table below (e.g. indinavir, azole antifungals such as clotrimazole).

##### **Medicinal products that affect darunavir exposure (cobicistat as pharmacoenhancer)**

Darunavir and cobicistat are metabolised by CYP3A, and co-administration with CYP3A inducers may therefore result in subtherapeutic plasma exposure to darunavir. Darunavir boosted with cobicistat is more sensitive to CYP3A induction than ritonavir-boosted darunavir: co-administration of darunavir/cobicistat with medicinal products that are strong inducers of CYP3A (e.g. St John's wort, rifampicin, carbamazepine, phenobarbital, and phenytoin) is contraindicated (see section 4.3). Co-administration of darunavir/cobicistat with weak to moderate CYP3A inducers (e.g. efavirenz, etravirine, nevirapine, boceprevir, fluticasone, and bosentan) is not recommended (see interaction table below).

For co-administration with strong CYP3A4 inhibitors, the same recommendations apply independent of whether darunavir is boosted with ritonavir or with cobicistat (see section above).

#### **Medicinal products that may be affected by darunavir boosted with ritonavir**

Darunavir and ritonavir are inhibitors of CYP3A, CYP2D6 and P-gp. Co-administration of darunavir/ritonavir with medicinal products primarily metabolised by CYP3A and/or CYP2D6 or transported by P-gp may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions.

Darunavir co-administered with low dose ritonavir must not be combined with medicinal products that are highly dependent on CYP3A for clearance and for which increased systemic exposure is associated with serious and/or life-threatening events (narrow therapeutic index) (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 twice daily. Therefore, darunavir must only be used in combination with a pharmacokinetic enhancer (see sections 4.4 and 5.2).

A clinical study utilising a cocktail of medicinal products that are metabolised by cytochromes CYP2C9, CYP2C19 and CYP2D6 demonstrated an increase in CYP2C9 and CYP2C19 activity and inhibition of CYP2D6 activity in the presence of darunavir/ritonavir, which may be attributed to the presence of low dose ritonavir. Co-administration of darunavir and ritonavir with medicinal products which are primarily metabolised by CYP2D6 (such as flecainide, propafenone, metoprolol) may result in increased plasma concentrations of these medicinal products, which could increase or prolong their therapeutic effect and adverse reactions. Co-administration of darunavir and ritonavir with medicinal products primarily metabolised by CYP2C9 (such as warfarin) and CYP2C19 (such as methadone) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Although the effect on CYP2C8 has only been studied *in vitro*, co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP2C8 (such as paclitaxel, rosiglitazone, repaglinide) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Ritonavir inhibits the transporters P-glycoprotein, OATP1B1 and OATP1B3, and co-administration with substrates of these transporters can result in increased plasma concentrations of these compounds (e.g. dabigatran etexilate, digoxin, statins and bosentan; see the Interaction table below).

#### **Medicinal products that may be affected by darunavir boosted with cobicistat**

The recommendations for darunavir boosted with ritonavir are adequate also for darunavir boosted with cobicistat with regard to substrates of CYP3A4, CYP2D6, P-glycoprotein, OATP1B1 and OATP1B3 (see contraindications and recommendations presented in the section above). Cobicistat 150 mg given with darunavir 800 mg once daily enhances darunavir pharmacokinetic parameters in a comparable way to ritonavir (see section 5.2).

Unlike ritonavir, cobicistat does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1. For further information on cobicistat, consult the cobicistat Summary of Product Characteristics.

#### **Interaction table**

Interaction studies have only been performed in adults.

Several of the interaction studies (indicated by <sup>#</sup> in the table below) have been performed at lower than recommended doses of darunavir or with a different dosing regimen (see section 4.2 Posology). The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated.

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer. Darunavir may therefore have different recommendations for concomitant medications depending on whether the compound is boosted with ritonavir or cobicistat. The same recommendations apply, unless specifically indicated. For further information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Interactions between darunavir/ritonavir and antiretroviral and non-antiretroviral medicinal products are listed in the table below. The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within ( $\leftrightarrow$ ), below ( $\downarrow$ ) or above ( $\uparrow$ ) the 80-125% range (not determined as “ND”).

In the table below the specific pharmacokinetic enhancer is specified when recommendations differ. When the recommendation is the same for PREZISTA when co-administered with a low dose ritonavir or cobicistat, the term “boosted PREZISTA” is used.

The below list of examples of drug drug interactions is not comprehensive and therefore the label of each drug that is co-administered with PREZISTA should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

| <b>INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS</b> |   |  |
|--|---|--|
| <b>Medicinal products by therapeutic areas</b>                             | <b>Interaction<br/>Geometric mean change (%)</b>  | <b>Recommendations concerning co-administration</b>  |
| <b>HIV ANTIRETROVIRALS</b>   |   |  |
| <b><i>Integrase strand transfer inhibitors</i></b>                         |   |  |
| Dolutegravir   | dolutegravir AUC $\downarrow$ 22%<br>dolutegravir C <sub>24h</sub> $\downarrow$ 38%<br>dolutegravir C <sub>max</sub> $\downarrow$ 11%<br>darunavir $\leftrightarrow$ *<br>* Using cross-study comparisons to historical pharmacokinetic data        | Boosted PREZISTA and dolutegravir can be used without dose adjustment.   |
| Raltegravir  | Some clinical studies suggest raltegravir may cause a modest decrease in darunavir plasma concentrations.   | At present the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically relevant. Boosted PREZISTA and raltegravir can be used without dose adjustments.                                      |
| <b><i>Nucleo(s)ide reverse transcriptase inhibitors (NRTIs)</i></b>        |   |  |
| Didanosine<br>400 mg once daily  | didanosine AUC $\downarrow$ 9%<br>didanosine C <sub>min</sub> ND<br>didanosine C <sub>max</sub> $\downarrow$ 16%<br>darunavir AUC $\leftrightarrow$<br>darunavir C <sub>min</sub> $\leftrightarrow$<br>darunavir C <sub>max</sub> $\leftrightarrow$ | Boosted PREZISTA and didanosine can be used without dose adjustments.<br>Didanosine is to be administered on an empty stomach, thus it should be administered 1 hour before or 2 hours after boosted PREZISTA given with food. |

|  |  |   |
|--|--|---|
| Tenofovir disoproxil<br>245 mg once daily <sup>†</sup>                   | tenofovir AUC ↑ 22%<br>tenofovir C <sub>min</sub> ↑ 37%<br>tenofovir C <sub>max</sub> ↑ 24%<br># darunavir AUC ↑ 21%<br># darunavir C <sub>min</sub> ↑ 24%<br># darunavir C <sub>max</sub> ↑ 16%<br>(↑ tenofovir from effect on MDR-1 transport in the renal tubules)  | Monitoring of renal function may be indicated when boosted PREZISTA is given in combination with tenofovir disoproxil, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.<br><br>PREZISTA co-administered with cobicistat lowers the creatinine clearance. Refer to section 4.4 if creatinine clearance is used for dose adjustment of tenofovir disoproxil.   |
| Emtricitabine/tenofovir alafenamide                                      | Tenofovir alafenamide ↔<br>Tenofovir ↑   | The recommended dose of emtricitabine/tenofovir alafenamide is 200/10 mg once daily when used with boosted PREZISTA.  |
| Abacavir<br>Emtricitabine<br>Lamivudine<br>Stavudine<br>Zidovudine       | Not studied. Based on the different elimination pathways of the other NRTIs zidovudine, emtricitabine, stavudine, lamivudine, that are primarily renally excreted, and abacavir for which metabolism is not mediated by CYP450, no interactions are expected for these medicinal compounds and boosted PREZISTA. | Boosted PREZISTA can be used with these NRTIs without dose adjustment.<br><br>PREZISTA co-administered with cobicistat lowers the creatinine clearance. Refer to section 4.4 if creatinine clearance is used for dose adjustment of emtricitabine or lamivudine.  |
| <b><i>Non-nucleo(s)ide reverse transcriptase inhibitors (NNRTIs)</i></b> |  |   |
| Efavirenz<br>600 mg once daily   | efavirenz AUC ↑ 21%<br>efavirenz C <sub>min</sub> ↑ 17%<br>efavirenz C <sub>max</sub> ↑ 15%<br># darunavir AUC ↓ 13%<br># darunavir C <sub>min</sub> ↓ 31%<br># darunavir C <sub>max</sub> ↓ 15%<br>(↑ efavirenz from CYP3A inhibition)<br>(↓ darunavir from CYP3A induction)                                    | Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when PREZISTA co-administered with low dose ritonavir is given in combination with efavirenz.<br><br>Efavirenz in combination with PREZISTA/ritonavir 800/100 mg once daily may result in sub-optimal darunavir C <sub>min</sub> . If efavirenz is to be used in combination with PREZISTA/ritonavir, the PREZISTA/ritonavir 600/100 mg twice daily regimen should be used (see section 4.4).<br><br>Co-administration with PREZISTA co-administered with cobicistat is not recommended (see section 4.4). |
| Etravirine<br>100 mg twice daily   | etravirine AUC ↓ 37%<br>etravirine C <sub>min</sub> ↓ 49%<br>etravirine C <sub>max</sub> ↓ 32%<br>darunavir AUC ↑ 15%<br>darunavir C <sub>min</sub> ↔<br>darunavir C <sub>max</sub> ↔  | PREZISTA co-administered with low dose ritonavir and etravirine 200 mg twice daily can be used without dose adjustments.<br><br>Co-administration with PREZISTA co-administered with cobicistat is not recommended (see section 4.4).   |

|   |   |  |
|---|---|--|
| Nevirapine<br>200 mg twice daily  | nevirapine AUC ↑ 27%<br>nevirapine C <sub>min</sub> ↑ 47%<br>nevirapine C <sub>max</sub> ↑ 18%<br>#darunavir: concentrations were consistent with historical data (↑ nevirapine from CYP3A inhibition)  | PREZISTA co-administered with low dose ritonavir and nevirapine can be used without dose adjustments.<br><br>Co-administration with PREZISTA co-administered with cobicistat is not recommended (see section 4.4).   |
| Rilpivirine<br>150 mg once daily  | rilpivirine AUC ↑ 130%<br>rilpivirine C <sub>min</sub> ↑ 178%<br>rilpivirine C <sub>max</sub> ↑ 79%<br>darunavir AUC ↔<br>darunavir C <sub>min</sub> ↓ 11%<br>darunavir C <sub>max</sub> ↔  | Boosted PREZISTA and rilpivirine can be used without dose adjustments.   |
| <b>HIV Protease inhibitors (PIs) - without additional co-administration of low dose ritonavir<sup>†</sup></b> |   |  |
| Atazanavir<br>300 mg once daily   | atazanavir AUC ↔<br>atazanavir C <sub>min</sub> ↑ 52%<br>atazanavir C <sub>max</sub> ↓ 11%<br>#darunavir AUC ↔<br>#darunavir C <sub>min</sub> ↔<br>#darunavir C <sub>max</sub> ↔<br><br>Atazanavir: comparison of atazanavir/ritonavir 300/100 mg once daily vs. atazanavir 300 mg once daily in combination with darunavir/ritonavir 400/100 mg twice daily.<br>Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg twice daily in combination with atazanavir 300 mg once daily. | PREZISTA co-administered with low dose ritonavir and atazanavir can be used without dose adjustments.<br><br>PREZISTA co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5).   |
| Indinavir<br>800 mg twice daily   | indinavir AUC ↑ 23%<br>indinavir C <sub>min</sub> ↑ 125%<br>indinavir C <sub>max</sub> ↔<br>#darunavir AUC ↑ 24%<br>#darunavir C <sub>min</sub> ↑ 44%<br>#darunavir C <sub>max</sub> ↑ 11%<br><br>Indinavir: comparison of indinavir/ritonavir 800/100 mg twice daily vs. indinavir/darunavir/ritonavir 800/400/100 mg twice daily.<br>Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with indinavir 800 mg twice daily.                                       | When used in combination with PREZISTA co-administered with low dose ritonavir, dose adjustment of indinavir from 800 mg twice daily to 600 mg twice daily may be warranted in case of intolerance.<br><br>PREZISTA co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5). |

|   |  |  |
|---|--|--|
| Saquinavir<br>1,000 mg twice daily  | <p># darunavir AUC ↓ 26%<br/># darunavir C<sub>min</sub> ↓ 42%<br/># darunavir C<sub>max</sub> ↓ 17%<br/>saquinavir AUC ↓ 6%<br/>saquinavir C<sub>min</sub> ↓ 18%<br/>saquinavir C<sub>max</sub> ↓ 6%</p> <p>Saquinavir: comparison of saquinavir/ritonavir 1,000/100 mg twice daily vs. saquinavir/darunavir/ritonavir 1,000/400/100 mg twice daily<br/>Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with saquinavir 1,000 mg twice daily.</p> | <p>It is not recommended to combine PREZISTA co-administered with low dose ritonavir with saquinavir.</p> <p>PREZISTA co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5).</p> |
| <b>HIV Protease inhibitors (PIs) - with co-administration of low dose ritonavir<sup>†</sup></b> |  |  |
| Lopinavir/ritonavir<br>400/100 mg twice daily   | lopinavir AUC ↑ 9%<br>lopinavir C <sub>min</sub> ↑ 23%<br>lopinavir C <sub>max</sub> ↓ 2%<br>darunavir AUC ↓ 38% <sup>‡</sup><br>darunavir C <sub>min</sub> ↓ 51% <sup>‡</sup><br>darunavir C <sub>max</sub> ↓ 21% <sup>‡</sup>  | Due to a decrease in the exposure (AUC) of darunavir by 40%, appropriate doses of the combination have not been established. Hence, concomitant use of boosted PREZISTA and the combination product lopinavir/ritonavir is contraindicated (see section 4.3).  |
| Lopinavir/ritonavir<br>533/133.3 mg twice daily   | lopinavir AUC ↔<br>lopinavir C <sub>min</sub> ↑ 13%<br>lopinavir C <sub>max</sub> ↑ 11%<br>darunavir AUC ↓ 41%<br>darunavir C <sub>min</sub> ↓ 55%<br>darunavir C <sub>max</sub> ↓ 21%<br><sup>‡</sup> based upon non dose normalised values   |  |
| <b>CCR5 ANTAGONIST</b>  |  |  |
| Maraviroc<br>150 mg twice daily   | maraviroc AUC ↑ 305%<br>maraviroc C <sub>min</sub> ND<br>maraviroc C <sub>max</sub> ↑ 129%<br>darunavir, ritonavir concentrations were consistent with historical data   | The maraviroc dose should be 150 mg twice daily when co-administered with boosted PREZISTA.  |
| <b>α1-ADRENORECEPTOR ANTAGONIST</b>   |  |  |
| Alfuzosin   | Based on theoretical considerations PREZISTA is expected to increase alfuzosin plasma concentrations. (CYP3A inhibition)   | Co-administration of boosted PREZISTA and alfuzosin is contraindicated (see section 4.3).  |
| <b>ANAESTHETIC</b>  |  |  |
| Alfentanil  | Not studied. The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by boosted PREZISTA.   | The concomitant use with boosted PREZISTA may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.  |

| <b>ANTIANGINA/ANTIARRHYTHMIC</b>   |  |   |
|--|--|---|
| Disopyramide<br>Flecainide<br>Lidocaine (systemic)<br>Mexiletine<br>Propafenone<br><br><br><br><br>Amiodarone<br>Bepidil<br>Dronedarone<br>Ivabradine<br>Quinidine<br>Ranolazine | Not studied. Boosted PREZISTA is expected to increase these antiarrhythmic plasma concentrations.<br>(CYP3A and/or CYP2D6 inhibition)  | Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with boosted PREZISTA.<br><br>Co-administration of boosted PREZISTA and amiodarone, bepridil, dronedarone, ivabradine, quinidine, or ranolazine is contraindicated (see section 4.3).                              |
| Digoxin<br>0.4 mg single dose  | digoxin AUC ↑ 61%<br>digoxin C <sub>min</sub> ND<br>digoxin C <sub>max</sub> ↑ 29%<br>(↑ digoxin from probable inhibition of P-gp)   | 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 boosted PREZISTA therapy. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject. |
| <b>ANTIBIOTIC</b>  |  |   |
| Clarithromycin<br>500 mg twice daily   | clarithromycin AUC ↑ 57%<br>clarithromycin C <sub>min</sub> ↑ 174%<br>clarithromycin C <sub>max</sub> ↑ 26%<br># darunavir AUC ↓ 13%<br># darunavir C <sub>min</sub> ↑ 1%<br># darunavir C <sub>max</sub> ↓ 17%<br>14-OH-clarithromycin concentrations were not detectable when combined with PREZISTA/ritonavir.<br>(↑ clarithromycin from CYP3A inhibition and possible P-gp inhibition) | Caution should be exercised when clarithromycin is combined with boosted PREZISTA.<br><br>For patients with renal impairment the Summary of Product Characteristics for clarithromycin should be consulted for the recommended dose.  |
| <b>ANTICOAGULANT/PLATELET AGGREGATION INHIBITOR</b>  |  |   |
| Apixaban<br>Edoxaban<br>Rivaroxaban  | Not studied. Co-administration of boosted PREZISTA with these anticoagulants may increase concentrations of the anticoagulant, which may lead to an increased bleeding risk.<br>(CYP3A and/or P-gp inhibition)   | The use of boosted PREZISTA and these anticoagulants is not recommended.  |
| Dabigatran<br>Ticagrelor   | Not studied. Co-administration with boosted PREZISTA may lead to a substantial increase in exposure to dabigatran or ticagrelor.   | Concomitant administration of boosted PREZISTA with dabigatran or ticagrelor is contraindicated (see section 4.3).<br><br>Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended.   |
| Warfarin   | Not studied. Warfarin concentrations may be affected when co-administered with boosted PREZISTA.   | It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with boosted PREZISTA.   |

| <b>ANTICONVULSANTS</b>   |   |  |
|--|---|--|
| Phenobarbital<br>Phenytoin   | Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir and its pharmacoenhancer. (induction of CYP450 enzymes)  | PREZISTA co-administered with low dose ritonavir should not be used in combination with these medicines.<br><br>The use of these medicines with PREZISTA/cobicistat is contraindicated (see section 4.3).  |
| Carbamazepine<br>200 mg twice daily                                      | carbamazepine AUC ↑ 45%<br>carbamazepine C <sub>min</sub> ↑ 54%<br>carbamazepine C <sub>max</sub> ↑ 43%<br>darunavir AUC ↔<br>darunavir C <sub>min</sub> ↓ 15%<br>darunavir C <sub>max</sub> ↔  | No dose adjustment for PREZISTA/ritonavir is recommended. If there is a need to combine PREZISTA/ritonavir and carbamazepine, patients should be monitored for potential carbamazepine-related adverse events. Carbamazepine concentrations should be monitored and its dose should be titrated for adequate response. Based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of PREZISTA/ritonavir.<br><br>The use of carbamazepine with PREZISTA co-administered with cobicistat is contraindicated (see section 4.3). |
| Clonazepam   | Not studied. Co-administration of boosted PREZISTA with clonazepam may increase concentrations of clonazepam. (CYP3A inhibition)  | Clinical monitoring is recommended when co-administering boosted PREZISTA and clonazepam.  |
| <b>ANTIDEPRESSANTS</b>   |   |  |
| Paroxetine<br>20 mg once daily<br><br>Sertraline<br>50 mg once daily     | paroxetine AUC ↓ 39%<br>paroxetine C <sub>min</sub> ↓ 37%<br>paroxetine C <sub>max</sub> ↓ 36%<br># darunavir AUC ↔<br># darunavir C <sub>min</sub> ↔<br># darunavir C <sub>max</sub> ↔<br>sertraline AUC ↓ 49%<br>sertraline C <sub>min</sub> ↓ 49%<br>sertraline C <sub>max</sub> ↓ 44%<br># darunavir AUC ↔<br># darunavir C <sub>min</sub> ↓ 6%<br># darunavir C <sub>max</sub> ↔<br><br>In contrast to these data with PREZISTA/ritonavir, PREZISTA/cobicistat may increase these antidepressant plasma concentrations (CYP2D6 and/or CYP3A inhibition). | If antidepressants are co-administered with boosted PREZISTA, the recommended approach is a dose titration of the antidepressant based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of these antidepressants who start treatment with boosted PREZISTA should be monitored for antidepressant response.   |
| Amitriptyline<br>Desipramine<br>Imipramine<br>Nortriptyline<br>Trazodone | Concomitant use of boosted PREZISTA and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or CYP3A inhibition)   | Clinical monitoring is recommended when co-administering boosted PREZISTA with these antidepressants and a dose adjustment of the antidepressant may be needed.  |



|  |  |  |
|--|--|--|
| <b>ANTI-DIABETICS</b>  |  |  |
| Metformin  | Not studied. Based on theoretical considerations PREZISTA co-administered with cobicistat is expected to increase metformin plasma concentrations. (MATE1 inhibition)  | Careful patient monitoring and dose adjustment of metformin is recommended in patients who are taking PREZISTA co-administered with cobicistat. (not applicable for PREZISTA co-administered with ritonavir)   |
| <b>ANTIEMETICS</b>   |  |  |
| Domperidone  | Not studied.   | Co-administration of domperidone with boosted PREZISTA is contraindicated.   |
| <b>ANTIFUNGALS</b>   |  |  |
| Voriconazole   | Not studied. Ritonavir may decrease plasma concentrations of voriconazole. (induction of CYP450 enzymes)<br><br>Concentrations of voriconazole may increase or decrease when co-administered with PREZISTA co-administered with cobicistat. (inhibition of CYP450 enzymes)   | Voriconazole should not be combined with boosted PREZISTA unless an assessment of the benefit/risk ratio justifies the use of voriconazole.  |
| Fluconazole<br>Isavuconazole<br>Itraconazole<br>Posaconazole<br><br><br>Clotrimazole | Not studied. Boosted PREZISTA may increase antifungal plasma concentrations and posaconazole, isavuconazole, itraconazole or fluconazole may increase darunavir concentrations. (CYP3A and/or P-gp inhibition)<br><br>Not Studied. Concomitant systemic use of clotrimazole and boosted PREZISTA may increase plasma concentrations of darunavir and/or clotrimazole. darunavir AUC <sub>24h</sub> ↑ 33% (based on population pharmacokinetic model) | Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of itraconazole should not exceed 200 mg.   |
| <b>ANTIGOUT MEDICINES</b>  |  |  |
| Colchicine   | Not studied. Concomitant use of colchicine and boosted PREZISTA may increase the exposure to colchicine. (CYP3A and/ or P-gp inhibition)   | A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with boosted PREZISTA is required. For patients with renal or hepatic impairment colchicine with boosted PREZISTA is contraindicated (see sections 4.3 and 4.4). |
| <b>ANTIMALARIALS</b>   |  |  |
| Artemether/Lumefantrine<br>80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours      | artemether AUC ↓ 16%<br>artemether C <sub>min</sub> ↔<br>artemether C <sub>max</sub> ↓ 18%<br>dihydroartemisinin AUC ↓ 18%<br>dihydroartemisinin C <sub>min</sub> ↔<br>dihydroartemisinin C <sub>max</sub> ↓ 18%<br>lumefantrine AUC ↑ 175%<br>lumefantrine C <sub>min</sub> ↑ 126%<br>lumefantrine C <sub>max</sub> ↑ 65%<br>darunavir AUC ↔<br>darunavir C <sub>min</sub> ↓ 13%<br>darunavir C <sub>max</sub> ↔                                    | The combination of boosted PREZISTA and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.  |

| ANTIMYCOBACTERIALS                                   |  |  |
|--|--|--|
| Rifampicin<br>Rifapentine                            | Not studied. Rifapentine and rifampicin are strong CYP3A inducers and have been shown to cause profound decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction). During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with low dose ritonavir, a high frequency of liver reactions was seen with rifampicin.  | <p>The combination of rifapentine and boosted PREZISTA is not recommended.</p> <p>The combination of rifampicin and boosted PREZISTA is contraindicated (see section 4.3).</p>   |
| Rifabutin<br>150 mg once every other day             | <p>rifabutin AUC<sup>**</sup> ↑ 55%<br/> rifabutin C<sub>min</sub><sup>**</sup> ↑ ND<br/> rifabutin C<sub>max</sub><sup>**</sup> ↔<br/> darunavir AUC ↑ 53%<br/> darunavir C<sub>min</sub> ↑ 68%<br/> darunavir C<sub>max</sub> ↑ 39%<br/> <sup>**</sup> sum of active moieties of rifabutin (parent drug + 25-<i>O</i>-desacetyl metabolite)</p> <p>The interaction trial showed a comparable daily systemic exposure for rifabutin between treatment at 300 mg once daily alone and 150 mg once every other day in combination with PREZISTA/ritonavir (600/100 mg twice daily) with an about 10-fold increase in the daily exposure to the active metabolite 25-<i>O</i>-desacetyl rifabutin. Furthermore, AUC of the sum of active moieties of rifabutin (parent drug + 25-<i>O</i>-desacetyl metabolite) was increased 1.6-fold, while C<sub>max</sub> remained comparable.</p> <p>Data on comparison with a 150 mg once daily reference dose is lacking.</p> <p>(Rifabutin is an inducer and substrate of CYP3A.) An increase of systemic exposure to darunavir was observed when PREZISTA co-administered with 100 mg ritonavir was co-administered with rifabutin (150 mg once every other day).</p> | <p>A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg once every other day) and increased monitoring for rifabutin related adverse events is warranted in patients receiving the combination with PREZISTA co-administered with ritonavir. In case of safety issues, a further increase of the dosing interval for rifabutin and/or monitoring of rifabutin levels should be considered.</p> <p>Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients.</p> <p>Based upon the safety profile of PREZISTA/ritonavir, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for PREZISTA/ritonavir.</p> <p>Based on pharmacokinetic modeling, this dosage reduction of 75% is also applicable if patients receive rifabutin at doses other than 300 mg/day.</p> <p>Co-administration of PREZISTA co-administered with cobicistat and rifabutin is not recommended.</p> |
| ANTINEOPLASTICS                                      |  |  |
| Dasatinib<br>Nilotinib<br>Vinblastine<br>Vincristine | Not studied. Boosted PREZISTA is expected to increase these antineoplastic plasma concentrations. (CYP3A inhibition)   | <p>Concentrations of these medicinal products may be increased when co-administered with boosted PREZISTA resulting in the potential for increased adverse events usually associated with these agents.</p> <p>Caution should be exercised when combining one of these antineoplastic agents with boosted PREZISTA.</p>  |
| Everolimus<br>Irinotecan                             |  | Concomitant use of everolimus or irinotecan and boosted PREZISTA is not recommended.   |

| <b>ANTIPSYCHOTICS/NEUROLEPTICS</b>   |   |  |
|--|---|--|
| Quetiapine   | Not studied. Boosted PREZISTA is expected to increase these antipsychotic plasma concentrations.<br>(CYP3A inhibition)  | Concomitant administration of boosted PREZISTA and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased concentrations of quetiapine may lead to coma (see section 4.3).  |
| Perphenazine<br>Risperidone<br>Thioridazine<br><br>Lurasidone<br>Pimozide<br>Sertindole  | Not studied. Boosted PREZISTA is expected to increase these antipsychotic plasma concentrations.<br>(CYP3A, CYP2D6 and/or P-gp inhibition)  | A dose decrease may be needed for these drugs when co-administered with boosted PREZISTA.<br><br>Concomitant administration of boosted PREZISTA and lurasidone, pimozide or sertindole is contraindicated (see section 4.3).   |
| <b>β-BLOCKERS</b>  |   |  |
| Carvedilol<br>Metoprolol<br>Timolol  | Not studied. Boosted PREZISTA is expected to increase these β-blocker plasma concentrations.<br>(CYP2D6 inhibition)   | Clinical monitoring is recommended when co-administering boosted PREZISTA with β-blockers. A lower dose of the β-blocker should be considered.   |
| <b>CALCIUM CHANNEL BLOCKERS</b>  |   |  |
| Amlodipine<br>Diltiazem<br>Felodipine<br>Nicardipine<br>Nifedipine<br>Verapamil  | Not studied. Boosted PREZISTA can be expected to increase the plasma concentrations of calcium channel blockers.<br>(CYP3A and/or CYP2D6 inhibition)  | Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with boosted PREZISTA.   |
| <b>CORTICOSTEROIDS</b>   |   |  |
| Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone) | Fluticasone: in a clinical study where ritonavir 100 mg capsules twice daily 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% CI 82-89%). Greater effects may be expected when fluticasone 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. The effects of high fluticasone systemic exposure on ritonavir plasma levels are unknown.<br><br>Other corticosteroids: interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with boosted PREZISTA, resulting in reduced serum cortisol concentrations. | Concomitant use of boosted PREZISTA and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.<br>Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects.<br>Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long term use. |
| Dexamethasone (systemic)   | Not studied. Dexamethasone may decrease plasma concentrations of darunavir.<br>(CYP3A induction)  | Systemic dexamethasone should be used with caution when combined with boosted PREZISTA.  |

| <b>ENDOTHELIN RECEPTOR ANTAGONISTS</b>                  |  |  |
|---|--|--|
| Bosentan  | <p>Not studied. Concomitant use of bosentan and boosted PREZISTA may increase plasma concentrations of bosentan.</p> <p>Bosentan is expected to decrease plasma concentrations of darunavir and/or its pharmacoenhancer. (CYP3A induction)</p>   | <p>When administered concomitantly with PREZISTA and low dose ritonavir, the patient's tolerability of bosentan should be monitored.</p> <p>Co-administration of PREZISTA co-administered with cobicistat and bosentan is not recommended.</p>   |
| <b>HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS</b> |  |  |
| <b>NS3-4A protease inhibitors</b>                       |  |  |
| Elbasvir/grazoprevir                                    | Boosted PREZISTA may increase the exposure to grazoprevir. (CYP3A and OATP1B inhibition)   | Concomitant use of boosted PREZISTA and elbasvir/grazoprevir is contraindicated (see section 4.3).   |
| Boceprevir<br>800 mg three times daily                  | <p>boceprevir AUC ↓ 32%</p> <p>boceprevir C<sub>min</sub> ↓ 35%</p> <p>boceprevir C<sub>max</sub> ↓ 25%</p> <p>darunavir AUC ↓ 44%</p> <p>darunavir C<sub>min</sub> ↓ 59%</p> <p>darunavir C<sub>max</sub> ↓ 36%</p>   | It is not recommended to co-administer boosted PREZISTA and boceprevir.  |
| Glecaprevir/pibrentasvir                                | Based on theoretical considerations boosted PREZISTA may increase the exposure to glecaprevir and pibrentasvir. (P-gp, BCRP and/or OATP1B1/3 inhibition)   | It is not recommended to co-administer boosted PREZISTA with glecaprevir/pibrentasvir.   |
| Simeprevir  | <p>simeprevir AUC ↑ 159%</p> <p>simeprevir C<sub>min</sub> ↑ 358%</p> <p>simeprevir C<sub>max</sub> ↑ 79%</p> <p>darunavir AUC ↑ 18%</p> <p>darunavir C<sub>min</sub> ↑ 31%</p> <p>darunavir C<sub>max</sub> ↔</p> <p>The dose of simeprevir in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir, compared to 150 mg in the simeprevir alone treatment group.</p> | It is not recommended to co-administer boosted PREZISTA and simeprevir.  |
| <b>HERBAL PRODUCTS</b>                                  |  |  |
| St John's wort<br>( <i>Hypericum perforatum</i> )       | Not studied. St John's wort is expected to decrease the plasma concentrations of darunavir or its pharmacoenhancers. (CYP450 induction)  | Boosted PREZISTA must not be used concomitantly with products containing St John's wort ( <i>Hypericum perforatum</i> ) (see section 4.3). 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. |
| <b>HMG CO-A REDUCTASE INHIBITORS</b>                    |  |  |
| Lovastatin<br>Simvastatin                               | Not studied. Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with boosted PREZISTA. (CYP3A inhibition)   | Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of boosted PREZISTA with lovastatin and simvastatin is therefore contraindicated (see section 4.3).   |

|  |  |   |
|--|--|---|
| Atorvastatin<br>10 mg once daily                         | atorvastatin AUC ↑ 3-4 fold<br>atorvastatin C <sub>min</sub> ↑ ≈5.5-10 fold<br>atorvastatin C <sub>max</sub> ↑ ≈2 fold<br># darunavir/ritonavir<br><br>atorvastatin AUC ↑ 290% <sup>Ω</sup><br>atorvastatin C <sub>max</sub> ↑ 319% <sup>Ω</sup><br>atorvastatin C <sub>min</sub> ND <sup>Ω</sup><br><sup>Ω</sup> with darunavir/cobicistat 800/150 mg             | When administration of atorvastatin and boosted PREZISTA is desired, it is recommended to start with an atorvastatin dose of 10 mg once daily. A gradual dose increase of atorvastatin may be tailored to the clinical response.    |
| Pravastatin<br>40 mg single dose                         | pravastatin AUC ↑ 81% <sup>¶</sup><br>pravastatin C <sub>min</sub> ND<br>pravastatin C <sub>max</sub> ↑ 63%<br><sup>¶</sup> an up to five-fold increase was seen in a limited subset of subjects   | When administration of pravastatin and boosted PREZISTA is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effect while monitoring for safety.             |
| Rosuvastatin<br>10 mg once daily                         | rosuvastatin AUC ↑ 48% <sup>¶¶</sup><br>rosuvastatin C <sub>max</sub> ↑ 144% <sup>¶¶</sup><br><sup>¶¶</sup> based on published data with darunavir/ritonavir<br><br>rosuvastatin AUC ↑ 93% <sup>§</sup><br>rosuvastatin C <sub>max</sub> ↑ 277% <sup>§</sup><br>rosuvastatin C <sub>min</sub> ND <sup>§</sup><br><sup>§</sup> with darunavir/cobicistat 800/150 mg | When administration of rosuvastatin and boosted PREZISTA is required, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.           |
| <b>OTHER LIPID MODIFYING AGENTS</b>                      |  |   |
| Lomitapide   | Based on theoretical considerations boosted PREZISTA is expected to increase the exposure of lomitapide when co-administered.<br>(CYP3A inhibition)  | Co-administration is contraindicated (see section 4.3)  |
| <b>H<sub>2</sub>-RECEPTOR ANTAGONISTS</b>                |  |   |
| Ranitidine<br>150 mg twice daily                         | # darunavir AUC ↔<br># darunavir C <sub>min</sub> ↔<br># darunavir C <sub>max</sub> ↔  | Boosted PREZISTA can be co-administered with H <sub>2</sub> -receptor antagonists without dose adjustments.   |
| <b>IMMUNOSUPPRESSANTS</b>                                |  |   |
| Ciclosporin<br>Sirolimus<br>Tacrolimus<br><br>Everolimus | Not studied. Exposure to these immunosuppressants will be increased when co-administered with boosted PREZISTA.<br>(CYP3A inhibition)  | Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs.<br><br>Concomitant use of everolimus and boosted PREZISTA is not recommended.  |
| <b>INHALED BETA AGONISTS</b>                             |  |   |
| Salmeterol   | Not studied. Concomitant use of salmeterol and boosted darunavir may increase plasma concentrations of salmeterol.   | Concomitant use of salmeterol and boosted PREZISTA is not recommended. The combination may result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia. |

| <b>NARCOTIC ANALGESICS / TREATMENT OF OPIOID DEPENDENCE</b>                |  |  |
|--|--|--|
| Methadone<br>individual dose ranging<br>from 55 mg to 150 mg<br>once daily | R(-) methadone AUC ↓ 16%<br>R(-) methadone C <sub>min</sub> ↓ 15%<br>R(-) methadone C <sub>max</sub> ↓ 24%<br><br>PREZISTA/cobicistat may, in contrast,<br>increase methadone plasma<br>concentrations (see cobicistat SmPC).  | No adjustment of methadone<br>dosage is required when initiating<br>co-administration with boosted<br>PREZISTA. However, adjustment<br>of the methadone dose may be<br>necessary when concomitantly<br>administered for a longer period of<br>time. Therefore, clinical<br>monitoring is recommended, as<br>maintenance therapy may need to<br>be adjusted in some patients. |
| Buprenorphine/naloxone<br>8/2 mg–16/4 mg once<br>daily                     | buprenorphine AUC ↓ 11%<br>buprenorphine C <sub>min</sub> ↔<br>buprenorphine C <sub>max</sub> ↓ 8%<br>norbuprenorphine AUC ↑ 46%<br>norbuprenorphine C <sub>min</sub> ↑ 71%<br>norbuprenorphine C <sub>max</sub> ↑ 36%<br>naloxone AUC ↔<br>naloxone C <sub>min</sub> ND<br>naloxone C <sub>max</sub> ↔  | The clinical relevance of the<br>increase in norbuprenorphine<br>pharmacokinetic parameters has<br>not been established. Dose<br>adjustment for buprenorphine may<br>not be necessary when<br>co-administered with boosted<br>PREZISTA but a careful clinical<br>monitoring for signs of opiate<br>toxicity is recommended.  |
| Fentanyl<br>Oxycodone<br>Tramadol  | Based on theoretical considerations<br>boosted PREZISTA may increase plasma<br>concentrations of these analgesics.<br>(CYP2D6 and/or CYP3A inhibition)   | Clinical monitoring is<br>recommended when<br>co-administering boosted<br>PREZISTA with these analgesics.  |
| <b>OESTROGEN-BASED CONTRACEPTIVES</b>                                      |  |  |
| Drospirenone<br>Ethinylestradiol<br>(3 mg/0.02 mg once<br>daily)           | drospirenone AUC ↑ 58% <sup>ε</sup><br>drospirenone C <sub>min</sub> ND <sup>ε</sup><br>drospirenone C <sub>max</sub> ↑ 15% <sup>ε</sup><br>ethinylestradiol AUC ↓ 30% <sup>ε</sup><br>ethinylestradiol C <sub>min</sub> ND <sup>ε</sup><br>ethinylestradiol C <sub>max</sub> ↓ 14% <sup>ε</sup><br><sup>ε</sup> with darunavir/cobicistat     | Alternative or additional<br>contraceptive measures are<br>recommended when<br>oestrogen-based contraceptives are<br>co-administered with boosted<br>PREZISTA. Patients using<br>oestrogens as hormone<br>replacement therapy should be<br>clinically monitored for signs of<br>oestrogen deficiency.  |
| Ethinylestradiol<br>Norethindrone<br>35 µg/1 mg once daily                 | ethinylestradiol AUC ↓ 44% <sup>β</sup><br>ethinylestradiol C <sub>min</sub> ↓ 62% <sup>β</sup><br>ethinylestradiol C <sub>max</sub> ↓ 32% <sup>β</sup><br>norethindrone AUC ↓ 14% <sup>β</sup><br>norethindrone C <sub>min</sub> ↓ 30% <sup>β</sup><br>norethindrone C <sub>max</sub> ↔ <sup>β</sup><br><sup>β</sup> with darunavir/ritonavir | When PREZISTA is co-<br>administered with a drospirenone-<br>containing product, clinical<br>monitoring is recommended due to<br>the potential for hyperkalaemia.  |
| <b>OPIOID ANTAGONIST</b>   |  |  |
| Naloxegol  | Not studied.   | Co-administration of boosted<br>PREZISTA and naloxegol is<br>contraindicated.  |

| <b>PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS</b>  |   |  |
|--|---|--|
| For the treatment of erectile dysfunction<br>Avanafil<br>Sildenafil<br>Tadalafil<br>Vardenafil | In an interaction study <sup>#</sup> , 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 and low dose ritonavir. | The combination of avanafil and boosted PREZISTA is contraindicated (see section 4.3). Concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with boosted PREZISTA should be done with caution. If concomitant use of boosted PREZISTA with sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended.  |
| For the treatment of pulmonary arterial hypertension<br>Sildenafil<br>Tadalafil                | Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and boosted PREZISTA may increase plasma concentrations of sildenafil or tadalafil. (CYP3A inhibition)                           | A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with boosted PREZISTA has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope). Therefore, co-administration of boosted PREZISTA and sildenafil when used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3). Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with boosted PREZISTA is not recommended. |
| <b>PROTON PUMP INHIBITORS</b>  |   |  |
| Omeprazole<br>20 mg once daily   | <sup>#</sup> darunavir AUC ↔<br><sup>#</sup> darunavir C <sub>min</sub> ↔<br><sup>#</sup> darunavir C <sub>max</sub> ↔  | Boosted PREZISTA can be co-administered with proton pump inhibitors without dose adjustments.  |





during pregnancy, and women who become pregnant during therapy with PREZISTA/cobicistat should be switched to an alternative regimen (see sections 4.2 and 4.4).

#### Breast-feeding

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 (1,000 mg/kg/day) resulted in toxicity. Because of both the potential for HIV transmission and the potential for adverse reactions in breast-fed infants, mothers should be instructed not to breast-feed under any circumstances 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**

PREZISTA in combination with cobicistat or ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing PREZISTA co-administered with cobicistat or low dose 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**

#### Summary of the safety profile

During the clinical development program (N=2,613 treatment-experienced subjects who initiated therapy with PREZISTA/ritonavir 600/100 mg twice daily), 51.3% of subjects experienced at least one adverse reaction. The total mean treatment duration for subjects was 95.3 weeks. The most frequent adverse reactions reported in clinical trials and as spontaneous reports are diarrhoea, nausea, rash, headache and vomiting. The most frequent serious reactions are acute renal failure, myocardial infarction, immune reconstitution inflammatory syndrome, thrombocytopenia, osteonecrosis, diarrhoea, hepatitis and pyrexia.

In the 96 week analysis, the safety profile of PREZISTA/ritonavir 800/100 mg once daily in treatment-naïve subjects was similar to that seen with PREZISTA/ritonavir 600/100 mg twice daily in treatment-experienced subjects except for nausea which was observed more frequently in treatment-naïve subjects. This was driven by mild intensity nausea. No new safety findings were identified in the 192 week analysis of the treatment-naïve subjects in which the mean treatment duration of PREZISTA/ritonavir 800/100 mg once daily was 162.5 weeks.

During the Phase III clinical trial GS-US-216-130 with darunavir/cobicistat (N=313 treatment-naïve and treatment-experienced subjects), 66.5% of subjects experienced at least one adverse reaction. The mean treatment duration was 58.4 weeks. The most frequent adverse reactions reported were diarrhoea (28%), nausea (23%), and rash (16%). Serious adverse reactions are diabetes mellitus, (drug) hypersensitivity, immune reconstitution inflammatory syndrome, rash and vomiting.

For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

#### Tabulated list of adverse reactions

Adverse reactions are listed by system organ class (SOC) and frequency category. Within each frequency category, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as follows: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and not known (frequency cannot be estimated from the available data).

*Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing*

| MedDRA system organ class<br>Frequency category | Adverse reaction  |
|---|---|
| <i>Infections and infestations</i>              |   |
| uncommon  | herpes simplex  |
| <i>Blood and lymphatic system disorders</i>     |   |
| uncommon  | thrombocytopenia, neutropenia, anaemia, leukopenia  |
| rare  | increased eosinophil count  |
| <i>Immune system disorders</i>                  |   |
| uncommon  | immune reconstitution inflammatory syndrome, (drug) hypersensitivity  |
| <i>Endocrine disorders</i>                      |   |
| uncommon  | hypothyroidism, increased blood thyroid stimulating hormone   |
| <i>Metabolism and nutrition disorders</i>       |   |
| common  | diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia  |
| uncommon  | gout, anorexia, decreased appetite, decreased weight, increased weight, hyperglycaemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase |
| <i>Psychiatric disorders</i>                    |   |
| common  | insomnia  |
| uncommon  | depression, disorientation, anxiety, sleep disorder, abnormal dreams, nightmare, decreased libido   |
| rare  | confusional state, altered mood, restlessness   |
| <i>Nervous system disorders</i>                 |   |
| common  | headache, peripheral neuropathy, dizziness  |
| uncommon  | lethargy, paraesthesia, hypoaesthesia, dysgeusia, disturbance in attention, memory impairment, somnolence   |
| rare  | syncope, convulsion, ageusia, sleep phase rhythm disturbance  |
| <i>Eye disorders</i>                            |   |
| uncommon  | conjunctival hyperaemia, dry eye  |
| rare  | visual disturbance  |
| <i>Ear and labyrinth disorders</i>              |   |
| uncommon  | vertigo   |
| <i>Cardiac disorders</i>                        |   |
| uncommon  | myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia   |
| rare  | acute myocardial infarction, sinus bradycardia, palpitations  |

|  |   |
|--|---|
| <i>Vascular disorders</i>                              |   |
| uncommon   | hypertension, flushing  |
| <i>Respiratory, thoracic and mediastinal disorders</i> |   |
| uncommon   | dyspnoea, cough, epistaxis, throat irritation   |
| rare   | rhinorrhoea   |
| <i>Gastrointestinal disorders</i>                      |   |
| very common  | diarrhoea   |
| common   | vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence  |
| uncommon   | pancreatitis, gastritis, gastrooesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia  |
| rare   | stomatitis, haematemesis, cheilitis, dry lip, coated tongue   |
| <i>Hepatobiliary disorders</i>                         |   |
| common   | increased alanine aminotransferase  |
| uncommon   | hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-glutamyltransferase |
| <i>Skin and subcutaneous tissue disorders</i>          |   |
| common   | rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus  |
| uncommon   | angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation  |
| rare   | DRESS, Stevens-Johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma  |
| not known  | toxic epidermal necrolysis, acute generalised exanthematous pustulosis  |
| <i>Musculoskeletal and connective tissue disorders</i> |   |
| uncommon   | myalgia, osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphokinase   |
| rare   | musculoskeletal stiffness, arthritis, joint stiffness   |
| <i>Renal and urinary disorders</i>                     |   |
| uncommon   | acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria   |
| rare   | decreased creatinine renal clearance  |

|   |  |
|---|--|
| <i>Reproductive system and breast disorders</i>             |  |
| uncommon  | erectile dysfunction, gynaecomastia  |
| <i>General disorders and administration site conditions</i> |  |
| common  | asthenia, fatigue  |
| uncommon  | pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain |
| rare  | chills, abnormal feeling, xerosis  |

*Adverse reactions observed with darunavir/cobicistat in adult patients*

| MedDRA system organ class<br>Frequency category        | Adverse reaction   |
|--|--|
| <i>Immune system disorders</i>                         |  |
| common   | (drug) hypersensitivity  |
| uncommon   | immune reconstitution inflammatory syndrome  |
| <i>Metabolism and nutrition disorders</i>              |  |
| common   | anorexia, diabetes mellitus, hypercholesterolaemia, hypertriglyceridaemia, hyperlipidaemia                               |
| <i>Psychiatric disorders</i>                           |  |
| common   | abnormal dreams  |
| <i>Nervous system disorders</i>                        |  |
| very common  | headache   |
| <i>Gastrointestinal disorders</i>                      |  |
| very common  | diarrhoea, nausea  |
| common   | vomiting, abdominal pain, abdominal distension, dyspepsia, flatulence, pancreatic enzymes increased                      |
| uncommon   | pancreatitis acute   |
| <i>Hepatobiliary disorders</i>                         |  |
| common   | hepatic enzyme increased   |
| uncommon   | hepatitis*, cytolytic hepatitis*   |
| <i>Skin and subcutaneous tissue disorders</i>          |  |
| very common  | rash (including macular, maculopapular, papular, erythematous, pruritic rash, generalised rash, and allergic dermatitis) |
| common   | angioedema, pruritus, urticaria  |
| rare   | drug reaction with eosinophilia and systemic symptoms*, Stevens-Johnson syndrome*  |
| not known  | toxic epidermal necrolysis*, acute generalised exanthematous pustulosis*   |
| <i>Musculoskeletal and connective tissue disorders</i> |  |
| common   | myalgia  |
| uncommon   | osteonecrosis*   |
| <i>Reproductive system and breast disorders</i>        |  |
| uncommon   | gynaecomastia*   |

|   |                            |
|---|----------------------------|
| <i>General disorders and administration site conditions</i> |                            |
| common  | fatigue                    |
| uncommon  | asthenia                   |
| <i>Investigations</i>                                       |                            |
| common  | increased blood creatinine |

\* these adverse drug reactions have not been reported in clinical trial experience with darunavir/cobicistat but have been noted with darunavir/ritonavir treatment and could be expected with darunavir/cobicistat too.

### Description of selected adverse reactions

#### *Rash*

In clinical trials, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In cases of severe skin reaction see the warning in section 4.4. In a single arm trial investigating darunavir 800 mg once daily in combination with cobicistat 150 mg once daily and other antiretrovirals 2.2% of patients discontinued treatment due to rash.

During the clinical development program of raltegravir in treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing PREZISTA/ritonavir + raltegravir compared to those containing PREZISTA/ritonavir without raltegravir or raltegravir without PREZISTA/ritonavir. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR), respectively; and for drug-related rash were 2.4, 1.1, and 2.3 per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy (see section 4.4).

#### *Metabolic parameters*

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

#### *Musculoskeletal abnormalities*

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).

#### *Immune reconstitution inflammatory syndrome*

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

#### *Bleeding in haemophiliac patients*

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

### Paediatric population

The safety assessment in paediatric patients is based on the 48-week analysis of safety data from three Phase II trials. The following patient populations were evaluated (see section 5.1):

- 80 ART-experienced HIV-1 infected paediatric patients aged from 6 to 17 years and weighing at least 20 kg who received PREZISTA tablets with low dose ritonavir twice daily in combination with other antiretroviral agents.

- 21 ART-experienced HIV-1 infected paediatric patients aged from 3 to < 6 years and weighing 10 kg to < 20 kg (16 participants from 15 kg to < 20 kg) who received PREZISTA oral suspension with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 12 ART-naïve HIV-1 infected paediatric patients aged from 12 to 17 years and weighing at least 40 kg who received PREZISTA tablets with low dose ritonavir once daily in combination with other antiretroviral agents (see section 5.1).

Overall, the safety profile in these paediatric patients was similar to that observed in the adult population.

#### Other special populations

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

Among 1,968 treatment-experienced patients receiving PREZISTA co-administered with ritonavir 600/100 mg twice daily, 236 patients were co-infected with 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).

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

## **4.9 Overdose**

Human experience of acute overdose with PREZISTA co-administered with cobicistat or low dose ritonavir is limited. Single doses up to 3,200 mg of darunavir as oral solution alone and up to 1,600 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. 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: Antivirals for systemic use, protease inhibitors, ATC code: J05AE10.

#### Mechanism of action

Darunavir is an inhibitor of the dimerisation and of the catalytic activity 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  $\mu M$ .

## Resistance

*In vitro* selection of darunavir-resistant virus from wild type HIV-1 was lengthy (> 3 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23-50-fold) harboured 2 to 4 amino acid substitutions in the protease gene. The decreased susceptibility to darunavir of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations.

The clinical trial data from ART-experienced patients (*TITAN* trial and the pooled analysis of the *POWER* 1, 2 and 3 and *DUET* 1 and 2 trials) showed that virologic response to PREZISTA co-administered with low dose ritonavir was decreased when 3 or more darunavir RAMs (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) were present at baseline or when these mutations developed during treatment.

Increasing baseline darunavir fold change in EC<sub>50</sub> (FC) was associated with decreasing virologic response. A lower and upper clinical cut-off of 10 and 40 were identified. Isolates with baseline FC ≤ 10 are susceptible; isolates with FC > 10 to 40 have decreased susceptibility; isolates with FC > 40 are resistant (see Clinical results).

Viruses isolated from patients on PREZISTA/ritonavir 600/100 mg twice daily experiencing virologic failure by rebound that were susceptible to tipranavir at baseline remained susceptible to tipranavir after treatment in the vast majority of cases.

The lowest rates of developing resistant HIV virus are observed in ART-naïve patients who are treated for the first time with darunavir in combination with other ART.

The table below shows the development of HIV-1 protease mutations and loss of susceptibility to PIs in virologic failures at endpoint in the *ARTEMIS*, *ODIN* and *TITAN* trials.

|   | ARTEMIS<br>Week 192   | ODIN<br>Week 48   |  | TITAN<br>Week 48   |
|---|---|---|--|--|
|   | PREZISTA/<br>ritonavir<br>800/100 mg<br>once daily<br>N=343 | PREZISTA/<br>ritonavir<br>800/100 mg<br>once daily<br>N=294 | PREZISTA/<br>ritonavir<br>600/100 mg<br>twice daily<br>N=296 | PREZISTA/<br>ritonavir<br>600/100 mg<br>twice daily<br>N=298 |
| Total number of<br>virologic failures <sup>a</sup> , n<br>(%)   | 55 (16.0%)  | 65 (22.1%)  | 54 (18.2%)   | 31 (10.4%)   |
| Rebounders  | 39 (11.4%)  | 11 (3.7%)   | 11 (3.7%)  | 16 (5.4%)  |
| Never suppressed<br>subjects  | 16 (4.7%)   | 54 (18.4%)  | 43 (14.5%)   | 15 (5.0%)  |
| Number of subjects with virologic failure and paired baseline/endpoint genotypes, developing mutations <sup>b</sup> at<br>endpoint, n/N                           |   |   |  |  |
| Primary (major) PI<br>mutations   | 0/43  | 1/60  | 0/42   | 6/28   |
| PI RAMs   | 4/43  | 7/60  | 4/42   | 10/28  |
| Number of subjects with virologic failure and paired baseline/endpoint phenotypes, showing loss of<br>susceptibility to PIs at endpoint compared to baseline, n/N |   |   |  |  |
| PI  |   |   |  |  |
| darunavir   | 0/39  | 1/58  | 0/41   | 3/26   |
| amprenavir  | 0/39  | 1/58  | 0/40   | 0/22   |
| atazanavir  | 0/39  | 2/56  | 0/40   | 0/22   |
| indinavir   | 0/39  | 2/57  | 0/40   | 1/24   |
| lopinavir   | 0/39  | 1/58  | 0/40   | 0/23   |
| saquinavir  | 0/39  | 0/56  | 0/40   | 0/22   |
| tipranavir  | 0/39  | 0/58  | 0/41   | 1/25   |

<sup>a</sup> TLOVR non-VF censored algorithm based on HIV-1 RNA < 50 copies/ml, except for *TITAN* (HIV-1 RNA < 400 copies/ml)

<sup>b</sup> IAS-USA lists

Low rates of developing resistant HIV-1 virus were observed in ART-naïve patients who are treated for the first time with darunavir/cobicistat once daily in combination with other ART, and in ART-experienced patients with no darunavir RAMs receiving darunavir/cobicistat in combination with other ART. The table below shows the development of HIV-1 protease mutations and resistance to PIs in virologic failures at endpoint in the GS-US-216-130 trial.

|  | GS-US-216-130<br>Week 48  |  |
|--|---|--|
|  | Treatment-naïve<br>darunavir/cobicistat 800/150 mg<br>once daily<br>N=295 | Treatment-experienced<br>darunavir/cobicistat 800/150 mg<br>once daily<br>N=18 |
| Number of subjects with virologic failure <sup>a</sup> and genotype data that develop mutations <sup>b</sup> at endpoint, n/N        |   |  |
| Primary (major) PI mutations   | 0/8   | 1/7  |
| PI RAMs  | 2/8   | 1/7  |
| Number of subjects with virologic failure <sup>a</sup> and phenotype data that show resistance to PIs at endpoint <sup>c</sup> , n/N |   |  |
| HIV PI   |   |  |
| darunavir  | 0/8   | 0/7  |
| amprenavir   | 0/8   | 0/7  |
| atazanavir   | 0/8   | 0/7  |
| indinavir  | 0/8   | 0/7  |
| lopinavir  | 0/8   | 0/7  |
| saquinavir   | 0/8   | 0/7  |
| tipranavir   | 0/8   | 0/7  |

<sup>a</sup> Virologic failures were defined as: never suppressed: confirmed HIV-1 RNA < 1 log<sub>10</sub> reduction from baseline and ≥ 50 copies/ml at the week-8; rebound: HIV-1 RNA < 50 copies/ml followed by confirmed HIV-1 RNA to ≥ 400 copies/ml or confirmed > 1 log<sub>10</sub> HIV-1 RNA increase from the nadir; discontinuations with HIV-1 RNA ≥ 400 copies/ml at last visit

<sup>b</sup> IAS-USA lists

<sup>c</sup> In GS-US216-130 baseline phenotype was not available

### Cross-resistance

Darunavir FC was less than 10 for 90% of 3,309 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.

In the virologic failures of the *ARTEMIS* trial no cross-resistance with other PIs was observed. In the virologic failures of the GS-US-216-130 trial no cross-resistance with other HIV PIs was observed.

### Clinical results

The pharmacokinetic enhancing effect of cobicistat on darunavir was evaluated in a Phase I study in healthy subjects that were administered darunavir 800 mg with either cobicistat at 150 mg or ritonavir at 100 mg once daily. The steady-state pharmacokinetic parameters of darunavir were comparable when boosted with cobicistat versus ritonavir. For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

### Adult patients

#### *Efficacy of darunavir 800 mg once daily co-administered with 150 mg cobicistat once daily in ART-naïve and ART-experienced patients*

GS-US-216-130 is a single arm, open-label, Phase III trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with cobicistat in 313 HIV-1 infected adult patients (295 treatment-naïve and 18 treatment-experienced). These patients received darunavir 800 mg once daily in combination with cobicistat 150 mg once daily with an investigator selected background regimen consisting of 2 active NRTIs.



HIV-1 infected patients who were eligible for this trial had a screening genotype showing no darunavir RAMs and plasma HIV-1 RNA  $\geq 1,000$  copies/ml. The table below shows the efficacy data of the 48 week analyses from the GS-US-216-130 trial:

| Outcomes at Week 48   | GS-US-216-130  |  |  |
|---|--|--|--|
|   | Treatment-naïve darunavir/cobicistat 800/150 mg once daily+ OBR<br>N=295 | Treatment-experienced darunavir/cobicistat 800/150 mg once daily + OBR<br>N=18 | All subjects darunavir/cobicistat 800/150 mg once daily + OBR<br>N=313 |
| HIV-1 RNA < 50 copies/ml <sup>a</sup>                                 | 245 (83.1%)  | 8 (44.4%)  | 253 (80.8%)  |
| mean HIV-1 RNA log change from baseline (log <sub>10</sub> copies/ml) | -3.01  | -2.39  | -2.97  |
| CD4+ cell count mean change from baseline <sup>b</sup>                | +174   | +102   | +170   |

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

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

*Efficacy of PREZISTA 800 mg once daily co-administered with 100 mg ritonavir once daily in ART-naïve patients*

The evidence of efficacy of PREZISTA/ritonavir 800/100 mg once daily is based on the analyses of 192 week data from the randomised, controlled, open-label Phase III trial *ARTEMIS* in antiretroviral treatment-naïve HIV-1 infected patients comparing PREZISTA/ritonavir 800/100 mg once daily with lopinavir/ritonavir 800/200 mg per day (given as a twice-daily or as a once-daily regimen). Both arms used a fixed background regimen consisting of tenofovir disoproxil fumarate 300 mg once daily and emtricitabine 200 mg once daily.

The table below shows the efficacy data of the 48 week and 96 week analyses from the *ARTEMIS* trial:

| ARTEMIS   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| Outcomes  | Week 48 <sup>a</sup>                              |   |   | Week 96 <sup>b</sup>                              |   |   |
|   | PREZISTA/ritonavir 800/100 mg once daily<br>N=343 | Lopinavir/ritonavir 800/200 mg per day<br>N=346 | Treatment difference (95% CI of difference) | PREZISTA/ritonavir 800/100 mg once daily<br>N=343 | Lopinavir/ritonavir 800/200 mg per day<br>N=346 | Treatment difference (95% CI of difference) |
| HIV-1 RNA < 50 copies/ml <sup>c</sup><br>All patients                           | 83.7%<br>(287)                                    | 78.3%<br>(271)                                  | 5.3%<br>(-0.5; 11.2) <sup>d</sup>           | 79.0%<br>(271)                                    | 70.8%<br>(245)                                  | 8.2%<br>(1.7; 14.7) <sup>d</sup>            |
| With baseline HIV-RNA < 100,000   | 85.8%<br>(194/226)                                | 84.5%<br>(191/226)                              | 1.3%<br>(-5.2; 7.9) <sup>d</sup>            | 80.5%<br>(182/226)                                | 75.2%<br>(170/226)                              | 5.3%<br>(-2.3; 13.0) <sup>d</sup>           |
| With baseline HIV-RNA $\geq 100,000$  | 79.5%<br>(93/117)                                 | 66.7%<br>(80/120)                               | 12.8%<br>(1.6; 24.1) <sup>d</sup>           | 76.1%<br>(89/117)                                 | 62.5%<br>(75/120)                               | 13.6%<br>(1.9; 25.3) <sup>d</sup>           |
| With baseline CD4+ cell count < 200   | 79.4%<br>(112/141)                                | 70.3%<br>(104/148)                              | 9.2%<br>(-0.8; 19.2) <sup>d</sup>           | 78.7%<br>(111/141)                                | 64.9%<br>(96/148)                               | 13.9%<br>(3.5; 24.2) <sup>d</sup>           |
| With baseline CD4+ cell count $\geq 200$  | 86.6%<br>(175/202)                                | 84.3%<br>(167/198)                              | 2.3%<br>(-4.6; 9.2) <sup>d</sup>            | 79.2%<br>(160/202)                                | 75.3%<br>(149/198)                              | 4.0%<br>(-4.3; 12.2) <sup>d</sup>           |
| median CD4+ cell count change from baseline (x 10 <sup>6</sup> /l) <sup>e</sup> | 137   | 141   |   | 171   | 188   |   |

- <sup>a</sup> Data based on analyses at week 48  
<sup>b</sup> Data based on analyses at week 96  
<sup>c</sup> Imputations according to the TLOVR algorithm  
<sup>d</sup> Based on normal approximation to the difference in % response  
<sup>e</sup> Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0

Non-inferiority in virologic response to the PREZISTA/ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/ml, was demonstrated (at the pre-defined 12% non-inferiority margin) for both Intent-To-Treat (ITT) and On Protocol (OP) populations in the 48 week analysis. These results were confirmed in the analyses of data at 96 weeks of treatment in the *ARTEMIS* trial. These results were sustained up to 192 weeks of treatment in the *ARTEMIS* trial.

**Efficacy of PREZISTA 600 mg twice daily co-administered with 100 mg ritonavir twice daily in ART-experienced patients**

The evidence of efficacy of PREZISTA co-administered with ritonavir (600/100 mg twice daily) in ART-experienced patients is based on the 96 weeks analysis of the Phase III trial *TITAN* in ART-experienced lopinavir naïve patients, on the 48 week analysis of the Phase III trial *ODIN* in ART-experienced patients with no DRV-RAMs, and on the analyses of 96 weeks data from the Phase IIb trials *POWER* 1 and 2 in ART-experienced patients with high level of PI resistance.

***TITAN*** is a randomised, controlled, open-label Phase III trial comparing PREZISTA co-administered with ritonavir (600/100 mg twice daily) versus lopinavir/ritonavir (400/100 mg twice daily) in ART-experienced, lopinavir naïve HIV-1 infected adult patients. Both arms used an Optimised Background Regimen (OBR) consisting of at least 2 antiretrovirals (NRTIs with or without NNRTIs).

The table below shows the efficacy data of the 48 week analysis from the *TITAN* trial.

| TITAN  |  |   |  |
|--|--|---|--|
| Outcomes   | PREZISTA/ritonavir<br>600/100 mg twice daily +<br>OBR<br>N=298 | Lopinavir/ritonavir<br>400/100 mg twice daily +<br>OBR<br>N=297 | Treatment difference<br>(95% CI of difference) |
| HIV-1 RNA<br>< 50 copies/ml <sup>a</sup>   | 70.8% (211)  | 60.3% (179)   | 10.5% (2.9; 18.1) <sup>b</sup>                 |
| median CD4+ cell<br>count change<br>from baseline<br>(x 10 <sup>6</sup> /l) <sup>c</sup> | 88   | 81  |  |

- <sup>a</sup> Imputations according to the TLOVR algorithm  
<sup>b</sup> Based on a normal approximation of the difference in % response  
<sup>c</sup> NC=F

At 48 weeks non-inferiority in virologic response to the PREZISTA/ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 400 and < 50 copies/ml, was demonstrated (at the pre-defined 12% non-inferiority margin) for both ITT and OP populations. These results were confirmed in the analysis of data at 96 weeks of treatment in the *TITAN* trial, with 60.4% of patients in the PREZISTA/ritonavir arm having HIV-1 RNA < 50 copies/ml at week 96 compared to 55.2% in the lopinavir/ritonavir arm [difference: 5.2%, 95% CI (-2.8; 13.1)].

***ODIN*** is a Phase III, randomised, open-label trial comparing PREZISTA/ritonavir 800/100 mg once daily versus PREZISTA/ritonavir 600/100 mg twice daily in ART-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a screening HIV-1 RNA > 1,000 copies/ml. Efficacy analysis is based on 48 weeks of treatment (see table below). Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs.

| ODIN  |   |  |  |
|---|---|--|--|
| Outcomes  | PREZISTA/ritonavir<br>800/100 mg once daily +<br>OBR<br>N=294 | PREZISTA/ritonavir<br>600/100 mg twice daily +<br>OBR<br>N=296 | Treatment difference<br>(95% CI of difference) |
| HIV-1 RNA<br>< 50 copies/ml <sup>a</sup>  | 72.1% (212)   | 70.9% (210)  | 1.2% (-6.1; 8.5) <sup>b</sup>                  |
| With Baseline HIV-1<br>RNA (copies/ml)  |   |  |  |
| < 100,000   | 77.6% (198/255)   | 73.2% (194/265)  | 4.4% (-3.0; 11.9)                              |
| ≥ 100,000   | 35.9% (14/39)   | 51.6% (16/31)  | -15.7% (-39.2; 7.7)                            |
| With Baseline CD4+<br>cell count (x 10 <sup>6</sup> /l)                             |   |  |  |
| ≥ 100   | 75.1% (184/245)   | 72.5% (187/258)  | 2.6% (-5.1; 10.3)                              |
| < 100   | 57.1% (28/49)   | 60.5% (23/38)  | -3.4% (-24.5; 17.8)                            |
| With HIV-1 clade  |   |  |  |
| Type B  | 70.4% (126/179)   | 64.3% (128/199)  | 6.1% (-3.4; 15.6)                              |
| Type AE   | 90.5% (38/42)   | 91.2% (31/34)  | -0.7% (-14.0; 12.6)                            |
| Type C  | 72.7% (32/44)   | 78.8% (26/33)  | -6.1% (-2.6; 13.7)                             |
| Other <sup>c</sup>  | 55.2% (16/29)   | 83.3% (25/30)  | -28.2% (-51.0; -5.3)                           |
| mean CD4+ cell count<br>change from baseline<br>(x 10 <sup>6</sup> /l) <sup>e</sup> | 108   | 112  | -5 <sup>d</sup> (-25; 16)                      |

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

<sup>b</sup> Based on a normal approximation of the difference in % response

<sup>c</sup> Clades A1, D, F1, G, K, CRF02\_AG, CRF12\_BF, and CRF06\_CPX

<sup>d</sup> Difference in means

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

At 48 weeks, virologic response, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/ml, with PREZISTA/ritonavir 800/100 mg once daily treatment was demonstrated to be non-inferior (at the pre-defined 12% non-inferiority margin) compared to PREZISTA/ritonavir 600/100 mg twice daily for both ITT and OP populations.

PREZISTA/ritonavir 800/100 mg once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10<sup>6</sup>/l (see section 4.2 and 4.4). Limited data is available in patients with HIV-1 clades other than B.

**POWER 1 and POWER 2** are randomised, controlled trials comparing PREZISTA co-administered with ritonavir (600/100 mg twice daily) with a control group receiving an investigator-selected PI(s) regimen in HIV-1 infected patients who had previously failed more than 1 PI containing regimen. An OBR consisting of at least 2 NRTIs with or without enfuvirtide (ENF) was used in both trials.

The table below shows the efficacy data of the 48-week and 96-week analyses from the pooled **POWER 1** and **POWER 2** trials.

| POWER 1 and POWER 2 pooled data   |  |                  |   |  |                  |                                    |
|---|--|------------------|---|--|------------------|------------------------------------|
| Outcomes  | Week 48  |                  |   | Week 96  |                  |                                    |
|   | PREZISTA/<br>ritonavir<br>600/100 mg<br>twice daily<br>n=131 | Control<br>n=124 | Treatment<br>difference                 | PREZISTA/<br>ritonavir<br>600/100 mg<br>twice daily<br>n=131 | Control<br>n=124 | Treatment<br>difference            |
| HIV RNA<br>< 50 copies/ml <sup>a</sup>  | 45.0%<br>(59)  | 11.3%<br>(14)    | 33.7%<br>(23.4%;<br>44.1%) <sup>c</sup> | 38.9%<br>(51)  | 8.9%<br>(11)     | 30.1%<br>(20.1; 40.0) <sup>c</sup> |
| CD4+ cell count<br>mean change from<br>baseline (x 10 <sup>6</sup> /l) <sup>b</sup> | 103  | 17               | 86<br>(57; 114) <sup>c</sup>            | 133  | 15               | 118<br>(83.9; 153.4) <sup>c</sup>  |

- <sup>a</sup> Imputations according to the TLOVR algorithm  
<sup>b</sup> Last Observation Carried Forward imputation  
<sup>c</sup> 95% confidence intervals.

Analyses of data through 96 weeks of treatment in the *POWER* trials demonstrated sustained antiretroviral efficacy and immunologic benefit.

Out of the 59 patients who responded with complete viral suppression (< 50 copies/ml) at week 48, 47 patients (80% of the responders at week 48) remained responders at week 96.

#### *Baseline genotype or phenotype and virologic outcome*

Baseline genotype and darunavir FC (shift in susceptibility relative to reference) were shown to be a predictive factor of virologic outcome.

*Proportion (%) of patients with response (HIV-1 RNA < 50 copies/ml at week 24) to PREZISTA co-administered with ritonavir (600/100 mg twice daily) by baseline genotype<sup>a</sup>, and baseline darunavir FC and by use of enfuvirtide (ENF): As treated analysis of the POWER and DUET trials.*

|  | Number of baseline mutations <sup>a</sup> |                |               |               | Baseline DRV FC <sup>b</sup> |                |               |             |
|--|---|----------------|---------------|---------------|------------------------------|----------------|---------------|-------------|
| Response (HIV-1 RNA < 50 copies/ml at week 24)<br>%, n/N | All ranges                                | 0-2            | 3             | ≥ 4           | All ranges                   | ≤ 10           | 10-40         | > 40        |
| All patients   | 45%<br>455/1,014                          | 54%<br>359/660 | 39%<br>67/172 | 12%<br>20/171 | 45%<br>455/1,014             | 55%<br>364/659 | 29%<br>59/203 | 8%<br>9/118 |
| Patients with no/non-naïve use of ENF <sup>c</sup>       | 39%<br>290/741                            | 50%<br>238/477 | 29%<br>35/120 | 7%<br>10/135  | 39%<br>290/741               | 51%<br>244/477 | 17%<br>25/147 | 5%<br>5/94  |
| Patients with naïve use of ENF <sup>d</sup>              | 60%<br>165/273                            | 66%<br>121/183 | 62%<br>32/52  | 28%<br>10/36  | 60%<br>165/273               | 66%<br>120/182 | 61%<br>34/56  | 17%<br>4/24 |

<sup>a</sup> Number of mutations from the list of mutations associated with a diminished response to PREZISTA/ritonavir (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V)

<sup>b</sup> fold change in EC<sub>50</sub>

<sup>c</sup> “Patients with no/non-naïve use of ENF” are patients who did not use ENF or who used ENF but not for the first time

<sup>d</sup> “Patients with naïve use of ENF” are patients who used ENF for the first time

#### Paediatric patients

*ART-experienced paediatric patients from the age of 6 to < 18 years, and weighing at least 20 kg*  
**DELPHI** is an open-label, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of PREZISTA with low dose ritonavir in 80 ART-experienced HIV-1 infected paediatric patients aged 6 to 17 years and weighing at least 20 kg. These patients received PREZISTA/ritonavir twice daily in combination with other antiretroviral agents (see section 4.2 for dosage recommendations per body weight). Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 log<sub>10</sub> versus baseline.

In the study, patients who were at risk of discontinuing therapy due to intolerance of ritonavir oral solution (e.g. taste aversion) were allowed to switch to the capsule formulation. Of the 44 patients taking ritonavir oral solution, 27 switched to the 100 mg capsule formulation and exceeded the weight-based ritonavir dose without changes in observed safety.

| DELPHI   |                            |
|--|----------------------------|
| Outcomes at week 48                                    | PREZISTA/ritonavir<br>N=80 |
| HIV-1 RNA < 50 copies/ml <sup>a</sup>                  | 47.5% (38)                 |
| CD4+ cell count mean change from baseline <sup>b</sup> | 147                        |

<sup>a</sup> Imputations according to the TLOVR algorithm.

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

According to the TLOVR non-virologic failure censored algorithm 24 (30.0%) patients experienced virological failure, of which 17 (21.3%) patients were rebounders and 7 (8.8%) patients were non-responders.

#### *ART-experienced paediatric patients from the age of 3 to < 6 years*

The pharmacokinetics, safety, tolerability and efficacy of PREZISTA/ritonavir twice daily in combination with other antiretroviral agents in 21 ART-experienced HIV-1 infected paediatric patients aged 3 to < 6 years and weighing 10 kg to < 20 kg was evaluated in an open-label, Phase II trial, **ARIEL**. Patients received a weight-based twice daily treatment regimen, patients weighing 10 kg to < 15 kg received darunavir/ritonavir 25/3 mg/kg twice daily, and patients weighing 15 kg to < 20 kg received darunavir/ritonavir 375/50 mg twice daily. At week 48, the virologic response, defined as the percentage of patients with confirmed plasma viral load < 50 HIV-1 RNA copies/ml, was evaluated in 16 paediatric patients 15 kg to < 20 kg and 5 paediatric patients 10 kg to < 15 kg receiving PREZISTA/ritonavir in combination with other antiretroviral agents (see section 4.2 for dosage recommendations per body weight).

| ARIEL  |                         |                          |
|--|-------------------------|--------------------------|
| Outcomes at week 48                                    | PREZISTA/ritonavir      |                          |
|  | 10 kg to < 15 kg<br>N=5 | 15 kg to < 20 kg<br>N=16 |
| HIV-1 RNA < 50 copies/ml <sup>a</sup>                  | 80.0% (4)               | 81.3% (13)               |
| CD4+ percent change from baseline <sup>b</sup>         | 4                       | 4                        |
| CD4+ cell count mean change from baseline <sup>b</sup> | 16                      | 241                      |

<sup>a</sup> Imputations according to the TLOVR algorithm.

<sup>b</sup> NC=F

Limited efficacy data are available in paediatric patients below 15 kg and no recommendation on a posology can be made.

#### *ART-naïve paediatric patients from the age of 12 years to < 18 years, and weighing at least 40 kg*

**DIONE** is an open-label, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of PREZISTA with low dose ritonavir in 12 ART-naïve HIV-1 infected paediatric patients aged 12 to less than 18 years and weighing at least 40 kg. These patients received PREZISTA/ritonavir 800/100 mg once daily in combination with other antiretroviral agents. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 log<sub>10</sub> versus baseline.

| DIONE   |                            |
|---|----------------------------|
| Outcomes at week 48   | PREZISTA/ritonavir<br>N=12 |
|   |                            |
| HIV-1 RNA < 50 copies/ml <sup>a</sup>                               | 83.3% (10)                 |
| CD4+ percent change from baseline <sup>b</sup>                      | 14                         |
| CD4+ cell count mean change from baseline <sup>b</sup>              | 221                        |
| ≥ 1.0 log <sub>10</sub> decrease from baseline in plasma viral load | 100%                       |

<sup>a</sup> Imputations according to the TLOVR algorithm.

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

#### *Pregnancy and postpartum*

Darunavir/ritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 36 pregnant women (18 in each arm) during the second and third trimesters, and postpartum. Virologic response was preserved throughout the study period in both arms. No mother to child transmission occurred in the infants born to the 31 subjects who stayed on the antiretroviral treatment through delivery. There were no new clinically

relevant safety findings compared with the known safety profile of darunavir/ritonavir in HIV-1 infected adults (see sections 4.2, 4.4 and 5.2).

## 5.2 Pharmacokinetic properties

The pharmacokinetic properties of darunavir, co-administered with cobicistat or 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. Cobicistat and ritonavir inhibit CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

For information on cobicistat pharmacokinetic properties, consult the cobicistat Summary of Product Characteristics.

### 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 twice daily ritonavir. The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily (see section 4.4).

When administered without food, the relative bioavailability of darunavir in the presence of cobicistat or low dose ritonavir is lower as compared to intake with food. Therefore, PREZISTA tablets should be taken with cobicistat or 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.

### Biotransformation

*In vitro* experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolised by the hepatic CYP system and almost exclusively by isozyme CYP3A4. A  $^{14}$ C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir 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  $^{14}$ C-darunavir with ritonavir dose, approximately 79.5% and 13.9% of the administered dose of  $^{14}$ C-darunavir could be retrieved in faeces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in faeces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir.

The intravenous clearance of darunavir alone (150 mg) and in the presence of low dose ritonavir was 32.8 l/h and 5.9 l/h, respectively.

### Special populations

#### *Paediatric population*

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 74 treatment-experienced paediatric patients, aged 6 to 17 years and weighing at least 20 kg, showed that the administered weight-based doses of PREZISTA/ritonavir resulted in darunavir exposure comparable to that in adults receiving PREZISTA/ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 14 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 15 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving PREZISTA/ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 12 ART-naïve paediatric patients, aged 12 to < 18 years and weighing at least 40 kg, showed that PREZISTA/ritonavir 800/100 mg once daily results in darunavir exposure that was comparable to that achieved in adults receiving PREZISTA/ritonavir 800/100 mg once daily. Therefore the same once daily dosage may be used in treatment-experienced adolescents aged 12 to < 18 years and weighing at least 40 kg without darunavir resistance associated mutations (DRV-RAMs)\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100 \text{ cells} \times 10^6/\text{l}$  (see section 4.2).

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 10 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 14 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving PREZISTA/ritonavir 800/100 mg once daily (see section 4.2). In addition, pharmacokinetic modeling and simulation of darunavir exposures in paediatric patients across the ages of 3 to < 18 years confirmed the darunavir exposures as observed in the clinical studies and allowed the identification of weight-based PREZISTA/ritonavir once daily dosing regimens for paediatric patients weighing at least 15 kg that are either ART-naïve or treatment-experienced paediatric patients without DRV-RAMs\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100 \text{ cells} \times 10^6/\text{l}$  (see section 4.2).

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

#### *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 total plasma concentrations of darunavir in subjects with mild (Child-Pugh Class A, n=8) and moderate (Child-Pugh Class B, n=8) hepatic impairment were comparable with those in healthy subjects. However, unbound darunavir concentrations were approximately 55% (Child-Pugh Class A) and 100% (Child-Pugh Class B) higher, respectively. The clinical relevance of this increase is unknown therefore, PREZISTA should be used with caution. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see sections 4.2, 4.3 and 4.4).

### *Pregnancy and postpartum*

The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 600/100 mg twice daily and darunavir/ritonavir 800/100 mg once daily as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum. However, for unbound (i.e. active) darunavir, the pharmacokinetic parameters were less reduced during pregnancy compared to postpartum, due to an increase in the unbound fraction of darunavir during pregnancy compared to postpartum.

| <b>Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 600/100 mg twice daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum</b> |   |  |                                       |
|---|---|--|---------------------------------------|
| <b>Pharmacokinetics of total darunavir (mean ± SD)</b>  | <b>Second trimester of pregnancy (n=12)<sup>a</sup></b> | <b>Third trimester of pregnancy (n=12)</b> | <b>Postpartum (6-12 weeks) (n=12)</b> |
| $C_{max}$ , ng/ml   | 4,668 ± 1,097   | 5,328 ± 1,631                              | 6,659 ± 2,364                         |
| $AUC_{12h}$ , ng.h/ml   | 39,370 ± 9,597  | 45,880 ± 17,360                            | 56,890 ± 26,340                       |
| $C_{min}$ , ng/ml   | 1,922 ± 825   | 2,661 ± 1,269                              | 2,851 ± 2,216                         |

<sup>a</sup> n=11 for  $AUC_{12h}$

| <b>Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 800/100 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum</b> |   |  |                                       |
|--|---|--|---------------------------------------|
| <b>Pharmacokinetics of total darunavir (mean ± SD)</b>   | <b>Second trimester of pregnancy (n=17)</b> | <b>Third Trimester of pregnancy (n=15)</b> | <b>Postpartum (6-12 weeks) (n=16)</b> |
| $C_{max}$ , ng/ml  | 4,964 ± 1,505                               | 5,132 ± 1,198                              | 7,310 ± 1,704                         |
| $AUC_{24h}$ , ng.h/ml  | 62,289 ± 16,234                             | 61,112 ± 13,790                            | 92,116 ± 29,241                       |
| $C_{min}$ , ng/ml  | 1,248 ± 542                                 | 1,075 ± 594                                | 1,473 ± 1,141                         |

In women receiving darunavir/ritonavir 600/100 mg twice daily during the second trimester of pregnancy, mean intra-individual values for total darunavir  $C_{max}$ ,  $AUC_{12h}$  and  $C_{min}$  were 28%, 26% and 26% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir  $C_{max}$ ,  $AUC_{12h}$  and  $C_{min}$  values were 18%, 16% lower and 2% higher, respectively, as compared with postpartum.

In women receiving darunavir/ritonavir 800/100 mg once daily during the second trimester of pregnancy, mean intra-individual values for total darunavir  $C_{max}$ ,  $AUC_{24h}$  and  $C_{min}$  were 33%, 31% and 30% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir  $C_{max}$ ,  $AUC_{24h}$  and  $C_{min}$  values were 29%, 32% and 50% lower, respectively, as compared with postpartum.

Treatment with darunavir/cobicistat 800/150 mg once daily during pregnancy results in low darunavir exposure. In women receiving darunavir/cobicistat during the second trimester of pregnancy, mean intra-individual values for total darunavir  $C_{max}$ ,  $AUC_{24h}$  and  $C_{min}$  were 49%, 56% and 92% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir  $C_{max}$ ,  $AUC_{24h}$  and  $C_{min}$  values were 37%, 50% and 89% lower, respectively, as compared with postpartum. The unbound fraction was also substantially reduced, including around 90% reductions of



$C_{min}$  levels. The main cause of these low exposures is a marked reduction in cobicistat exposure as a consequence of pregnancy-associated enzyme induction (see below).

| <b>Pharmacokinetic results of total darunavir after administration of darunavir/cobicistat 800/150 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy, and postpartum</b> |  |   |                                      |
|---|--|---|--------------------------------------|
| <b>Pharmacokinetics of total darunavir (mean <math>\pm</math> SD)</b>   | <b>Second trimester of pregnancy (n=7)</b> | <b>Third trimester of pregnancy (n=6)</b> | <b>Postpartum (6-12 weeks) (n=6)</b> |
| $C_{max}$ , ng/mL   | 4,340 $\pm$ 1,616                          | 4,910 $\pm$ 970                           | 7,918 $\pm$ 2,199                    |
| AUC <sub>24h</sub> , ng.h/mL  | 47,293 $\pm$ 19,058                        | 47,991 $\pm$ 9,879                        | 99,613 $\pm$ 34,862                  |
| $C_{min}$ , ng/mL   | 168 $\pm$ 149                              | 184 $\pm$ 99                              | 1,538 $\pm$ 1,344                    |

The exposure to cobicistat was lower during pregnancy, potentially leading to suboptimal boosting of darunavir. During the second trimester of pregnancy, cobicistat  $C_{max}$ , AUC<sub>24h</sub>, and  $C_{min}$  were 50%, 63%, and 83% lower, respectively, as compared with postpartum. During the third trimester of pregnancy, cobicistat  $C_{max}$ , AUC<sub>24h</sub>, and  $C_{min}$ , were 27%, 49%, and 83% lower, respectively, as compared with postpartum.

### 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 1,000 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 receiving darunavir up to days 23-26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher than in adult rats after comparable doses in mg/kg between days 5 and 11 of age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals. No treatment related mortalities were noted in juvenile rats dosed at 1,000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats.

Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, PREZISTA with low dose ritonavir should not be used in paediatric patients below 3 years of age.

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1,000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumours in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

After 2 years administration of darunavir at exposures at or below the human exposure, kidney changes were observed in mice (nephrosis) and rats (chronic progressive nephropathy).

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Hydroxypropylcellulose  
Microcrystalline cellulose  
Carmellose sodium  
Citric acid monohydrate  
Sucralose  
Strawberry cream flavour  
Masking flavour  
Sodium methyl parahydroxybenzoate (E219)  
Hydrochloric acid (for pH adjustment)  
Purified water

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years

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

Do not store above 30°C.  
Do not refrigerate or freeze. Avoid exposure to excessive heat.  
Store in the original container.

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

Amber-coloured multiple-dose glass bottle for 200 ml suspension with a polypropylene closure with LDPE liner packaged with a 6 ml oral dosing pipette with 0.2 ml gradations. The bottle neck is filled with a low density polyethylene (LDPE) insert that accommodates the dosing pipette.

PREZISTA oral suspension is available in packs of one bottle.

## **6.6 Special precautions for disposal and other handling**

No special requirements for disposal.

Shake the bottle vigorously prior to each dose. The supplied oral dosing pipette should not be used for any other medicinal products.

## **7. MARKETING AUTHORISATION HOLDER**

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

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

EU/1/06/380/006

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

Date of first authorisation: 12 February 2007  
Date of latest renewal: 19 September 2013

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

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **1. NAME OF THE MEDICINAL PRODUCT**

PREZISTA 75 mg film-coated tablets  
PREZISTA 150 mg film-coated tablets  
PREZISTA 300 mg film-coated tablets  
PREZISTA 600 mg film-coated tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

### PREZISTA 75 mg film-coated tablets

Each film-coated tablet contains 75 mg of darunavir (as ethanolate).

### PREZISTA 150 mg film-coated tablets

Each film-coated tablet contains 150 mg of darunavir (as ethanolate).

### PREZISTA 300 mg film-coated tablets

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

Excipient with known effect: Each tablet contains 1.375 mg sunset yellow FCF (E110).

### PREZISTA 600 mg film-coated tablets

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

Excipient with known effect: Each tablet contains a maximum of 2.750 mg sunset yellow FCF (E110).

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

### PREZISTA 75 mg film-coated tablets

Film-coated tablet.

White caplet shaped tablet of 9.2 mm, debossed with “75” on one side and “TMC” on the other side.

### PREZISTA 150 mg film-coated tablets

Film-coated tablet.

White oval shaped tablet of 13.7 mm, debossed with “150” on one side and “TMC” on the other side.

### PREZISTA 300 mg film-coated tablets

Film-coated tablet.

Orange oval shaped tablet of 17.3 mm, debossed with “300MG” on one side and “TMC114” on the other side.

### PREZISTA 600 mg film-coated tablets

Film-coated tablet.

Orange oval shaped tablet of 21.1 mm, debossed with “600MG” on one side and “TMC” on the other side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

PREZISTA, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection (see section 4.2).

PREZISTA 75 mg, 150 mg, 300 mg, and 600 mg tablets may be used to provide suitable dose regimens (see section 4.2):

- For the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced adult patients, including those that have been highly pre-treated.
- For the treatment of HIV-1 infection in paediatric patients from the age of 3 years and at least 15 kg body weight.

In deciding to initiate treatment with PREZISTA co-administered with low dose 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 (see sections 4.2, 4.4 and 5.1).

## 4.2 Posology and method of administration

Therapy should be initiated by a health care provider experienced in the management of HIV infection. After therapy with PREZISTA has been initiated, patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their health care provider.

### Posology

PREZISTA must always be given orally with low dose 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.

PREZISTA is also available as an oral suspension for use in patients who are unable to swallow PREZISTA tablets (please refer to the Summary of Product Characteristics for PREZISTA oral suspension).

### *ART-experienced adult patients*

The recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. PREZISTA 75 mg, 150 mg, 300 mg, and 600 mg tablets can be used to construct the twice daily 600 mg regimen.

The use of 75 mg and 150 mg tablets to achieve the recommended dose is appropriate when there is a possibility of hypersensitivity to specific colouring agents, or difficulty in swallowing the 300 mg or 600 mg tablets.

### *ART-naïve adult patients*

For dosage recommendations in ART-naïve patients see the Summary of Product Characteristics for PREZISTA 400 mg and 800 mg tablets.

### *ART-naïve paediatric patients (3 to 17 years of age and weighing at least 15 kg)*

The weight-based dose of PREZISTA and ritonavir in paediatric patients is provided in the table below.

| <b>Recommended dose for treatment-naïve paediatric patients (3 to 17 years) with PREZISTA tablets and ritonavir<sup>a</sup></b> |   |
|---|---|
| <b>Body weight (kg)</b>   | <b>Dose (once daily with food)</b>          |
| ≥ 15 kg to < 30 kg  | 600 mg PREZISTA/100 mg ritonavir once daily |
| ≥ 30 kg to < 40 kg  | 675 mg PREZISTA/100 mg ritonavir once daily |
| ≥ 40 kg   | 800 mg PREZISTA/100 mg ritonavir once daily |

<sup>a</sup> ritonavir oral solution: 80 mg/ml

### *ART-experienced paediatric patients (3 to 17 years of age and weighing at least 15 kg)*

PREZISTA twice daily taken with ritonavir taken with food is usually recommended.

A once daily dose regimen of PREZISTA taken with ritonavir taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without darunavir resistance associated

mutations (DRV-RAMs)\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100$  cells  $\times 10^6/l$ .

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The weight-based dose of PREZISTA and ritonavir in paediatric patients is provided in the table below. The recommended dose of PREZISTA with low dose ritonavir should not exceed the recommended adult dose (600/100 mg twice daily or 800/100 mg once daily).

| <b>Recommended dose for treatment-experienced paediatric patients (3 to 17 years) with PREZISTA tablets and ritonavir<sup>a</sup></b> |   |  |
|---|---|--|
| <b>Body weight (kg)</b>   | <b>Dose (once daily with food)</b>          | <b>Dose (twice daily with food)</b>          |
| $\geq 15$ kg–< 30 kg  | 600 mg PREZISTA/100 mg ritonavir once daily | 375 mg PREZISTA/50 mg ritonavir twice daily  |
| $\geq 30$ kg–< 40 kg  | 675 mg PREZISTA/100 mg ritonavir once daily | 450 mg PREZISTA/60 mg ritonavir twice daily  |
| $\geq 40$ kg  | 800 mg PREZISTA/100 mg ritonavir once daily | 600 mg PREZISTA/100 mg ritonavir twice daily |

<sup>a</sup> ritonavir oral solution: 80 mg/ml

For ART-experienced paediatric patients HIV genotypic testing is recommended. However, when HIV genotypic testing is not feasible, the PREZISTA/ritonavir once daily dosing regimen is recommended in HIV protease inhibitor-naïve paediatric patients and the twice daily dosing regimen is recommended in HIV protease inhibitor-experienced patients.

The use of only 75 mg and 150 mg tablets or the 100 mg/ml oral suspension to achieve the recommended dose of PREZISTA could be appropriate when there is a possibility of hypersensitivity to specific colouring agents.

#### *Advice on missed doses*

In case a dose of PREZISTA and/or ritonavir is 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 is noticed later than 6 hours after 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.

#### Special populations

##### *Elderly*

Limited information is available in this population, and therefore, PREZISTA should be used with caution in this age group (see sections 4.4 and 5.2).

##### *Hepatic impairment*

Darunavir is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, PREZISTA should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its safety profile. Therefore, PREZISTA must 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).

##### *Paediatric population*

PREZISTA/ritonavir should not be used in children with a body weight of less than 15 kg as the dose for this population has not been established in a sufficient number of patients (see section 5.1).

PREZISTA/ritonavir should not be used in children below 3 years of age because of safety concerns (see sections 4.4 and 5.3).

The weight-based dose regimen for PREZISTA and ritonavir is provided in the tables above.

#### *Pregnancy and postpartum*

No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. PREZISTA/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk (see sections 4.4, 4.6 and 5.2).

#### Method of administration

Patients should be instructed to take PREZISTA with low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir (see sections 4.4, 4.5 and 5.2).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Combination of rifampicin with PREZISTA with concomitant low dose ritonavir (see section 4.5).

Co-administration with the combination product lopinavir/ritonavir (see section 4.5).

Co-administration with herbal preparations containing St John's wort (*Hypericum perforatum*) (see section 4.5).

Co-administration of PREZISTA with low dose 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. These active substances include e.g.:

- alfuzosin
- amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine
- astemizole, terfenadine
- colchicine when used in patients with renal and/or hepatic impairment (see section 4.5)
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- elbasvir/grazoprevir
- cisapride
- dapoxetine
- domperidone
- naloxegol
- lurasidone, pimozide, quetiapine, sertindole (see section 4.5)
- triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5)
- sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil
- simvastatin, lovastatin and lomitapide (see section 4.5)
- dabigatran, ticagrelor (see section 4.5).

### **4.4 Special warnings and precautions for use**

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Regular assessment of virological response is advised. In the setting of lack or loss of virological response, resistance testing should be performed.

PREZISTA must always be given orally with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products (see section 5.2). The Summary of Product Characteristics of ritonavir as appropriate, must therefore be consulted prior to initiation of therapy with PREZISTA.

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

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 (see section 4.5).

#### ART-experienced patients – once daily dosing

PREZISTA used in combination with cobicistat or low dose ritonavir once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA  $\geq 100,000$  copies/ml or CD4+ cell count  $< 100$  cells  $\times 10^6/l$  (see section 4.2). Combinations with optimised background regimen (OBRs) other than  $\geq 2$  NRTIs have not been studied in this population. Limited data are available in patients with HIV-1 clades other than B (see section 5.1).

#### Paediatric population

PREZISTA is not recommended for use in paediatric patients below 3 years of age or less than 15 kg body weight (see sections 4.2 and 5.3).

#### Pregnancy

PREZISTA/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk. Caution should be used in pregnant women with concomitant medications which may further decrease darunavir exposure (see sections 4.5 and 5.2).

#### 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).

#### Severe skin reactions

During the darunavir/ritonavir clinical development program (N=3,063), severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens-Johnson Syndrome has been rarely ( $< 0.1\%$ ) reported, and during post-marketing experience toxic epidermal necrolysis and acute generalised exanthematous pustulosis have been reported. PREZISTA should be discontinued immediately if signs or symptoms of severe skin reactions develop. These can include, but are not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash occurred more commonly in treatment-experienced patients receiving regimens containing PREZISTA/ritonavir + raltegravir compared to patients receiving PREZISTA/ritonavir without raltegravir or raltegravir without PREZISTA (see section 4.8).

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

#### Hepatotoxicity

Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA. During the darunavir/ritonavir clinical development program (N=3,063), hepatitis was reported in 0.5% of patients receiving combination antiretroviral therapy with PREZISTA/ritonavir. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for



liver function abnormalities including severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

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

If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients using PREZISTA/ritonavir, interruption or discontinuation of treatment should be considered promptly.

### Patients with coexisting conditions

#### *Hepatic impairment*

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 hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, PREZISTA should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

#### *Renal impairment*

No special precautions or dose adjustments for darunavir/ritonavir 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.

#### *Weight and metabolic parameters*

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

### Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

### Immune reconstitution inflammatory syndrome

In HIV infected patients with severe immune deficiency at the time of initiation 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 jirovecii* (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 low dose ritonavir.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.8).

#### Interactions with medicinal products

Several of the interaction studies have been performed with darunavir at lower than recommended doses. 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.

Efavirenz in combination with boosted PREZISTA once daily may result in sub-optimal darunavir  $C_{min}$ . If efavirenz is to be used in combination with PREZISTA, the PREZISTA/ritonavir 600/100 mg twice daily regimen should be used (see section 4.5).

Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A and P-glycoprotein (P-gp; see sections 4.3 and 4.5).

PREZISTA 300 mg tablets and 600 mg tablets contain sunset yellow FCF (E110) which may cause an allergic reaction.

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

Interaction studies have only been performed in adults.

#### Medicinal products that may be affected by darunavir boosted with ritonavir

Darunavir and ritonavir are inhibitors of CYP3A, CYP2D6 and P-gp. Co-administration of darunavir/ritonavir with medicinal products primarily metabolised by CYP3A and/or CYP2D6 or transported by P-gp 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 low dose ritonavir must not be combined with medicinal products that are highly dependent on CYP3A for clearance and for which increased systemic exposure is associated with serious and/or life-threatening events (narrow therapeutic index) (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 twice daily. Therefore, PREZISTA must only be used in combination with low dose ritonavir as a pharmacokinetic enhancer (see sections 4.4 and 5.2).

A clinical study utilising a cocktail of medicinal products that are metabolised by cytochromes CYP2C9, CYP2C19 and CYP2D6 demonstrated an increase in CYP2C9 and CYP2C19 activity and inhibition of CYP2D6 activity in the presence of darunavir/ritonavir, which may be attributed to the presence of low dose ritonavir. Co-administration of darunavir and ritonavir with medicinal products which are primarily metabolised by CYP2D6 (such as flecainide, propafenone, metoprolol) may result in increased plasma concentrations of these medicinal products, which could increase or prolong their therapeutic effect and adverse reactions. Co-administration of darunavir and ritonavir with medicinal products primarily metabolised by CYP2C9 (such as warfarin) and CYP2C19 (such as methadone) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Although the effect on CYP2C8 has only been studied *in vitro*, co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP2C8 (such as paclitaxel, rosiglitazone,

repaglinide) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Ritonavir inhibits the transporters P-glycoprotein, OATP1B1 and OATP1B3, and co-administration with substrates of these transporters can result in increased plasma concentrations of these compounds (e.g. dabigatran etexilate, digoxin, statins and bosentan; see the Interaction table below).

#### **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, 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, azole antifungals like clotrimazole). These interactions are described in the interaction table below.

#### **Interaction table**

Interactions between PREZISTA/ritonavir and antiretroviral and non-antiretroviral medicinal products are listed in the table below. The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within ( $\leftrightarrow$ ), below ( $\downarrow$ ) or above ( $\uparrow$ ) the 80-125% range (not determined as "ND").

Several of the interaction studies (indicated by <sup>#</sup> in the table below) have been performed at lower than recommended doses of darunavir or with a different dosing regimen (see section 4.2 Posology). The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated.

The below list of examples of drug drug interactions is not comprehensive and therefore the label of each drug that is co-administered with PREZISTA should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

| <b>INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS</b> |  |   |
|--|--|---|
| <b>Medicinal products by therapeutic areas</b>                             | <b>Interaction<br/>Geometric mean change (%)</b>   | <b>Recommendations concerning co-administration</b>   |
| <b>HIV ANTIRETROVIRALS</b>   |  |   |
| <b><i>Integrase strand transfer inhibitors</i></b>                         |  |   |
| Dolutegravir   | dolutegravir AUC $\downarrow$ 22%<br>dolutegravir C <sub>24h</sub> $\downarrow$ 38%<br>dolutegravir C <sub>max</sub> $\downarrow$ 11%<br>darunavir $\leftrightarrow$ *<br>* Using cross-study comparisons to historical pharmacokinetic data | PREZISTA co-administered with low dose ritonavir and dolutegravir can be used without dose adjustment.  |
| Raltegravir  | Some clinical studies suggest raltegravir may cause a modest decrease in darunavir plasma concentrations.  | At present the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically relevant. PREZISTA co-administered with low dose ritonavir and raltegravir can be used without dose adjustments. |

| <b><i>Nucleo(s)ide reverse transcriptase inhibitors (NRTIs)</i></b>      |  |  |
|--|--|--|
| Didanosine<br>400 mg once daily  | didanosine AUC ↓ 9%<br>didanosine C <sub>min</sub> ND<br>didanosine C <sub>max</sub> ↓ 16%<br>darunavir AUC ↔<br>darunavir C <sub>min</sub> ↔<br>darunavir C <sub>max</sub> ↔  | PREZISTA co-administered with low dose ritonavir and didanosine can be used without dose adjustments.<br>Didanosine is to be administered on an empty stomach, thus it should be administered 1 hour before or 2 hours after PREZISTA/ritonavir given with food.   |
| Tenofovir disoproxil<br>245 mg once daily*                               | tenofovir AUC ↑ 22%<br>tenofovir C <sub>min</sub> ↑ 37%<br>tenofovir C <sub>max</sub> ↑ 24%<br># darunavir AUC ↑ 21%<br># darunavir C <sub>min</sub> ↑ 24%<br># darunavir C <sub>max</sub> ↑ 16%<br>(↑ tenofovir from effect on MDR-1 transport in the renal tubules)  | Monitoring of renal function may be indicated when PREZISTA co-administered with low dose ritonavir is given in combination with tenofovir disoproxil, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.   |
| Emtricitabine/tenofovir<br>alafenamide                                   | Tenofovir alafenamide ↔<br>Tenofovir ↑   | The recommended dose of emtricitabine/tenofovir alafenamide is 200/10 mg once daily when used with PREZISTA with low dose ritonavir.   |
| Abacavir<br>Emtricitabine<br>Lamivudine<br>Stavudine<br>Zidovudine       | Not studied. Based on the different elimination pathways of the other NRTIs zidovudine, emtricitabine, stavudine, lamivudine, that are primarily renally excreted, and abacavir for which metabolism is not mediated by CYP450, no interactions are expected for these medicinal compounds and PREZISTA co-administered with low dose ritonavir. | PREZISTA co-administered with low dose ritonavir can be used with these NRTIs without dose adjustment.   |
| <b><i>Non-nucleo(s)ide reverse transcriptase inhibitors (NNRTIs)</i></b> |  |  |
| Efavirenz<br>600 mg once daily   | efavirenz AUC ↑ 21%<br>efavirenz C <sub>min</sub> ↑ 17%<br>efavirenz C <sub>max</sub> ↑ 15%<br># darunavir AUC ↓ 13%<br># darunavir C <sub>min</sub> ↓ 31%<br># darunavir C <sub>max</sub> ↓ 15%<br>(↑ efavirenz from CYP3A inhibition)<br>(↓ darunavir from CYP3A induction)  | Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when PREZISTA co-administered with low dose ritonavir is given in combination with efavirenz.<br><br>Efavirenz in combination with PREZISTA/ritonavir 800/100 mg once daily may result in sub-optimal darunavir C <sub>min</sub> . If efavirenz is to be used in combination with PREZISTA/ritonavir, the PREZISTA/ritonavir 600/100 mg twice daily regimen should be used (see section 4.4). |
| Etravirine<br>100 mg twice daily   | etravirine AUC ↓ 37%<br>etravirine C <sub>min</sub> ↓ 49%<br>etravirine C <sub>max</sub> ↓ 32%<br>darunavir AUC ↑ 15%<br>darunavir C <sub>min</sub> ↔<br>darunavir C <sub>max</sub> ↔  | PREZISTA co-administered with low dose ritonavir and etravirine 200 mg twice daily can be used without dose adjustments.   |

|  |   |   |
|--|---|---|
| Nevirapine<br>200 mg twice daily   | nevirapine AUC ↑ 27%<br>nevirapine C <sub>min</sub> ↑ 47%<br>nevirapine C <sub>max</sub> ↑ 18%<br>#darunavir: concentrations were consistent with historical data (↑ nevirapine from CYP3A inhibition)  | PREZISTA co-administered with low dose ritonavir and nevirapine can be used without dose adjustments.   |
| Rilpivirine<br>150 mg once daily   | rilpivirine AUC ↑ 130%<br>rilpivirine C <sub>min</sub> ↑ 178%<br>rilpivirine C <sub>max</sub> ↑ 79%<br>darunavir AUC ↔<br>darunavir C <sub>min</sub> ↓ 11%<br>darunavir C <sub>max</sub> ↔  | PREZISTA co-administered with low dose ritonavir and rilpivirine can be used without dose adjustments.  |
| <b><i>HIV Protease inhibitors (PIs) - without additional co-administration of low dose ritonavir<sup>†</sup></i></b> |   |   |
| Atazanavir<br>300 mg once daily  | atazanavir AUC ↔<br>atazanavir C <sub>min</sub> ↑ 52%<br>atazanavir C <sub>max</sub> ↓ 11%<br>#darunavir AUC ↔<br>#darunavir C <sub>min</sub> ↔<br>#darunavir C <sub>max</sub> ↔<br><br>Atazanavir: comparison of atazanavir/ritonavir 300/100 mg once daily vs. atazanavir 300 mg once daily in combination with darunavir/ritonavir 400/100 mg twice daily.<br>Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg twice daily in combination with atazanavir 300 mg once daily. | PREZISTA co-administered with low dose ritonavir and atazanavir can be used without dose adjustments.   |
| Indinavir<br>800 mg twice daily  | indinavir AUC ↑ 23%<br>indinavir C <sub>min</sub> ↑ 125%<br>indinavir C <sub>max</sub> ↔<br>#darunavir AUC ↑ 24%<br>#darunavir C <sub>min</sub> ↑ 44%<br>#darunavir C <sub>max</sub> ↑ 11%<br><br>Indinavir: comparison of indinavir/ritonavir 800/100 mg twice daily vs. indinavir/darunavir/ritonavir 800/400/100 mg twice daily.<br>Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with indinavir 800 mg twice daily.                                       | When used in combination with PREZISTA co-administered with low dose ritonavir, dose adjustment of indinavir from 800 mg twice daily to 600 mg twice daily may be warranted in case of intolerance. |
| Saquinavir<br>1,000 mg twice daily   | #darunavir AUC ↓ 26%<br>#darunavir C <sub>min</sub> ↓ 42%<br>#darunavir C <sub>max</sub> ↓ 17%<br>saquinavir AUC ↓ 6%<br>saquinavir C <sub>min</sub> ↓ 18%<br>saquinavir C <sub>max</sub> ↓ 6%<br><br>Saquinavir: comparison of saquinavir/ritonavir 1,000/100 mg twice daily vs. saquinavir/darunavir/ritonavir 1,000/400/100 mg twice daily<br>Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with saquinavir 1,000 mg twice daily.                          | It is not recommended to combine PREZISTA co-administered with low dose ritonavir with saquinavir.  |

| HIV Protease inhibitors (PIs) - with co-administration of low dose ritonavir <sup>†</sup> |  |  |
|---|--|--|
| Lopinavir/ritonavir<br>400/100 mg twice daily   | lopinavir AUC ↑ 9%<br>lopinavir C <sub>min</sub> ↑ 23%<br>lopinavir C <sub>max</sub> ↓ 2%<br>darunavir AUC ↓ 38% <sup>‡</sup><br>darunavir C <sub>min</sub> ↓ 51% <sup>‡</sup><br>darunavir C <sub>max</sub> ↓ 21% <sup>‡</sup>              | Due to a decrease in the exposure (AUC) of darunavir by 40%, appropriate doses of the combination have not been established. Hence, concomitant use of PREZISTA co-administered with low dose ritonavir and the combination product lopinavir/ritonavir is contraindicated (see section 4.3).  |
| Lopinavir/ritonavir<br>533/133.3 mg twice daily   | lopinavir AUC ↔<br>lopinavir C <sub>min</sub> ↑ 13%<br>lopinavir C <sub>max</sub> ↑ 11%<br>darunavir AUC ↓ 41%<br>darunavir C <sub>min</sub> ↓ 55%<br>darunavir C <sub>max</sub> ↓ 21%<br><sup>‡</sup> based upon non dose normalised values |  |
| CCR5 ANTAGONIST   |  |  |
| Maraviroc<br>150 mg twice daily   | maraviroc AUC ↑ 305%<br>maraviroc C <sub>min</sub> ND<br>maraviroc C <sub>max</sub> ↑ 129%<br>darunavir, ritonavir concentrations were consistent with historical data   | The maraviroc dose should be 150 mg twice daily when co-administered with PREZISTA with low dose ritonavir.  |
| α1-ADRENORECEPTOR ANTAGONIST  |  |  |
| Alfuzosin   | Based on theoretical considerations PREZISTA is expected to increase alfuzosin plasma concentrations. (CYP3A inhibition)   | Co-administration of PREZISTA with low dose ritonavir and alfuzosin is contraindicated (see section 4.3).  |
| ANAESTHETIC   |  |  |
| Alfentanil  | Not studied. The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by PREZISTA co-administered with low dose ritonavir.   | The concomitant use with PREZISTA and low dose ritonavir may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.   |
| ANTIANGINA/ANTIARRHYTHMIC   |  |  |
| Disopyramide<br>Flecainide<br>Lidocaine (systemic)<br>Mexiletine<br>Propafenone           | Not studied. PREZISTA is expected to increase these antiarrhythmic plasma concentrations. (CYP3A and/or CYP2D6 inhibition)   | Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with PREZISTA with low dose ritonavir.  |
| Amiodarone<br>Bepridil<br>Dronedarone<br>Ivabradine<br>Quinidine<br>Ranolazine            |  | PREZISTA co-administered with low dose ritonavir and amiodarone, bepridil, dronedarone, ivabradine, quinidine, or ranolazine is contraindicated (see section 4.3).   |
| Digoxin<br>0.4 mg single dose   | digoxin AUC ↑ 61%<br>digoxin C <sub>min</sub> ND<br>digoxin C <sub>max</sub> ↑ 29%<br>(↑ digoxin from probable inhibition of P-gp)   | 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>ANTIBIOTIC</b>                                   |   |  |
|---|---|--|
| Clarithromycin<br>500 mg twice daily                | clarithromycin AUC ↑ 57%<br>clarithromycin C <sub>min</sub> ↑ 174%<br>clarithromycin C <sub>max</sub> ↑ 26%<br>#darunavir AUC ↓ 13%<br>#darunavir C <sub>min</sub> ↑ 1%<br>#darunavir C <sub>max</sub> ↓ 17%<br>14-OH-clarithromycin concentrations were not detectable when combined with PREZISTA/ritonavir.<br>(↑ clarithromycin from CYP3A inhibition and possible P-gp inhibition) | Caution should be exercised when clarithromycin is combined with PREZISTA co-administered with low dose ritonavir.<br><br>For patients with renal impairment the Summary of Product Characteristics for clarithromycin should be consulted for the recommended dose.   |
| <b>ANTICOAGULANT/PLATELET AGGREGATION INHIBITOR</b> |   |  |
| Apixaban<br>Edoxaban<br>Rivaroxaban                 | Not studied. Co-administration of PREZISTA with these anticoagulants may increase concentrations of the anticoagulant, which may lead to an increased bleeding risk.<br>(CYP3A and/or P-gp inhibition)  | The use of PREZISTA co-administered with low dose ritonavir and these anticoagulants is not recommended.   |
| Dabigatran<br>Ticagrelor                            | Not studied. Co-administration with boosted PREZISTA may lead to a substantial increase in exposure to dabigatran or ticagrelor.  | Concomitant administration of boosted PREZISTA with dabigatran or ticagrelor is contraindicated (see section 4.3).<br><br>Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended.  |
| Warfarin  | Not studied. Warfarin concentrations may be affected when co-administered with darunavir with low dose ritonavir.   | It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with PREZISTA co-administered with low dose ritonavir.  |
| <b>ANTICONVULSANTS</b>                              |   |  |
| Phenobarbital<br>Phenytoin                          | Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir and its pharmacoenhancer.<br>(induction of CYP450 enzymes)   | PREZISTA co-administered with low dose ritonavir should not be used in combination with these medicines.   |
| Carbamazepine<br>200 mg twice daily                 | carbamazepine AUC ↑ 45%<br>carbamazepine C <sub>min</sub> ↑ 54%<br>carbamazepine C <sub>max</sub> ↑ 43%<br>darunavir AUC ↔<br>darunavir C <sub>min</sub> ↓ 15%<br>darunavir C <sub>max</sub> ↔  | No dose adjustment for PREZISTA/ritonavir is recommended. If there is a need to combine PREZISTA/ritonavir and carbamazepine, patients should be monitored for potential carbamazepine-related adverse events. Carbamazepine concentrations should be monitored and its dose should be titrated for adequate response. Based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of PREZISTA/ritonavir. |
| Clonazepam  | Not studied. Co-administration of boosted PREZISTA with clonazepam may increase concentrations of clonazepam. (CYP3A inhibition)  | Clinical monitoring is recommended when co-administering PREZISTA with low dose ritonavir and clonazepam.  |

| <b>ANTIDEPRESSANTS</b>  |  |  |
|---|--|--|
| <p>Paroxetine<br/>20 mg once daily</p> <p>Sertraline<br/>50 mg once daily</p> <p>Amitriptyline<br/>Desipramine<br/>Imipramine<br/>Nortriptyline<br/>Trazodone</p> | <p>paroxetine AUC ↓ 39%<br/>paroxetine C<sub>min</sub> ↓ 37%<br/>paroxetine C<sub>max</sub> ↓ 36%<br/># darunavir AUC ↔<br/># darunavir C<sub>min</sub> ↔<br/># darunavir C<sub>max</sub> ↔<br/>sertraline AUC ↓ 49%<br/>sertraline C<sub>min</sub> ↓ 49%<br/>sertraline C<sub>max</sub> ↓ 44%<br/># darunavir AUC ↔<br/># darunavir C<sub>min</sub> ↓ 6%<br/># darunavir C<sub>max</sub> ↔</p> <p>Concomitant use of PREZISTA co-administered with low dose ritonavir and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or CYP3A inhibition)</p> | <p>If antidepressants are co-administered with PREZISTA with low dose ritonavir, the recommended approach is a dose titration of the antidepressant based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of these antidepressants who start treatment with PREZISTA with low dose ritonavir should be monitored for antidepressant response.</p> <p>Clinical monitoring is recommended when co-administering PREZISTA with low dose ritonavir with these antidepressants and a dose adjustment of the antidepressant may be needed.</p> |
| <b>ANTIEMETICS</b>  |  |  |
| Domperidone   | Not studied.   | Co-administration of domperidone with boosted PREZISTA is contraindicated.   |
| <b>ANTIFUNGALS</b>  |  |  |
| Voriconazole  | Not studied. Ritonavir may decrease plasma concentrations of voriconazole. (induction of CYP450 enzymes)   | Voriconazole should not be combined with PREZISTA co-administered with low dose ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.  |
| <p>Fluconazole<br/>Isavuconazole<br/>Itraconazole<br/>Posaconazole</p> <p>Clotrimazole</p>  | <p>Not studied. PREZISTA may increase antifungal plasma concentrations and posaconazole, isavuconazole, itraconazole, or fluconazole may increase darunavir concentrations. (CYP3A and/or P-gp inhibition)</p> <p>Not studied. Concomitant systemic use of clotrimazole and darunavir co-administered with low dose ritonavir may increase plasma concentrations of darunavir and/or clotrimazole. darunavir AUC<sub>24h</sub> ↑ 33% (based on population pharmacokinetic model)</p>   | Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of itraconazole should not exceed 200 mg.   |



| <b>ANTIGOUT MEDICINES</b>   |   |  |
|---|---|--|
| Colchicine  | Not studied. Concomitant use of colchicine and darunavir co-administered with low dose ritonavir may increase the exposure to colchicine.<br>(CYP3A and/ or P-gp inhibition)  | A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with PREZISTA co-administered with low dose ritonavir is required. For patients with renal or hepatic impairment colchicine with PREZISTA co-administered with low dose ritonavir is contraindicated (see sections 4.3 and 4.4). |
| <b>ANTIMALARIALS</b>  |   |  |
| Artemether/Lumefantrine<br>80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours | artemether AUC ↓ 16%<br>artemether C <sub>min</sub> ↔<br>artemether C <sub>max</sub> ↓ 18%<br>dihydroartemisinin AUC ↓ 18%<br>dihydroartemisinin C <sub>min</sub> ↔<br>dihydroartemisinin C <sub>max</sub> ↓ 18%<br>lumefantrine AUC ↑ 175%<br>lumefantrine C <sub>min</sub> ↑ 126%<br>lumefantrine C <sub>max</sub> ↑ 65%<br>darunavir AUC ↔<br>darunavir C <sub>min</sub> ↓ 13%<br>darunavir C <sub>max</sub> ↔   | The combination of PREZISTA and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.  |
| <b>ANTIMYCOBACTERIALS</b>   |   |  |
| Rifampicin<br>Rifapentine   | Not studied. Rifapentine and rifampicin are strong CYP3A inducers and have been shown to cause profound decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction). During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with low dose ritonavir, a high frequency of liver reactions was seen with rifampicin. | The combination of rifapentine and PREZISTA with concomitant low dose ritonavir is not recommended.<br><br>The combination of rifampicin and PREZISTA with concomitant low dose ritonavir is contraindicated (see section 4.3).  |

|   |   |  |
|---|---|--|
| <p>Rifabutin<br/>150 mg once every other day</p>  | <p>rifabutin AUC<sup>**</sup> ↑ 55%<br/>rifabutin C<sub>min</sub><sup>**</sup> ↑ ND<br/>rifabutin C<sub>max</sub><sup>**</sup> ↔<br/>darunavir AUC ↑ 53%<br/>darunavir C<sub>min</sub> ↑ 68%<br/>darunavir C<sub>max</sub> ↑ 39%<br/><sup>**</sup> sum of active moieties of rifabutin (parent drug + 25-<i>O</i>-desacetyl metabolite)</p> <p>The interaction trial showed a comparable daily systemic exposure for rifabutin between treatment at 300 mg once daily alone and 150 mg once every other day in combination with PREZISTA/ritonavir (600/100 mg twice daily) with an about 10-fold increase in the daily exposure to the active metabolite 25-<i>O</i>-desacetyl rifabutin. Furthermore, AUC of the sum of active moieties of rifabutin (parent drug + 25-<i>O</i>-desacetyl metabolite) was increased 1.6-fold, while C<sub>max</sub> remained comparable.<br/>Data on comparison with a 150 mg once daily reference dose is lacking.</p> <p>(Rifabutin is an inducer and substrate of CYP3A.) An increase of systemic exposure to darunavir was observed when PREZISTA co-administered with 100 mg ritonavir was co-administered with rifabutin (150 mg once every other day).</p> | <p>A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg once every other day) and increased monitoring for rifabutin related adverse events is warranted in patients receiving the combination with PREZISTA co-administered with ritonavir. In case of safety issues, a further increase of the dosing interval for rifabutin and/or monitoring of rifabutin levels should be considered.<br/>Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients.<br/>Based upon the safety profile of PREZISTA/ritonavir, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for PREZISTA/ritonavir.<br/>Based on pharmacokinetic modeling, this dosage reduction of 75% is also applicable if patients receive rifabutin at doses other than 300 mg/day.</p> |
| <b>ANTINEOPLASTICS</b>  |   |  |
| <p>Dasatinib<br/>Nilotinib<br/>Vinblastine<br/>Vincristine</p> <p>Everolimus<br/>Irinotecan</p> | <p>Not studied. PREZISTA is expected to increase these antineoplastic plasma concentrations.<br/>(CYP3A inhibition)</p>   | <p>Concentrations of these medicinal products may be increased when co-administered with PREZISTA with low dose ritonavir resulting in the potential for increased adverse events usually associated with these agents.<br/>Caution should be exercised when combining one of these antineoplastic agents with PREZISTA with low dose ritonavir.</p> <p>Concomitant use of everolimus or irinotecan and PREZISTA co-administered with low dose ritonavir is not recommended.</p>   |
| <b>ANTIPSYCHOTICS/NEUROLEPTICS</b>  |   |  |
| <p>Quetiapine</p>   | <p>Not studied. PREZISTA is expected to increase these antipsychotic plasma concentrations.<br/>(CYP3A inhibition)</p>  | <p>Concomitant administration of PREZISTA with low dose ritonavir and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased concentrations of quetiapine may lead to coma (see section 4.3).</p>   |

|  |   |  |
|--|---|--|
| Perphenazine<br>Risperidone<br>Thioridazine<br><br>Lurasidone<br>Pimozide<br>Sertindole  | Not studied. PREZISTA is expected to increase these antipsychotic plasma concentrations.<br>(CYP3A, CYP2D6 and/or P-gp inhibition)  | A dose decrease may be needed for these drugs when co-administered with PREZISTA co-administered with low dose ritonavir.<br><br>Concomitant administration of PREZISTA with low dose ritonavir and lurasidone, pimozide or sertindole is contraindicated (see section 4.3).   |
| <b>β-BLOCKERS</b>  |   |  |
| Carvedilol<br>Metoprolol<br>Timolol  | Not studied. PREZISTA is expected to increase these β-blocker plasma concentrations.<br>(CYP2D6 inhibition)   | Clinical monitoring is recommended when co-administering PREZISTA with β-blockers. A lower dose of the β-blocker should be considered.   |
| <b>CALCIUM CHANNEL BLOCKERS</b>  |   |  |
| Amlodipine<br>Diltiazem<br>Felodipine<br>Nicardipine<br>Nifedipine<br>Verapamil  | Not studied. PREZISTA co-administered with low dose ritonavir can be expected to increase the plasma concentrations of calcium channel blockers.<br>(CYP3A and/or CYP2D6 inhibition)  | Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with PREZISTA with low dose ritonavir.   |
| <b>CORTICOSTEROIDS</b>   |   |  |
| Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone) | Fluticasone: in a clinical study where ritonavir 100 mg capsules twice daily 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% CI 82-89%). Greater effects may be expected when fluticasone 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. The effects of high fluticasone systemic exposure on ritonavir plasma levels are unknown.<br><br>Other corticosteroids: interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with PREZISTA with low dose ritonavir, resulting in reduced serum cortisol concentrations. | Concomitant use of PREZISTA with low dose ritonavir and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.<br>Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects.<br>Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long term use. |
| Dexamethasone (systemic)   | Not studied. Dexamethasone may decrease plasma concentrations of darunavir.<br>(CYP3A induction)  | Systemic dexamethasone should be used with caution when combined with PREZISTA co-administered with low dose ritonavir.  |

| <b>ENDOTHELIN RECEPTOR ANTAGONISTS</b>                  |   |  |
|---|---|--|
| Bosentan  | Not studied. Concomitant use of bosentan and PREZISTA co-administered with low dose ritonavir may increase plasma concentrations of bosentan. Bosentan is expected to decrease plasma concentrations of darunavir and/or its pharmacoenhancer. (CYP3A induction)  | When administered concomitantly with PREZISTA and low dose ritonavir, the patient's tolerability of bosentan should be monitored.  |
| <b>HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS</b> |   |  |
| <b>NS3-4A protease inhibitors</b>                       |   |  |
| Elbasvir/grazoprevir                                    | PREZISTA with low dose ritonavir may increase the exposure to grazoprevir. (CYP3A and OATP1B inhibition)  | Concomitant use of PREZISTA with low dose ritonavir and elbasvir/grazoprevir is contraindicated (see section 4.3).   |
| Boceprevir<br>800 mg three times daily                  | boceprevir AUC ↓ 32%<br>boceprevir C <sub>min</sub> ↓ 35%<br>boceprevir C <sub>max</sub> ↓ 25%<br>darunavir AUC ↓ 44%<br>darunavir C <sub>min</sub> ↓ 59%<br>darunavir C <sub>max</sub> ↓ 36%   | It is not recommended to co-administer PREZISTA with low dose ritonavir and boceprevir.  |
| Glecaprevir/pibrentasvir                                | Based on theoretical considerations boosted PREZISTA may increase the exposure to glecaprevir and pibrentasvir. (P-gp, BCRP and/or OATP1B1/3 inhibition)  | It is not recommended to co-administer boosted PREZISTA with glecaprevir/pibrentasvir.   |
| Simeprevir  | simeprevir AUC ↑ 159%<br>simeprevir C <sub>min</sub> ↑ 358%<br>simeprevir C <sub>max</sub> ↑ 79%<br>darunavir AUC ↑ 18%<br>darunavir C <sub>min</sub> ↑ 31%<br>darunavir C <sub>max</sub> ↔<br><br>The dose of simeprevir in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir, compared to 150 mg in the simeprevir alone treatment group. | It is not recommended to co-administer PREZISTA with low dose ritonavir and simeprevir.  |
| <b>HERBAL PRODUCTS</b>                                  |   |  |
| St John's wort<br>( <i>Hypericum perforatum</i> )       | Not studied. St John's wort is expected to decrease the plasma concentrations of darunavir and ritonavir. (CYP450 induction)  | PREZISTA co-administered with low dose ritonavir must not be used concomitantly with products containing St John's wort ( <i>Hypericum perforatum</i> ) (see section 4.3). 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. |

| <b>HMG CO-A REDUCTASE INHIBITORS</b>                     |  |  |
|--|--|--|
| Lovastatin<br>Simvastatin                                | Not studied. Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with PREZISTA co-administered with low dose ritonavir. (CYP3A inhibition) | Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of PREZISTA co-administered with low dose ritonavir with lovastatin and simvastatin is therefore contraindicated (see section 4.3).   |
| Atorvastatin<br>10 mg once daily                         | atorvastatin AUC ↑ 3-4 fold<br>atorvastatin C <sub>min</sub> ↑ ≈5.5-10 fold<br>atorvastatin C <sub>max</sub> ↑ ≈2 fold<br># darunavir/ritonavir  | When administration of atorvastatin and PREZISTA co-administered with low dose ritonavir is desired, it is recommended to start with an atorvastatin dose of 10 mg once daily. A gradual dose increase of atorvastatin may be tailored to the clinical response. |
| Pravastatin<br>40 mg single dose                         | pravastatin AUC ↑ 81% <sup>¶</sup><br>pravastatin C <sub>min</sub> ND<br>pravastatin C <sub>max</sub> ↑ 63%<br><sup>¶</sup> an up to five-fold increase was seen in a limited subset of subjects     | When administration of pravastatin and PREZISTA co-administered with low dose ritonavir is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effect while monitoring for safety.          |
| Rosuvastatin<br>10 mg once daily                         | rosuvastatin AUC ↑ 48% <sup>  </sup><br>rosuvastatin C <sub>max</sub> ↑ 144% <sup>  </sup><br><sup>  </sup> based on published data with darunavir/ritonavir   | When administration of rosuvastatin and PREZISTA co-administered with low dose ritonavir is required, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.        |
| <b>OTHER LIPID MODIFYING AGENTS</b>                      |  |  |
| Lomitapide   | Based on theoretical considerations boosted PREZISTA is expected to increase the exposure of lomitapide when co-administered. (CYP3A inhibition)   | Co-administration is contraindicated (see section 4.3)   |
| <b>H<sub>2</sub>-RECEPTOR ANTAGONISTS</b>                |  |  |
| Ranitidine<br>150 mg twice daily                         | # darunavir AUC ↔<br># darunavir C <sub>min</sub> ↔<br># darunavir C <sub>max</sub> ↔  | PREZISTA co-administered with low dose ritonavir can be co-administered with H <sub>2</sub> -receptor antagonists without dose adjustments.  |
| <b>IMMUNOSUPPRESSANTS</b>                                |  |  |
| Ciclosporin<br>Sirolimus<br>Tacrolimus<br><br>Everolimus | Not studied. Exposure to these immunosuppressants will be increased when co-administered with PREZISTA co-administered with low dose ritonavir. (CYP3A inhibition)                                   | Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs.<br><br>Concomitant use of everolimus and PREZISTA co-administered with low dose ritonavir is not recommended.   |

| <b>INHALED BETA AGONISTS</b>  |   |   |
|---|---|---|
| Salmeterol  | Not studied. Concomitant use of salmeterol and darunavir co-administered with low dose ritonavir may increase plasma concentrations of salmeterol.  | Concomitant use of salmeterol and PREZISTA co-administered with low dose ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia.   |
| <b>NARCOTIC ANALGESICS / TREATMENT OF OPIOID DEPENDENCE</b>   |   |   |
| Methadone<br>individual dose ranging from 55 mg to 150 mg once daily  | R(-) methadone AUC ↓ 16%<br>R(-) methadone C <sub>min</sub> ↓ 15%<br>R(-) methadone C <sub>max</sub> ↓ 24%  | No adjustment of methadone dosage is required when initiating co-administration with PREZISTA/ritonavir. However, increased methadone dose may be necessary when concomitantly administered for a longer period of time due to induction of metabolism by ritonavir. Therefore, clinical monitoring is recommended, as maintenance therapy may need to be adjusted in some patients.  |
| Buprenorphine/naloxone<br>8/2 mg–16/4 mg once daily   | buprenorphine AUC ↓ 11%<br>buprenorphine C <sub>min</sub> ↔<br>buprenorphine C <sub>max</sub> ↓ 8%<br>norbuprenorphine AUC ↑ 46%<br>norbuprenorphine C <sub>min</sub> ↑ 71%<br>norbuprenorphine C <sub>max</sub> ↑ 36%<br>naloxone AUC ↔<br>naloxone C <sub>min</sub> ND<br>naloxone C <sub>max</sub> ↔   | The clinical relevance of the increase in norbuprenorphine pharmacokinetic parameters has not been established. Dose adjustment for buprenorphine may not be necessary when co-administered with PREZISTA/ritonavir but a careful clinical monitoring for signs of opiate toxicity is recommended.  |
| Fentanyl<br>Oxycodone<br>Tramadol   | Based on theoretical considerations boosted PREZISTA may increase plasma concentrations of these analgesics. (CYP2D6 and/or CYP3A inhibition)   | Clinical monitoring is recommended when co-administering PREZISTA with low dose ritonavir with these analgesics.  |
| <b>OESTROGEN-BASED CONTRACEPTIVES</b>   |   |   |
| Drospirenone<br>Ethinylestradiol<br>(3 mg/0.02 mg once daily)<br><br>Ethinylestradiol<br>Norethindrone<br>35 µg/1 mg once daily | Not studied with darunavir/ritonavir.<br><br>ethinylestradiol AUC ↓ 44% <sup>β</sup><br>ethinylestradiol C <sub>min</sub> ↓ 62% <sup>β</sup><br>ethinylestradiol C <sub>max</sub> ↓ 32% <sup>β</sup><br>norethindrone AUC ↓ 14% <sup>β</sup><br>norethindrone C <sub>min</sub> ↓ 30% <sup>β</sup><br>norethindrone C <sub>max</sub> ↔ <sup>β</sup><br><sup>β</sup> with darunavir/ritonavir | When PREZISTA is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalaemia.<br><br>Alternative or additional contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with PREZISTA and low dose ritonavir.<br><br>Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency. |

| <b>OPIOID ANTAGONIST</b>   |  |  |
|--|--|--|
| Naloxegol  | Not studied.   | Co-administration of boosted PREZISTA and naloxegol is contraindicated.  |
| <b>PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS</b>  |  |  |
| For the treatment of erectile dysfunction<br>Avanafil<br>Sildenafil<br>Tadalafil<br>Vardenafil | In an interaction study <sup>#</sup> , 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 and low dose ritonavir.        | The combination of avanafil and PREZISTA with low dose ritonavir is contraindicated (see section 4.3). Concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with PREZISTA co-administered with low dose ritonavir should be done with caution. If concomitant use of PREZISTA co-administered with low dose 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 in 72 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended.  |
| For the treatment of pulmonary arterial hypertension<br>Sildenafil<br>Tadalafil                | Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and darunavir co-administered with low dose ritonavir may increase plasma concentrations of sildenafil or tadalafil. (CYP3A inhibition) | A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with PREZISTA and low dose ritonavir has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope). Therefore, co-administration of PREZISTA with low dose ritonavir and sildenafil when used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3). Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with PREZISTA and low dose ritonavir is not recommended. |
| <b>PROTON PUMP INHIBITORS</b>  |  |  |
| Omeprazole<br>20 mg once daily   | <sup>#</sup> darunavir AUC ↔<br><sup>#</sup> darunavir C <sub>min</sub> ↔<br><sup>#</sup> darunavir C <sub>max</sub> ↔   | PREZISTA co-administered with low dose ritonavir can be co-administered with proton pump inhibitors without dose adjustments.  |





### Breast-feeding

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 (1,000 mg/kg/day) resulted in toxicity. Because of both the potential for HIV transmission and the potential for adverse reactions in breast-fed infants, mothers should be instructed not to breast-feed under any circumstances 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**

PREZISTA in combination with ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing PREZISTA co-administered with low dose 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**

### Summary of the safety profile

During the clinical development program (N=2,613 treatment-experienced subjects who initiated therapy with PREZISTA/ritonavir 600/100 mg twice daily), 51.3% of subjects experienced at least one adverse reaction. The total mean treatment duration for subjects was 95.3 weeks. The most frequent adverse reactions reported in clinical trials and as spontaneous reports are diarrhoea, nausea, rash, headache and vomiting. The most frequent serious reactions are acute renal failure, myocardial infarction, immune reconstitution inflammatory syndrome, thrombocytopenia, osteonecrosis, diarrhoea, hepatitis and pyrexia.

In the 96 week analysis, the safety profile of PREZISTA/ritonavir 800/100 mg once daily in treatment-naïve subjects was similar to that seen with PREZISTA/ritonavir 600/100 mg twice daily in treatment-experienced subjects except for nausea which was observed more frequently in treatment-naïve subjects. This was driven by mild intensity nausea. No new safety findings were identified in the 192 week analysis of the treatment-naïve subjects in which the mean treatment duration of PREZISTA/ritonavir 800/100 mg once daily was 162.5 weeks.

### Tabulated list of adverse reactions

Adverse reactions are listed by system organ class (SOC) and frequency category. Within each frequency category, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as follows: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and not known (frequency cannot be estimated from the available data).

### *Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing*

| MedDRA system organ class<br>Frequency category | Adverse reaction   |
|---|--|
| <i>Infections and infestations</i>              |  |
| uncommon  | herpes simplex   |
| <i>Blood and lymphatic system disorders</i>     |  |
| uncommon  | thrombocytopenia, neutropenia, anaemia, leukopenia                   |
| rare  | increased eosinophil count   |
| <i>Immune system disorders</i>                  |  |
| uncommon  | immune reconstitution inflammatory syndrome, (drug) hypersensitivity |

|  |   |
|--|---|
| <i>Endocrine disorders</i>                             |   |
| uncommon   | hypothyroidism, increased blood thyroid stimulating hormone   |
| <i>Metabolism and nutrition disorders</i>              |   |
| common   | diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia  |
| uncommon   | gout, anorexia, decreased appetite, decreased weight, increased weight, hyperglycaemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase |
| <i>Psychiatric disorders</i>                           |   |
| common   | insomnia  |
| uncommon   | depression, disorientation, anxiety, sleep disorder, abnormal dreams, nightmare, decreased libido   |
| rare   | confusional state, altered mood, restlessness   |
| <i>Nervous system disorders</i>                        |   |
| common   | headache, peripheral neuropathy, dizziness  |
| uncommon   | lethargy, paraesthesia, hypoaesthesia, dysgeusia, disturbance in attention, memory impairment, somnolence   |
| rare   | syncope, convulsion, ageusia, sleep phase rhythm disturbance  |
| <i>Eye disorders</i>                                   |   |
| uncommon   | conjunctival hyperaemia, dry eye  |
| rare   | visual disturbance  |
| <i>Ear and labyrinth disorders</i>                     |   |
| uncommon   | vertigo   |
| <i>Cardiac disorders</i>                               |   |
| uncommon   | myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia   |
| rare   | acute myocardial infarction, sinus bradycardia, palpitations  |
| <i>Vascular disorders</i>                              |   |
| uncommon   | hypertension, flushing  |
| <i>Respiratory, thoracic and mediastinal disorders</i> |   |
| uncommon   | dyspnoea, cough, epistaxis, throat irritation   |
| rare   | rhinorrhoea   |
| <i>Gastrointestinal disorders</i>                      |   |
| very common  | diarrhoea   |
| common   | vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence  |

|   |   |
|---|---|
| uncommon  | pancreatitis, gastritis, gastroesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia   |
| rare  | stomatitis, haematemesis, cheilitis, dry lip, coated tongue   |
| <i>Hepatobiliary disorders</i>                              |   |
| common  | increased alanine aminotransferase  |
| uncommon  | hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-glutamyltransferase |
| <i>Skin and subcutaneous tissue disorders</i>               |   |
| common  | rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus  |
| uncommon  | angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation  |
| rare  | DRESS, Stevens-Johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma  |
| not known   | toxic epidermal necrolysis, acute generalised exanthematous pustulosis  |
| <i>Musculoskeletal and connective tissue disorders</i>      |   |
| uncommon  | myalgia, osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphokinase   |
| rare  | musculoskeletal stiffness, arthritis, joint stiffness   |
| <i>Renal and urinary disorders</i>                          |   |
| uncommon  | acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria   |
| rare  | decreased creatinine renal clearance  |
| <i>Reproductive system and breast disorders</i>             |   |
| uncommon  | erectile dysfunction, gynaecomastia   |
| <i>General disorders and administration site conditions</i> |   |
| common  | asthenia, fatigue   |
| uncommon  | pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain  |
| rare  | chills, abnormal feeling, xerosis   |

## Description of selected adverse reactions

### *Rash*

In clinical trials, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In cases of severe skin reaction see the warning in section 4.4.

During the clinical development program of raltegravir in treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing PREZISTA/ritonavir + raltegravir compared to those containing PREZISTA/ritonavir without raltegravir or raltegravir without PREZISTA/ritonavir. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR), respectively; and for drug-related rash were 2.4, 1.1, and 2.3 per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy (see section 4.4).

### *Metabolic parameters*

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

### *Musculoskeletal abnormalities*

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).

### *Immune reconstitution inflammatory syndrome*

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

### *Bleeding in haemophiliac patients*

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

## Paediatric population

The safety assessment in paediatric patients is based on the 48-week analysis of safety data from three Phase II trials. The following patient populations were evaluated (see section 5.1):

- 80 ART-experienced HIV-1 infected paediatric patients aged from 6 to 17 years and weighing at least 20 kg who received PREZISTA tablets with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 21 ART-experienced HIV-1 infected paediatric patients aged from 3 to < 6 years and weighing 10 kg to < 20 kg (16 participants from 15 kg to < 20 kg) who received PREZISTA oral suspension with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 12 ART-naïve HIV-1 infected paediatric patients aged from 12 to 17 years and weighing at least 40 kg who received PREZISTA tablets with low dose ritonavir once daily in combination with other antiretroviral agents (see section 5.1).

Overall, the safety profile in these paediatric patients was similar to that observed in the adult population.

## Other special populations

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

Among 1,968 treatment-experienced patients receiving PREZISTA co-administered with ritonavir 600/100 mg twice daily, 236 patients were co-infected with 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).

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

### **4.9 Overdose**

Human experience of acute overdose with PREZISTA co-administered with low dose ritonavir is limited. Single doses up to 3,200 mg of darunavir as oral solution alone and up to 1,600 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. 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: Antivirals for systemic use, protease inhibitors, ATC code: J05AE10.

#### Mechanism of action

Darunavir is an inhibitor of the dimerisation and of the catalytic activity 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.

#### Resistance

*In vitro* selection of darunavir-resistant virus from wild type HIV-1 was lengthy (> 3 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23-50-fold) harboured 2 to 4 amino acid substitutions in the protease gene. The decreased susceptibility to darunavir of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations.

The clinical trial data from ART-experienced patients (*TITAN* trial and the pooled analysis of the *POWER* 1, 2 and 3 and *DUET* 1 and 2 trials) showed that virologic response to PREZISTA co-administered with low dose ritonavir was decreased when 3 or more darunavir RAMs (V11I, V32I,

L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) were present at baseline or when these mutations developed during treatment.

Increasing baseline darunavir fold change in  $EC_{50}$  (FC) was associated with decreasing virologic response. A lower and upper clinical cut-off of 10 and 40 were identified. Isolates with baseline  $FC \leq 10$  are susceptible; isolates with  $FC > 10$  to 40 have decreased susceptibility; isolates with  $FC > 40$  are resistant (see Clinical results).

Viruses isolated from patients on PREZISTA/ritonavir 600/100 mg twice daily experiencing virologic failure by rebound that were susceptible to tipranavir at baseline remained susceptible to tipranavir after treatment in the vast majority of cases.

The lowest rates of developing resistant HIV virus are observed in ART-naïve patients who are treated for the first time with darunavir in combination with other ART.

The table below shows the development of HIV-1 protease mutations and loss of susceptibility to PIs in virologic failures at endpoint in the *ARTEMIS*, *ODIN* and *TITAN* trials.

|   | ARTEMIS<br>Week 192   | ODIN<br>Week 48   |  | TITAN<br>Week 48   |
|---|---|---|--|--|
|   | PREZISTA/<br>ritonavir<br>800/100 mg<br>once daily<br>N=343 | PREZISTA/<br>ritonavir<br>800/100 mg<br>once daily<br>N=294 | PREZISTA/<br>ritonavir<br>600/100 mg<br>twice daily<br>N=296 | PREZISTA/<br>ritonavir<br>600/100 mg<br>twice daily<br>N=298 |
| Total number of<br>virologic failures <sup>a</sup> , n<br>(%)   | 55 (16.0%)  | 65 (22.1%)  | 54 (18.2%)   | 31 (10.4%)   |
| Rebounders  | 39 (11.4%)  | 11 (3.7%)   | 11 (3.7%)  | 16 (5.4%)  |
| Never suppressed<br>subjects  | 16 (4.7%)   | 54 (18.4%)  | 43 (14.5%)   | 15 (5.0%)  |
| Number of subjects with virologic failure and paired baseline/endpoint genotypes, developing mutations <sup>b</sup> at<br>endpoint, n/N                           |   |   |  |  |
| Primary (major) PI<br>mutations   | 0/43  | 1/60  | 0/42   | 6/28   |
| PI RAMs   | 4/43  | 7/60  | 4/42   | 10/28  |
| Number of subjects with virologic failure and paired baseline/endpoint phenotypes, showing loss of<br>susceptibility to PIs at endpoint compared to baseline, n/N |   |   |  |  |
| PI  |   |   |  |  |
| darunavir   | 0/39  | 1/58  | 0/41   | 3/26   |
| amprenavir  | 0/39  | 1/58  | 0/40   | 0/22   |
| atazanavir  | 0/39  | 2/56  | 0/40   | 0/22   |
| indinavir   | 0/39  | 2/57  | 0/40   | 1/24   |
| lopinavir   | 0/39  | 1/58  | 0/40   | 0/23   |
| saquinavir  | 0/39  | 0/56  | 0/40   | 0/22   |
| tipranavir  | 0/39  | 0/58  | 0/41   | 1/25   |

<sup>a</sup> TLOVR non-VF censored algorithm based on HIV-1 RNA < 50 copies/ml, except for *TITAN* (HIV-1 RNA < 400 copies/ml)

<sup>b</sup> IAS-USA lists

### Cross-resistance

Darunavir FC was less than 10 for 90% of 3,309 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.

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

## Clinical results

### Adult patients

For clinical trial results in ART-naïve adult patients, refer to the Summary of Product Characteristics for PREZISTA 400 mg and 800 mg tablets or 100 mg/ml oral suspension.

### Efficacy of PREZISTA 600 mg twice daily co-administered with 100 mg ritonavir twice daily in ART-experienced patients

The evidence of efficacy of PREZISTA co-administered with ritonavir (600/100 mg twice daily) in ART-experienced patients is based on the 96 weeks analysis of the Phase III trial *TITAN* in ART-experienced lopinavir naïve patients, on the 48 week analysis of the Phase III trial *ODIN* in ART-experienced patients with no DRV-RAMs, and on the analyses of 96 weeks data from the Phase IIb trials *POWER* 1 and 2 in ART-experienced patients with high level of PI resistance.

*TITAN* is a randomised, controlled, open-label Phase III trial comparing PREZISTA co-administered with ritonavir (600/100 mg twice daily) versus lopinavir/ritonavir (400/100 mg twice daily) in ART-experienced, lopinavir naïve HIV-1 infected adult patients. Both arms used an Optimised Background Regimen (OBR) consisting of at least 2 antiretrovirals (NRTIs with or without NNRTIs).

The table below shows the efficacy data of the 48 week analysis from the *TITAN* trial.

| TITAN  |  |   |  |
|--|--|---|--|
| Outcomes   | PREZISTA/ritonavir<br>600/100 mg twice daily +<br>OBR<br>N=298 | Lopinavir/ritonavir<br>400/100 mg twice daily +<br>OBR<br>N=297 | Treatment difference<br>(95% CI of difference) |
| HIV-1 RNA<br>< 50 copies/ml <sup>a</sup>   | 70.8% (211)  | 60.3% (179)   | 10.5% (2.9; 18.1) <sup>b</sup>                 |
| median CD4+ cell<br>count change<br>from baseline<br>(x 10 <sup>6</sup> /l) <sup>c</sup> | 88   | 81  |  |

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

<sup>b</sup> Based on a normal approximation of the difference in % response

<sup>c</sup> NC=F

At 48 weeks non-inferiority in virologic response to the PREZISTA/ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 400 and < 50 copies/ml, was demonstrated (at the pre-defined 12% non-inferiority margin) for both ITT and OP populations. These results were confirmed in the analysis of data at 96 weeks of treatment in the *TITAN* trial, with 60.4% of patients in the PREZISTA/ritonavir arm having HIV-1 RNA < 50 copies/ml at week 96 compared to 55.2% in the lopinavir/ritonavir arm [difference: 5.2%, 95% CI (-2.8; 13.1)].

*ODIN* is a Phase III, randomised, open-label trial comparing PREZISTA/ritonavir 800/100 mg once daily versus PREZISTA/ritonavir 600/100 mg twice daily in ART-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a screening HIV-1 RNA > 1,000 copies/ml. Efficacy analysis is based on 48 weeks of treatment (see table below). Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs.

| ODIN  |   |  |  |
|---|---|--|--|
| Outcomes  | PREZISTA/ritonavir<br>800/100 mg once daily +<br>OBR<br>N=294 | PREZISTA/ritonavir<br>600/100 mg twice daily +<br>OBR<br>N=296 | Treatment difference<br>(95% CI of difference) |
| HIV-1 RNA<br>< 50 copies/ml <sup>a</sup>  | 72.1% (212)   | 70.9% (210)  | 1.2% (-6.1; 8.5) <sup>b</sup>                  |
| With Baseline HIV-1<br>RNA (copies/ml)  |   |  |  |
| < 100,000   | 77.6% (198/255)   | 73.2% (194/265)  | 4.4% (-3.0; 11.9)                              |
| ≥ 100,000   | 35.9% (14/39)   | 51.6% (16/31)  | -15.7% (-39.2; 7.7)                            |
| With Baseline CD4+<br>cell count (x 10 <sup>6</sup> /l)                             |   |  |  |
| ≥ 100   | 75.1% (184/245)   | 72.5% (187/258)  | 2.6% (-5.1; 10.3)                              |
| < 100   | 57.1% (28/49)   | 60.5% (23/38)  | -3.4% (-24.5; 17.8)                            |
| With HIV-1 clade  |   |  |  |
| Type B  | 70.4% (126/179)   | 64.3% (128/199)  | 6.1% (-3.4; 15.6)                              |
| Type AE   | 90.5% (38/42)   | 91.2% (31/34)  | -0.7% (-14.0; 12.6)                            |
| Type C  | 72.7% (32/44)   | 78.8% (26/33)  | -6.1% (-2.6; 13.7)                             |
| Other <sup>c</sup>  | 55.2% (16/29)   | 83.3% (25/30)  | -28.2% (-51.0; -5.3)                           |
| mean CD4+ cell count<br>change from baseline<br>(x 10 <sup>6</sup> /l) <sup>e</sup> | 108   | 112  | -5 <sup>d</sup> (-25; 16)                      |

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

<sup>b</sup> Based on a normal approximation of the difference in % response

<sup>c</sup> Clades A1, D, F1, G, K, CRF02\_AG, CRF12\_BF, and CRF06\_CPX

<sup>d</sup> Difference in means

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

At 48 weeks, virologic response, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/ml, with PREZISTA/ritonavir 800/100 mg once daily treatment was demonstrated to be non-inferior (at the pre-defined 12% non-inferiority margin) compared to PREZISTA/ritonavir 600/100 mg twice daily for both ITT and OP populations.

PREZISTA/ritonavir 800/100 mg once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10<sup>6</sup>/l (see section 4.2 and 4.4). Limited data is available in patients with HIV-1 clades other than B.

**POWER 1 and POWER 2** are randomised, controlled trials comparing PREZISTA co-administered with ritonavir (600/100 mg twice daily) with a control group receiving an investigator-selected PI(s) regimen in HIV-1 infected patients who had previously failed more than 1 PI containing regimen. An OBR consisting of at least 2 NRTIs with or without enfuvirtide (ENF) was used in both trials.

The table below shows the efficacy data of the 48-week and 96-week analyses from the pooled **POWER 1** and **POWER 2** trials.

| POWER 1 and POWER 2 pooled data   |  |                  |   |  |                  |                                    |
|---|--|------------------|---|--|------------------|------------------------------------|
| Outcomes  | Week 48  |                  |   | Week 96  |                  |                                    |
|   | PREZISTA/<br>ritonavir<br>600/100 mg<br>twice daily<br>n=131 | Control<br>n=124 | Treatment<br>difference                 | PREZISTA/<br>ritonavir<br>600/100 mg<br>twice daily<br>n=131 | Control<br>n=124 | Treatment<br>difference            |
| HIV RNA<br>< 50 copies/ml <sup>a</sup>  | 45.0%<br>(59)  | 11.3%<br>(14)    | 33.7%<br>(23.4%;<br>44.1%) <sup>c</sup> | 38.9%<br>(51)  | 8.9%<br>(11)     | 30.1%<br>(20.1; 40.0) <sup>c</sup> |
| CD4+ cell count<br>mean change from<br>baseline (x 10 <sup>6</sup> /l) <sup>b</sup> | 103  | 17               | 86<br>(57; 114) <sup>c</sup>            | 133  | 15               | 118<br>(83.9; 153.4) <sup>c</sup>  |



- <sup>a</sup> Imputations according to the TLOVR algorithm  
<sup>b</sup> Last Observation Carried Forward imputation  
<sup>c</sup> 95% confidence intervals.

Analyses of data through 96 weeks of treatment in the *POWER* trials demonstrated sustained antiretroviral efficacy and immunologic benefit.

Out of the 59 patients who responded with complete viral suppression (< 50 copies/ml) at week 48, 47 patients (80% of the responders at week 48) remained responders at week 96.

#### *Baseline genotype or phenotype and virologic outcome*

Baseline genotype and darunavir FC (shift in susceptibility relative to reference) were shown to be a predictive factor of virologic outcome.

*Proportion (%) of patients with response (HIV-1 RNA < 50 copies/ml at week 24) to PREZISTA co-administered with ritonavir (600/100 mg twice daily) by baseline genotype<sup>a</sup>, and baseline darunavir FC and by use of enfuvirtide (ENF): As treated analysis of the POWER and DUET trials.*

|  | Number of baseline mutations <sup>a</sup> |                |               |               | Baseline DRV FC <sup>b</sup> |                |               |             |
|--|---|----------------|---------------|---------------|------------------------------|----------------|---------------|-------------|
| Response (HIV-1 RNA < 50 copies/ml at week 24)<br>%, n/N | All ranges                                | 0-2            | 3             | ≥ 4           | All ranges                   | ≤ 10           | 10-40         | > 40        |
| All patients   | 45%<br>455/1,014                          | 54%<br>359/660 | 39%<br>67/172 | 12%<br>20/171 | 45%<br>455/1,014             | 55%<br>364/659 | 29%<br>59/203 | 8%<br>9/118 |
| Patients with no/non-naïve use of ENF <sup>c</sup>       | 39%<br>290/741                            | 50%<br>238/477 | 29%<br>35/120 | 7%<br>10/135  | 39%<br>290/741               | 51%<br>244/477 | 17%<br>25/147 | 5%<br>5/94  |
| Patients with naïve use of ENF <sup>d</sup>              | 60%<br>165/273                            | 66%<br>121/183 | 62%<br>32/52  | 28%<br>10/36  | 60%<br>165/273               | 66%<br>120/182 | 61%<br>34/56  | 17%<br>4/24 |

<sup>a</sup> Number of mutations from the list of mutations associated with a diminished response to PREZISTA/ritonavir (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V)

<sup>b</sup> fold change in EC<sub>50</sub>

<sup>c</sup> “Patients with no/non-naïve use of ENF” are patients who did not use ENF or who used ENF but not for the first time

<sup>d</sup> “Patients with naïve use of ENF” are patients who used ENF for the first time

#### Paediatric patients

For clinical trial results in ART-naïve paediatric patients aged 12 to 17 years, refer to the Summary of Product Characteristics for PREZISTA 400 mg and 800 mg tablets or PREZISTA 100 mg/ml oral suspension.

#### ART-experienced paediatric patients from the age of 6 to < 18 years, and weighing at least 20 kg

**DELPHI** is an open-label, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of PREZISTA with low dose ritonavir in 80 ART-experienced HIV-1 infected paediatric patients aged 6 to 17 years and weighing at least 20 kg. These patients received PREZISTA/ritonavir twice daily in combination with other antiretroviral agents (see section 4.2 for dosage recommendations per body weight). Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 log<sub>10</sub> versus baseline.

In the study, patients who were at risk of discontinuing therapy due to intolerance of ritonavir oral solution (e.g. taste aversion) were allowed to switch to the capsule formulation. Of the 44 patients taking ritonavir oral solution, 27 switched to the 100 mg capsule formulation and exceeded the weight-based ritonavir dose without changes in observed safety.

| DELPHI   |                            |
|--|----------------------------|
| Outcomes at week 48                                    | PREZISTA/ritonavir<br>N=80 |
| HIV-1 RNA < 50 copies/ml <sup>a</sup>                  | 47.5% (38)                 |
| CD4+ cell count mean change from baseline <sup>b</sup> | 147                        |

<sup>a</sup> Imputations according to the TLOVR algorithm.

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

According to the TLOVR non-virologic failure censored algorithm 24 (30.0%) patients experienced virological failure, of which 17 (21.3%) patients were rebounders and 7 (8.8%) patients were non-responders.

#### ART-experienced paediatric patients from the age of 3 to < 6 years

The pharmacokinetics, safety, tolerability and efficacy of PREZISTA/ritonavir twice daily in combination with other antiretroviral agents in 21 ART-experienced HIV-1 infected paediatric patients aged 3 to < 6 years and weighing 10 kg to < 20 kg was evaluated in an open-label, Phase II trial, **ARIEL**. Patients received a weight-based twice daily treatment regimen, patients weighing 10 kg to < 15 kg received darunavir/ritonavir 25/3 mg/kg twice daily, and patients weighing 15 kg to < 20 kg received darunavir/ritonavir 375/50 mg twice daily. At week 48, the virologic response, defined as the percentage of patients with confirmed plasma viral load < 50 HIV-1 RNA copies/ml, was evaluated in 16 paediatric patients 15 kg to < 20 kg and 5 paediatric patients 10 kg to < 15 kg receiving PREZISTA/ritonavir in combination with other antiretroviral agents (see section 4.2 for dosage recommendations per body weight).

| ARIEL  |                         |                          |
|--|-------------------------|--------------------------|
| Outcomes at week 48                                    | PREZISTA/ritonavir      |                          |
|  | 10 kg to < 15 kg<br>N=5 | 15 kg to < 20 kg<br>N=16 |
| HIV-1 RNA < 50 copies/ml <sup>a</sup>                  | 80.0% (4)               | 81.3% (13)               |
| CD4+ percent change from baseline <sup>b</sup>         | 4                       | 4                        |
| CD4+ cell count mean change from baseline <sup>b</sup> | 16                      | 241                      |

<sup>a</sup> Imputations according to the TLOVR algorithm.

<sup>b</sup> NC=F

Limited efficacy data are available in paediatric patients below 15 kg and no recommendation on a posology can be made.

#### Pregnancy and postpartum

Darunavir/ritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 36 pregnant women (18 in each arm) during the second and third trimesters, and postpartum. Virologic response was preserved throughout the study period in both arms. No mother to child transmission occurred in the infants born to the 31 subjects who stayed on the antiretroviral treatment through delivery. There were no new clinically relevant safety findings compared with the known safety profile of darunavir/ritonavir in HIV-1 infected adults (see sections 4.2, 4.4 and 5.2).

## **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 twice daily ritonavir. The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily (see 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.

### Biotransformation

*In vitro* experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolised by the hepatic CYP system and almost exclusively by isozyme CYP3A4. A  $^{14}$ C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir 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  $^{14}$ C-darunavir with ritonavir dose, approximately 79.5% and 13.9% of the administered dose of  $^{14}$ C-darunavir could be retrieved in faeces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in faeces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir.

The intravenous clearance of darunavir alone (150 mg) and in the presence of low dose ritonavir was 32.8 l/h and 5.9 l/h, respectively.

### Special populations

#### *Paediatric population*

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 74 treatment-experienced paediatric patients, aged 6 to 17 years and weighing at least 20 kg, showed that the administered weight-based doses of PREZISTA/ritonavir resulted in darunavir exposure comparable to that in adults receiving PREZISTA/ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 14 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 15 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving PREZISTA/ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 12 ART-naïve paediatric patients, aged 12 to < 18 years and weighing at least 40 kg, showed that PREZISTA/ritonavir 800/100 mg once daily results in darunavir exposure that was comparable to that

achieved in adults receiving PREZISTA/ritonavir 800/100 mg once daily. Therefore the same once daily dosage may be used in treatment-experienced adolescents aged 12 to < 18 years and weighing at least 40 kg without darunavir resistance associated mutations (DRV-RAMs)\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100$  cells  $\times 10^6/l$  (see section 4.2).

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 10 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 14 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving PREZISTA/ritonavir 800/100 mg once daily (see section 4.2). In addition, pharmacokinetic modeling and simulation of darunavir exposures in paediatric patients across the ages of 3 to < 18 years confirmed the darunavir exposures as observed in the clinical studies and allowed the identification of weight-based PREZISTA/ritonavir once daily dosing regimens for paediatric patients weighing at least 15 kg that are either ART-naïve or treatment-experienced paediatric patients without DRV-RAMs\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100$  cells  $\times 10^6/l$  (see section 4.2).

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

#### *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  $^{14}C$ -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 total plasma concentrations of darunavir in subjects with mild (Child-Pugh Class A, n=8) and moderate (Child-Pugh Class B, n=8) hepatic impairment were comparable with those in healthy subjects. However, unbound darunavir concentrations were approximately 55% (Child-Pugh Class A) and 100% (Child-Pugh Class B) higher, respectively. The clinical relevance of this increase is unknown therefore, PREZISTA should be used with caution. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see sections 4.2, 4.3 and 4.4).

#### *Pregnancy and postpartum*

The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 600/100 mg twice daily and darunavir/ritonavir 800/100 mg once daily as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum. However, for unbound (i.e. active) darunavir, the pharmacokinetic parameters were less reduced during pregnancy compared to postpartum, due to an increase in the unbound fraction of darunavir during pregnancy compared to postpartum.

| <b>Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 600/100 mg twice daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum</b> |   |  |                                       |
|---|---|--|---------------------------------------|
| <b>Pharmacokinetics of total darunavir (mean ± SD)</b>  | <b>Second trimester of pregnancy (n=12)<sup>a</sup></b> | <b>Third trimester of pregnancy (n=12)</b> | <b>Postpartum (6-12 weeks) (n=12)</b> |
| $C_{max}$ , ng/ml   | 4,668 ± 1,097   | 5,328 ± 1,631                              | 6,659 ± 2,364                         |
| $AUC_{12h}$ , ng.h/ml   | 39,370 ± 9,597  | 45,880 ± 17,360                            | 56,890 ± 26,340                       |
| $C_{min}$ , ng/ml   | 1,922 ± 825   | 2,661 ± 1,269                              | 2,851 ± 2,216                         |

<sup>a</sup> n=11 for  $AUC_{12h}$

| <b>Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 800/100 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum</b> |   |  |                                       |
|--|---|--|---------------------------------------|
| <b>Pharmacokinetics of total darunavir (mean ± SD)</b>   | <b>Second trimester of pregnancy (n=17)</b> | <b>Third Trimester of pregnancy (n=15)</b> | <b>Postpartum (6-12 weeks) (n=16)</b> |
| $C_{max}$ , ng/ml  | 4,964 ± 1,505                               | 5,132 ± 1,198                              | 7,310 ± 1,704                         |
| $AUC_{24h}$ , ng.h/ml  | 62,289 ± 16,234                             | 61,112 ± 13,790                            | 92,116 ± 29,241                       |
| $C_{min}$ , ng/ml  | 1,248 ± 542                                 | 1,075 ± 594                                | 1,473 ± 1,141                         |

In women receiving darunavir/ritonavir 600/100 mg twice daily during the second trimester of pregnancy, mean intra-individual values for total darunavir  $C_{max}$ ,  $AUC_{12h}$  and  $C_{min}$  were 28%, 26% and 26% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir  $C_{max}$ ,  $AUC_{12h}$  and  $C_{min}$  values were 18%, 16% lower and 2% higher, respectively, as compared with postpartum.

In women receiving darunavir/ritonavir 800/100 mg once daily during the second trimester of pregnancy, mean intra-individual values for total darunavir  $C_{max}$ ,  $AUC_{24h}$  and  $C_{min}$  were 33%, 31% and 30% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir  $C_{max}$ ,  $AUC_{24h}$  and  $C_{min}$  values were 29%, 32% and 50% lower, respectively, as compared with postpartum.

### 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 1,000 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 receiving darunavir up to days 23-26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher than in adult rats after comparable doses in mg/kg between days 5 and 11 of age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals. No treatment related mortalities were noted in juvenile rats dosed at 1,000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats.

Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, PREZISTA with low dose ritonavir should not be used in paediatric patients below 3 years of age.

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1,000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumours in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

After 2 years administration of darunavir at exposures at or below the human exposure, kidney changes were observed in mice (nephrosis) and rats (chronic progressive nephropathy).

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### PREZISTA 75 mg film-coated tablets

##### Tablet core

Microcrystalline cellulose  
Colloidal anhydrous silica  
Crospovidone  
Magnesium stearate

##### Tablet film-coat

Poly(vinyl alcohol) – partially hydrolysed  
Macrogol 3350  
Titanium dioxide (E171)  
Talc

#### PREZISTA 150 mg film-coated tablets

Tablet core

Microcrystalline cellulose  
Colloidal anhydrous silica  
Crospovidone  
Magnesium stearate

Tablet film-coat

Poly(vinyl alcohol) – partially hydrolysed  
Macrogol 3350  
Titanium dioxide (E171)  
Talc

PREZISTA 300 mg film-coated tablets

Tablet core

Microcrystalline cellulose  
Colloidal anhydrous silica  
Crospovidone  
Magnesium stearate

Tablet film-coat

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

PREZISTA 600 mg film-coated tablets

Tablet core

Microcrystalline cellulose  
Colloidal anhydrous silica  
Crospovidone  
Magnesium stearate

Tablet film-coat

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

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

PREZISTA 75 mg, 150 mg and 600 mg film-coated tablets

3 years

PREZISTA 300 mg film-coated tablets

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**

### PREZISTA 75 mg film-coated tablets

Opaque, white, high density polyethylene (HDPE) plastic, 160 ml bottle containing 480 tablets, fitted with polypropylene (PP) child resistant closure.

Pack size of one bottle.

### PREZISTA 150 mg film-coated tablets

Opaque, white, high density polyethylene (HDPE) plastic, 160 ml bottle containing 240 tablets, fitted with polypropylene (PP) child resistant closure.

Pack size of one bottle.

### PREZISTA 300 mg film-coated tablets

Opaque, white, high density polyethylene (HDPE) plastic, 160 ml bottle containing 120 tablets, fitted with polypropylene (PP) child resistant closure.

Pack size of one bottle.

### PREZISTA 600 mg film-coated tablets

Opaque, white, high density polyethylene (HDPE) plastic, 160 ml bottle containing 60 tablets, fitted with polypropylene (PP) child resistant closure.

Pack size of 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)**

### PREZISTA 75 mg film-coated tablets

EU/1/06/380/005

### PREZISTA 150 mg film-coated tablets

EU/1/06/380/004

### PREZISTA 300 mg film-coated tablets

EU/1/06/380/001

### PREZISTA 600 mg film-coated tablets

EU/1/06/380/002

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

Date of first authorisation: 12 February 2007

Date of latest renewal: 19 September 2013



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

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **1. NAME OF THE MEDICINAL PRODUCT**

PREZISTA 400 mg film-coated tablets  
PREZISTA 800 mg film-coated tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

### PREZISTA 400 mg film-coated tablets

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

Excipient with known effect: Each tablet contains 0.834 mg sunset yellow FCF (E110).

### PREZISTA 800 mg film-coated tablets

Each film-coated tablet contains 800 mg of darunavir (as ethanolate).

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

### PREZISTA 400 mg film-coated tablets

Film-coated tablet.

Light orange oval shaped tablet of 19.1 mm, debossed with “400MG” on one side and “TMC” on the other side.

### PREZISTA 800 mg film-coated tablets

Film-coated tablet.

Dark red oval shaped tablet of 20.0 mm, debossed with “800” on one side and “T” on the other side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

PREZISTA, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.

PREZISTA, co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients (see section 4.2).

PREZISTA 400 mg and 800 mg tablets may be used to provide suitable dose regimens for the treatment of HIV-1 infection in adult and paediatric patients from the age of 3 years and at least 40 kg body weight who are:

- antiretroviral therapy (ART)-naïve (see section 4.2).
- ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100$  cells  $\times 10^6/l$ . In deciding to initiate treatment with PREZISTA in such ART-experienced patients, genotypic testing should guide the use of PREZISTA (see sections 4.2, 4.3, 4.4 and 5.1).

### **4.2 Posology and method of administration**

Therapy should be initiated by a health care provider experienced in the management of HIV infection. After therapy with PREZISTA has been initiated, patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their health care provider.

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer. Darunavir may therefore have different contraindications and recommendations for concomitant medications depending on whether the compound is boosted with ritonavir or cobicistat (see sections 4.3, 4.4 and 4.5).

### Posology

PREZISTA must always be given orally with cobicistat or low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of cobicistat or ritonavir as appropriate, must therefore be consulted prior to initiation of therapy with PREZISTA. Cobicistat is not indicated for use in twice daily regimens or for use in the paediatric population.

PREZISTA is also available as an oral suspension for use in patients who are unable to swallow PREZISTA tablets (please refer to the Summary of Product Characteristics for PREZISTA oral suspension).

#### *ART-naïve adult patients*

The recommended dose regimen is 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food. PREZISTA 400 mg and 800 mg tablets can be used to construct the once daily 800 mg regimen.

#### *ART-experienced adult patients*

The recommended dose regimens are as follows:

- In ART-experienced patients with no darunavir resistance associated mutations (DRV-RAMs)\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100$  cells  $\times 10^6/l$  (see section 4.1) a regimen of 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food may be used. PREZISTA 400 mg and 800 mg tablets can be used to construct the once daily 800 mg regimen.
- In all other ART-experienced patients or if HIV-1 genotype testing is not available, the recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. See the Summary of Product Characteristics for PREZISTA 100 mg/ml oral suspension, 75 mg, 150 mg, 300 mg or 600 mg tablets.

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

#### *ART-naïve paediatric patients (3 to 17 years of age and weighing at least 40 kg)*

The recommended dose regimen is 800 mg once daily with ritonavir 100 mg once daily taken with food. The dose of cobicistat to be used with PREZISTA in children less than 18 years of age has not been established.

#### *ART-experienced paediatric patients (3 to 17 years of age and weighing at least 40 kg)*

The dose of cobicistat to be used with PREZISTA in children less than 18 years of age has not been established.

The recommended dose regimens are as follows:

- In ART-experienced patients without DRV-RAMs\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100$  cells  $\times 10^6/l$  (see section 4.1) a regimen of 800 mg once daily with ritonavir 100 mg once daily taken with food may be used. PREZISTA 400 mg and 800 mg tablets can be used to construct the once daily 800 mg regimen.
- In all other ART-experienced patients or if HIV-1 genotype testing is not available, the recommended dose regimen is described in the Summary of Product Characteristics for PREZISTA 100 mg/ml oral suspension, 75 mg, 150 mg, 300 mg and 600 mg tablets.

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

#### *Advice on missed doses*

If a once daily dose of PREZISTA and/or cobicistat or ritonavir is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of PREZISTA and cobicistat or ritonavir with food as soon as possible. If this is noticed later than 12 hours after the time

it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

This guidance is based on the half-life of darunavir in the presence of cobicistat or ritonavir and the recommended dosing interval of approximately 24 hours.

### Special populations

#### *Elderly*

Limited information is available in this population, and therefore, PREZISTA should be used with caution in this age group (see sections 4.4 and 5.2).

#### *Hepatic impairment*

Darunavir is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, PREZISTA should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its safety profile. Therefore, PREZISTA must 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 for darunavir/ritonavir in patients with renal impairment (see sections 4.4 and 5.2). Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients.

Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance. Hence, the use of creatinine clearance as an estimate of renal elimination capacity may be misleading. Cobicistat as a pharmacokinetic enhancer of darunavir should, therefore, not be initiated in patients with creatinine clearance less than 70 ml/min if any co-administered agent requires dose adjustment based on creatinine clearance: e.g. emtricitabine, lamivudine, tenofovir disoproxil (as fumarate, phosphate or succinate) or adefovir dipivoxil. For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

#### *Paediatric population*

PREZISTA should not be used in paediatric patients below 3 years of age or less than 15 kg body weight (see sections 4.4 and 5.3).

#### *ART-naïve paediatric patients (3 to 17 years of age and weighing at least 40 kg)*

The recommended dose regimen is 800 mg once daily with ritonavir 100 mg once daily taken with food.

#### *ART-experienced paediatric patients (3 to 17 years of age and weighing at least 40 kg)*

In ART-experienced patients without DRV-RAMs\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100$  cells  $\times 10^6/l$ , a regimen of 800 mg once daily with ritonavir 100 mg once daily taken with food may be used.

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

#### *Paediatric patients (3 to 17 years of age and weighing less than 40 kg)*

The 400 and 800 mg tablets are not suitable for this patient population. Other formulations are available, see the Summary of Product Characteristics for PREZISTA 75 mg, 150 mg, 300 mg, 600 mg tablets and 100 mg/ml oral suspension.

The dose of cobicistat to be used with PREZISTA has not been established in this patient population.

### *Pregnancy and postpartum*

No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. PREZISTA/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk (see sections 4.4, 4.6 and 5.2).

Treatment with darunavir/cobicistat 800/150 mg during pregnancy results in low darunavir exposure (see sections 4.4 and 5.2). Therefore, therapy with PREZISTA/cobicistat should not be initiated during pregnancy, and women who become pregnant during therapy with PREZISTA/cobicistat should be switched to an alternative regimen (see sections 4.4 and 4.6). PREZISTA/ritonavir may be considered as an alternative.

### Method of administration

Patients should be instructed to take PREZISTA with cobicistat or low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir (see sections 4.4, 4.5 and 5.2).

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Concomitant treatment with any of the following medicinal products given the expected decrease in plasma concentrations of darunavir, ritonavir and cobicistat and the potential for loss of therapeutic effect (see sections 4.4 and 4.5).

Applicable to darunavir boosted with either ritonavir or cobicistat:

- The combination product lopinavir/ritonavir (see section 4.5).
- The strong CYP3A inducers rifampicin and herbal preparations containing St John's wort (*Hypericum perforatum*). Co-administration is expected to reduce plasma concentrations of darunavir, ritonavir and cobicistat, which could lead to loss of therapeutic effect and possible development of resistance (see sections 4.4 and 4.5).

Applicable to darunavir boosted with cobicistat, not when boosted with ritonavir:

- Darunavir boosted with cobicistat is more sensitive for CYP3A induction than darunavir boosted with ritonavir. Concomitant use with strong CYP3A inducers is contraindicated, since these may reduce the exposure to cobicistat and darunavir leading to loss of therapeutic effect. Strong CYP3A inducers include e.g. carbamazepine, phenobarbital and phenytoin (see sections 4.4 and 4.5).

Darunavir boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the co-administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat). These active substances include e.g.:

- alfuzosin
- amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine
- astemizole, terfenadine
- colchicine when used in patients with renal and/or hepatic impairment (see section 4.5)
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- elbasvir/grazoprevir
- cisapride
- dapoxetine
- domperidone
- naloxegol
- lurasidone, pimozide, quetiapine, sertindole (see section 4.5)

- triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5)
- sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil
- simvastatin, lovastatin and lomitapide (see section 4.5)
- dabigatran, ticagrelor (see section 4.5).

#### **4.4 Special warnings and precautions for use**

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Regular assessment of virological response is advised. In the setting of lack or loss of virological response, resistance testing should be performed.

PREZISTA 400 mg or 800 mg must always be given orally with cobicistat or low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products (see section 5.2). The Summary of Product Characteristics of cobicistat or ritonavir as appropriate, must therefore be consulted prior to initiation of therapy with PREZISTA.

Increasing the dose of ritonavir from that recommended in section 4.2 did not significantly affect darunavir concentrations. It is not recommended to alter the dose of cobicistat or ritonavir.

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 (see section 4.5).

##### ART-experienced patients – once daily dosing

PREZISTA used in combination with cobicistat or low dose ritonavir once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA  $\geq 100,000$  copies/ml or CD4+ cell count  $< 100$  cells  $\times 10^6/l$  (see section 4.2). Combinations with optimised background regimen (OBRs) other than  $\geq 2$  NRTIs have not been studied in this population. Limited data are available in patients with HIV-1 clades other than B (see section 5.1).

##### Paediatric population

PREZISTA is not recommended for use in paediatric patients below 3 years of age or less than 15 kg body weight (see sections 4.2 and 5.3).

##### Pregnancy

PREZISTA/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk. Caution should be used in pregnant women with concomitant medications which may further decrease darunavir exposure (see sections 4.5 and 5.2).

Treatment with darunavir/cobicistat 800/150 mg once daily during the second and third trimester has been shown to result in low darunavir exposure, with a reduction of around 90% in  $C_{min}$  levels (see section 5.2). Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in darunavir exposure may result in virological failure and an increased risk of mother to child transmission of HIV infection. Therefore, therapy with PREZISTA/cobicistat should not be initiated during pregnancy, and women who become pregnant during therapy with PREZISTA/cobicistat should be switched to an alternative regimen (see sections 4.2 and 4.6). PREZISTA given with low dose ritonavir may be considered as an alternative.

##### 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).

#### Severe skin reactions

During the darunavir/ritonavir clinical development program (N=3,063), severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens-Johnson Syndrome has been rarely (< 0.1%) reported, and during post-marketing experience toxic epidermal necrolysis and acute generalised exanthematous pustulosis have been reported. PREZISTA should be discontinued immediately if signs or symptoms of severe skin reactions develop. These can include, but are not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash occurred more commonly in treatment-experienced patients receiving regimens containing PREZISTA/ritonavir + raltegravir compared to patients receiving PREZISTA/ritonavir without raltegravir or raltegravir without PREZISTA (see section 4.8).

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

#### Hepatotoxicity

Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA. During the darunavir/ritonavir clinical development program (N=3,063), hepatitis was reported in 0.5% of patients receiving combination antiretroviral therapy with PREZISTA/ritonavir. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

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

If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients using PREZISTA used in combination with cobicistat or low dose ritonavir, interruption or discontinuation of treatment should be considered promptly.

#### Patients with coexisting conditions

##### *Hepatic impairment*

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 hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, PREZISTA should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

##### *Renal impairment*

No special precautions or dose adjustments for darunavir/ritonavir 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). Cobicistat has not been studied in patients receiving dialysis, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients (see section 4.2).

Cobicistat decreases the estimated creatinine clearance due to inhibition of tubular secretion of creatinine. This should be taken into consideration if darunavir with cobicistat is administered to patients in whom the estimated creatinine clearance is used to adjust doses of co-administered medicinal products (see section 4.2 and cobicistat SmPC).

There are currently inadequate data to determine whether co-administration of tenofovir disoproxil and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil without cobicistat.

#### *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.

#### *Weight and metabolic parameters*

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

#### Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

#### Immune reconstitution inflammatory syndrome

In HIV infected patients with severe immune deficiency at the time of initiation 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 jirovecii* (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 low dose ritonavir.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.8).

#### Interactions with medicinal products

Several of the interaction studies have been performed with darunavir at lower than recommended doses. 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.

#### *Pharmacokinetic enhancer and concomitant medications*

Darunavir has different interaction profiles depending on whether the compound is boosted with ritonavir or cobicistat:

- Darunavir boosted with cobicistat is more sensitive for CYP3A induction: concomitant use of darunavir/cobicistat and strong CYP3A inducers is therefore contraindicated (see section 4.3),



and concomitant use with weak to moderate CYP3A inducers is not recommended (see section 4.5). Concomitant use of darunavir/ritonavir and darunavir/cobicistat with lopinavir/ritonavir, rifampicin and herbal products containing St John's wort, *Hypericum perforatum*, is contraindicated (see section 4.5).

- Unlike ritonavir, cobicistat does not have inducing effects on enzymes or transport proteins (see section 4.5). If switching the pharmacoenhancer from ritonavir to cobicistat, caution is required during the first two weeks of treatment with darunavir/cobicistat, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of ritonavir as a pharmacoenhancer. A dose reduction of the co-administered drug may be needed in these cases.

Efavirenz in combination with PREZISTA may result in sub-optimal darunavir  $C_{min}$ . If efavirenz is to be used in combination with PREZISTA, the PREZISTA/ritonavir 600/100 mg twice daily regimen should be used. See the Summary of Product Characteristics for PREZISTA 75 mg, 150 mg, 300 mg and 600 mg tablets (see section 4.5).

Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A and P-glycoprotein (P-gp; see sections 4.3 and 4.5).

PREZISTA 400 mg tablets contain sunset yellow FCF (E110) which may cause an allergic reaction.

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

The interaction profile of darunavir may differ depending on whether ritonavir or cobicistat is used as pharmacoenhancer. The recommendations given for concomitant use of darunavir and other medicinal products may therefore differ depending on whether darunavir is boosted with ritonavir or cobicistat (see sections 4.3 and 4.4), and caution is also required during the first time of treatment if switching the pharmacoenhancer from ritonavir to cobicistat (see section 4.4).

##### **Medicinal products that affect darunavir exposure (ritonavir as pharmacoenhancer)**

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 these compounds and consequently that of darunavir, leading to loss of therapeutic effect and possible development of resistance (see sections 4.3 and 4.4). CYP3A inducers that are contraindicated include rifampicin, St John's wort and lopinavir.

Co-administration of darunavir and ritonavir with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir, which may result in increased plasma concentrations of darunavir and ritonavir. Co-administration with strong CYP3A4 inhibitors is not recommended and caution is warranted, these interactions are described in the interaction table below (e.g. indinavir, azole antifungals like clotrimazole).

##### **Medicinal products that affect darunavir exposure (cobicistat as pharmacoenhancer)**

Darunavir and cobicistat are metabolised by CYP3A, and co-administration with CYP3A inducers may therefore result in subtherapeutic plasma exposure to darunavir. Darunavir boosted with cobicistat is more sensitive to CYP3A induction than ritonavir-boosted darunavir: co-administration of darunavir/cobicistat with medicinal products that are strong inducers of CYP3A (e.g. St John's wort, rifampicin, carbamazepine, phenobarbital, and phenytoin) is contraindicated (see section 4.3). Co-administration of darunavir/cobicistat with weak to moderate CYP3A inducers (e.g. efavirenz, etravirine, nevirapine, boceprevir, fluticasone, and bosentan) is not recommended (see interaction table below).

For co-administration with strong CYP3A4 inhibitors, the same recommendations apply independent of whether darunavir is boosted with ritonavir or with cobicistat (see section above).

### **Medicinal products that may be affected by darunavir boosted with ritonavir**

Darunavir and ritonavir are inhibitors of CYP3A, CYP2D6 and P-gp. Co-administration of darunavir/ritonavir with medicinal products primarily metabolised by CYP3A and/or CYP2D6 or transported by P-gp may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions.

Darunavir co-administered with low dose ritonavir must not be combined with medicinal products that are highly dependent on CYP3A for clearance and for which increased systemic exposure is associated with serious and/or life-threatening events (narrow therapeutic index) (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 twice daily. Therefore, darunavir must only be used in combination with a pharmacokinetic enhancer (see sections 4.4 and 5.2).

A clinical study utilising a cocktail of medicinal products that are metabolised by cytochromes CYP2C9, CYP2C19 and CYP2D6 demonstrated an increase in CYP2C9 and CYP2C19 activity and inhibition of CYP2D6 activity in the presence of darunavir/ritonavir, which may be attributed to the presence of low dose ritonavir. Co-administration of darunavir and ritonavir with medicinal products which are primarily metabolised by CYP2D6 (such as flecainide, propafenone, metoprolol) may result in increased plasma concentrations of these medicinal products, which could increase or prolong their therapeutic effect and adverse reactions. Co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP2C9 (such as warfarin) and CYP2C19 (such as methadone) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Although the effect on CYP2C8 has only been studied *in vitro*, co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP2C8 (such as paclitaxel, rosiglitazone, repaglinide) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Ritonavir inhibits the transporters P-glycoprotein, OATP1B1 and OATP1B3, and co-administration with substrates of these transporters can result in increased plasma concentrations of these compounds (e.g. dabigatran etexilate, digoxin, statins and bosentan; see the Interaction table below).

### **Medicinal products that may be affected by darunavir boosted with cobicistat**

The recommendations for darunavir boosted with ritonavir are adequate also for darunavir boosted with cobicistat with regard to substrates of CYP3A4, CYP2D6, P-glycoprotein, OATP1B1 and OATP1B3 (see contraindications and recommendations presented in the section above). Cobicistat 150 mg given with darunavir 800 mg once daily enhances darunavir pharmacokinetic parameters in a comparable way to ritonavir (see section 5.2).

Unlike ritonavir, cobicistat does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1. For further information on cobicistat, consult the cobicistat Summary of Product Characteristics.

### **Interaction table**

Interaction studies have only been performed in adults.

Several of the interaction studies (indicated by <sup>#</sup> in the table below) have been performed at lower than recommended doses of darunavir or with a different dosing regimen (see section 4.2 Posology). The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated.

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer. Darunavir may therefore have different recommendations for concomitant medications depending on whether the compound is boosted with ritonavir or cobicistat. No

interaction studies presented in the table have been performed with darunavir boosted with cobicistat. The same recommendations apply, unless specifically indicated. For further information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Interactions between darunavir/ritonavir and antiretroviral and non-antiretroviral medicinal products are listed in the table below. The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within ( $\leftrightarrow$ ), below ( $\downarrow$ ) or above ( $\uparrow$ ) the 80-125% range (not determined as “ND”).

In the table below the specific pharmacokinetic enhancer is specified when recommendations differ. When the recommendation is the same for PREZISTA when co-administered with a low dose ritonavir or cobicistat, the term “boosted PREZISTA” is used.

The below list of examples of drug drug interactions is not comprehensive and therefore the label of each drug that is co-administered with PREZISTA should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

| <b>INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS</b> |   |   |
|--|---|---|
| <b>Medicinal products by therapeutic areas</b>                             | <b>Interaction<br/>Geometric mean change (%)</b>  | <b>Recommendations concerning co-administration</b>   |
| <b>HIV ANTIRETROVIRALS</b>   |   |   |
| <i><b>Integrase strand transfer inhibitors</b></i>                         |   |   |
| Dolutegravir   | dolutegravir AUC $\downarrow$ 22%<br>dolutegravir $C_{24h}$ $\downarrow$ 38%<br>dolutegravir $C_{max}$ $\downarrow$ 11%<br>darunavir $\leftrightarrow$ *<br>* Using cross-study comparisons to historical pharmacokinetic data  | Boosted PREZISTA and dolutegravir can be used without dose adjustment.  |
| Raltegravir  | Some clinical studies suggest raltegravir may cause a modest decrease in darunavir plasma concentrations.   | At present the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically relevant. Boosted PREZISTA and raltegravir can be used without dose adjustments.   |
| <i><b>Nucleo(s)ide reverse transcriptase inhibitors (NRTIs)</b></i>        |   |   |
| Didanosine<br>400 mg once daily  | didanosine AUC $\downarrow$ 9%<br>didanosine $C_{min}$ ND<br>didanosine $C_{max}$ $\downarrow$ 16%<br>darunavir AUC $\leftrightarrow$<br>darunavir $C_{min}$ $\leftrightarrow$<br>darunavir $C_{max}$ $\leftrightarrow$   | Boosted PREZISTA and didanosine can be used without dose adjustments.<br>Didanosine is to be administered on an empty stomach, thus it should be administered 1 hour before or 2 hours after boosted PREZISTA given with food.  |
| Tenofovir disoproxil<br>245 mg once daily <sup>†</sup>                     | tenofovir AUC $\uparrow$ 22%<br>tenofovir $C_{min}$ $\uparrow$ 37%<br>tenofovir $C_{max}$ $\uparrow$ 24%<br># darunavir AUC $\uparrow$ 21%<br># darunavir $C_{min}$ $\uparrow$ 24%<br># darunavir $C_{max}$ $\uparrow$ 16%<br>( $\uparrow$ tenofovir from effect on MDR-1 transport in the renal tubules) | Monitoring of renal function may be indicated when boosted PREZISTA is given in combination with tenofovir disoproxil, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.<br><br>PREZISTA co-administered with cobicistat lowers the creatinine clearance. Refer to section 4.4 if creatinine clearance is used for dose adjustment of tenofovir disoproxil. |

|  |  |   |
|--|--|---|
| Emtricitabine/tenofovir alafenamide                                | Tenofovir alafenamide ↔<br>Tenofovir ↑   | The recommended dose of emtricitabine/tenofovir alafenamide is 200/10 mg once daily when used with boosted PREZISTA.  |
| Abacavir<br>Emtricitabine<br>Lamivudine<br>Stavudine<br>Zidovudine | Not studied. Based on the different elimination pathways of the other NRTIs zidovudine, emtricitabine, stavudine, lamivudine, that are primarily renally excreted, and abacavir for which metabolism is not mediated by CYP450, no interactions are expected for these medicinal compounds and boosted PREZISTA. | Boosted PREZISTA can be used with these NRTIs without dose adjustment.<br><br>PREZISTA co-administered with cobicistat lowers the creatinine clearance. Refer to section 4.4 if creatinine clearance is used for dose adjustment of emtricitabine or lamivudine.  |
| <b>Non-nucleo(s)ide reverse transcriptase inhibitors (NNRTIs)</b>  |  |   |
| Efavirenz<br>600 mg once daily                                     | efavirenz AUC ↑ 21%<br>efavirenz C <sub>min</sub> ↑ 17%<br>efavirenz C <sub>max</sub> ↑ 15%<br># darunavir AUC ↓ 13%<br># darunavir C <sub>min</sub> ↓ 31%<br># darunavir C <sub>max</sub> ↓ 15%<br>(↑ efavirenz from CYP3A inhibition)<br>(↓ darunavir from CYP3A induction)                                    | Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when PREZISTA co-administered with low dose ritonavir is given in combination with efavirenz.<br><br>Efavirenz in combination with PREZISTA/ritonavir 800/100 mg once daily may result in sub-optimal darunavir C <sub>min</sub> . If efavirenz is to be used in combination with PREZISTA/ritonavir, the PREZISTA/ritonavir 600/100 mg twice daily regimen should be used (see section 4.4).<br><br>Co-administration with PREZISTA co-administered with cobicistat is not recommended (see section 4.4). |
| Etravirine<br>100 mg twice daily                                   | etravirine AUC ↓ 37%<br>etravirine C <sub>min</sub> ↓ 49%<br>etravirine C <sub>max</sub> ↓ 32%<br>darunavir AUC ↑ 15%<br>darunavir C <sub>min</sub> ↔<br>darunavir C <sub>max</sub> ↔  | PREZISTA co-administered with low dose ritonavir and etravirine 200 mg twice daily can be used without dose adjustments.<br><br>Co-administration with PREZISTA co-administered with cobicistat is not recommended (see section 4.4).   |
| Nevirapine<br>200 mg twice daily                                   | nevirapine AUC ↑ 27%<br>nevirapine C <sub>min</sub> ↑ 47%<br>nevirapine C <sub>max</sub> ↑ 18%<br># darunavir: concentrations were consistent with historical data<br>(↑ nevirapine from CYP3A inhibition)   | PREZISTA co-administered with low dose ritonavir and nevirapine can be used without dose adjustments.<br><br>Co-administration with PREZISTA co-administered with cobicistat is not recommended (see section 4.4).  |
| Rilpivirine<br>150 mg once daily                                   | rilpivirine AUC ↑ 130%<br>rilpivirine C <sub>min</sub> ↑ 178%<br>rilpivirine C <sub>max</sub> ↑ 79%<br>darunavir AUC ↔<br>darunavir C <sub>min</sub> ↓ 11%<br>darunavir C <sub>max</sub> ↔   | Boosted PREZISTA and rilpivirine can be used without dose adjustments.  |

| <b>HIV Protease inhibitors (PIs) - without additional co-administration of low dose ritonavir<sup>†</sup></b> |   |   |
|---|---|---|
| Atazanavir<br>300 mg once daily   | <p>atazanavir AUC ↔<br/>           atazanavir C<sub>min</sub> ↑ 52%<br/>           atazanavir C<sub>max</sub> ↓ 11%<br/>           # darunavir AUC ↔<br/>           # darunavir C<sub>min</sub> ↔<br/>           # darunavir C<sub>max</sub> ↔</p> <p>Atazanavir: comparison of atazanavir/ritonavir 300/100 mg once daily vs. atazanavir 300 mg once daily in combination with darunavir/ritonavir 400/100 mg twice daily.<br/>           Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg twice daily in combination with atazanavir 300 mg once daily.</p> | <p>PREZISTA co-administered with low dose ritonavir and atazanavir can be used without dose adjustments.</p> <p>PREZISTA co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5).</p>   |
| Indinavir<br>800 mg twice daily   | <p>indinavir AUC ↑ 23%<br/>           indinavir C<sub>min</sub> ↑ 125%<br/>           indinavir C<sub>max</sub> ↔<br/>           # darunavir AUC ↑ 24%<br/>           # darunavir C<sub>min</sub> ↑ 44%<br/>           # darunavir C<sub>max</sub> ↑ 11%</p> <p>Indinavir: comparison of indinavir/ritonavir 800/100 mg twice daily vs. indinavir/darunavir/ritonavir 800/400/100 mg twice daily.<br/>           Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with indinavir 800 mg twice daily.</p>                                       | <p>When used in combination with PREZISTA co-administered with low dose ritonavir, dose adjustment of indinavir from 800 mg twice daily to 600 mg twice daily may be warranted in case of intolerance.</p> <p>PREZISTA co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5).</p> |
| Saquinavir<br>1,000 mg twice daily  | <p># darunavir AUC ↓ 26%<br/>           # darunavir C<sub>min</sub> ↓ 42%<br/>           # darunavir C<sub>max</sub> ↓ 17%<br/>           saquinavir AUC ↓ 6%<br/>           saquinavir C<sub>min</sub> ↓ 18%<br/>           saquinavir C<sub>max</sub> ↓ 6%</p> <p>Saquinavir: comparison of saquinavir/ritonavir 1,000/100 mg twice daily vs. saquinavir/darunavir/ritonavir 1,000/400/100 mg twice daily<br/>           Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with saquinavir 1,000 mg twice daily.</p>                          | <p>It is not recommended to combine PREZISTA co-administered with low dose ritonavir with saquinavir.</p> <p>PREZISTA co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5).</p>  |

| HIV Protease inhibitors (PIs) - with co-administration of low dose ritonavir <sup>†</sup> |  |  |
|---|--|--|
| Lopinavir/ritonavir<br>400/100 mg twice daily   | lopinavir AUC ↑ 9%<br>lopinavir C <sub>min</sub> ↑ 23%<br>lopinavir C <sub>max</sub> ↓ 2%<br>darunavir AUC ↓ 38% <sup>‡</sup><br>darunavir C <sub>min</sub> ↓ 51% <sup>‡</sup><br>darunavir C <sub>max</sub> ↓ 21% <sup>‡</sup>              | Due to a decrease in the exposure (AUC) of darunavir by 40%, appropriate doses of the combination have not been established. Hence, concomitant use of boosted PREZISTA and the combination product lopinavir/ritonavir is contraindicated (see section 4.3).  |
| Lopinavir/ritonavir<br>533/133.3 mg twice daily   | lopinavir AUC ↔<br>lopinavir C <sub>min</sub> ↑ 13%<br>lopinavir C <sub>max</sub> ↑ 11%<br>darunavir AUC ↓ 41%<br>darunavir C <sub>min</sub> ↓ 55%<br>darunavir C <sub>max</sub> ↓ 21%<br><sup>‡</sup> based upon non dose normalised values |  |
| CCR5 ANTAGONIST   |  |  |
| Maraviroc<br>150 mg twice daily   | maraviroc AUC ↑ 305%<br>maraviroc C <sub>min</sub> ND<br>maraviroc C <sub>max</sub> ↑ 129%<br>darunavir, ritonavir concentrations were consistent with historical data   | The maraviroc dose should be 150 mg twice daily when co-administered with boosted PREZISTA.  |
| α1-ADRENORECEPTOR ANTAGONIST  |  |  |
| Alfuzosin   | Based on theoretical considerations PREZISTA is expected to increase alfuzosin plasma concentrations. (CYP3A inhibition)   | Co-administration of boosted PREZISTA and alfuzosin is contraindicated (see section 4.3).  |
| ANAESTHETIC   |  |  |
| Alfentanil  | Not studied. The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by boosted PREZISTA.   | The concomitant use with boosted PREZISTA may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.  |
| ANTIANGINA/ANTIARRHYTHMIC   |  |  |
| Disopyramide<br>Flecainide<br>Lidocaine (systemic)<br>Mexiletine<br>Propafenone           | Not studied. Boosted PREZISTA is expected to increase these antiarrhythmic plasma concentrations. (CYP3A and/or CYP2D6 inhibition)   | Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with boosted PREZISTA.  |
| Amiodarone<br>Bepridil<br>Dronedarone<br>Ivabradine<br>Quinidine<br>Ranolazine            |  | Co-administration of boosted PREZISTA and amiodarone, bepridil, dronedarone, ivabradine, quinidine, or ranolazine is contraindicated (see section 4.3).  |
| Digoxin<br>0.4 mg single dose   | digoxin AUC ↑ 61%<br>digoxin C <sub>min</sub> ND<br>digoxin C <sub>max</sub> ↑ 29%<br>(↑ digoxin from probable inhibition of P-gp)   | 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 boosted PREZISTA therapy. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject |

| <b>ANTIBIOTIC</b>                                   |   |  |
|---|---|--|
| Clarithromycin<br>500 mg twice daily                | clarithromycin AUC ↑ 57%<br>clarithromycin C <sub>min</sub> ↑ 174%<br>clarithromycin C <sub>max</sub> ↑ 26%<br>#darunavir AUC ↓ 13%<br>#darunavir C <sub>min</sub> ↑ 1%<br>#darunavir C <sub>max</sub> ↓ 17%<br>14-OH-clarithromycin concentrations were not detectable when combined with PREZISTA/ritonavir.<br>(↑ clarithromycin from CYP3A inhibition and possible P-gp inhibition) | Caution should be exercised when clarithromycin is combined with boosted PREZISTA.<br><br>For patients with renal impairment the Summary of Product Characteristics for clarithromycin should be consulted for the recommended dose. |
| <b>ANTICOAGULANT/PLATELET AGGREGATION INHIBITOR</b> |   |  |
| Apixaban<br>Edoxaban<br>Rivaroxaban                 | Not studied. Co-administration of boosted PREZISTA with these anticoagulants may increase concentrations of the anticoagulant, which may lead to an increased bleeding risk.<br>(CYP3A and/or P-gp inhibition)  | The use of boosted PREZISTA and these anticoagulants is not recommended.   |
| Dabigatran<br>Ticagrelor                            | Not studied. Co-administration with boosted PREZISTA may lead to a substantial increase in exposure to dabigatran or ticagrelor.  | Concomitant administration of boosted PREZISTA with dabigatran or ticagrelor is contraindicated (see section 4.3).<br><br>Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended.    |
| Warfarin  | Not studied. Warfarin concentrations may be affected when co-administered with boosted PREZISTA.  | It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with boosted PREZISTA.  |
| <b>ANTICONVULSANTS</b>                              |   |  |
| Phenobarbital<br>Phenytoin                          | Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir and its pharmacoenhancer.<br>(induction of CYP450 enzymes)   | PREZISTA co-administered with low dose ritonavir should not be used in combination with these medicines.<br><br>The use of these medicines with PREZISTA/cobicistat is contraindicated (see section 4.3).                            |

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| Carbamazepine<br>200 mg twice daily  | carbamazepine AUC ↑ 45%<br>carbamazepine C <sub>min</sub> ↑ 54%<br>carbamazepine C <sub>max</sub> ↑ 43%<br>darunavir AUC ↔<br>darunavir C <sub>min</sub> ↓ 15%<br>darunavir C <sub>max</sub> ↔   | No dose adjustment for PREZISTA/ritonavir is recommended. If there is a need to combine PREZISTA/ritonavir and carbamazepine, patients should be monitored for potential carbamazepine-related adverse events. Carbamazepine concentrations should be monitored and its dose should be titrated for adequate response. Based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of PREZISTA/ritonavir.<br><br>The use of carbamazepine with PREZISTA co-administered with cobicistat is contraindicated (see section 4.3). |
| Clonazepam   | Not studied. Co-administration of boosted PREZISTA with clonazepam may increase concentrations of clonazepam. (CYP3A inhibition)   | Clinical monitoring is recommended when co-administering boosted PREZISTA and clonazepam.  |
| <b>ANTIDEPRESSANTS</b>   |  |  |
| Paroxetine<br>20 mg once daily<br><br>Sertraline<br>50 mg once daily<br><br>Amitriptyline<br>Desipramine<br>Imipramine<br>Nortriptyline<br>Trazodone | paroxetine AUC ↓ 39%<br>paroxetine C <sub>min</sub> ↓ 37%<br>paroxetine C <sub>max</sub> ↓ 36%<br>#darunavir AUC ↔<br>#darunavir C <sub>min</sub> ↔<br>#darunavir C <sub>max</sub> ↔<br>sertraline AUC ↓ 49%<br>sertraline C <sub>min</sub> ↓ 49%<br>sertraline C <sub>max</sub> ↓ 44%<br>#darunavir AUC ↔<br>#darunavir C <sub>min</sub> ↓ 6%<br>#darunavir C <sub>max</sub> ↔<br><br>In contrast to these data with PREZISTA/ritonavir, PREZISTA/cobicistat may increase these antidepressant plasma concentrations (CYP2D6 and/or CYP3A inhibition).<br><br>Concomitant use of boosted PREZISTA and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or CYP3A inhibition) | If antidepressants are co-administered with boosted PREZISTA, the recommended approach is a dose titration of the antidepressant based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of these antidepressants who start treatment with boosted PREZISTA should be monitored for antidepressant response.<br><br>Clinical monitoring is recommended when co-administering boosted PREZISTA with these antidepressants and a dose adjustment of the antidepressant may be needed.  |
| <b>ANTI-DIABETICS</b>  |  |  |
| Metformin  | Not studied. Based on theoretical considerations PREZISTA co-administered with cobicistat is expected to increase metformin plasma concentrations. (MATE1 inhibition)  | Careful patient monitoring and dose adjustment of metformin is recommended in patients who are taking PREZISTA co-administered with cobicistat. (not applicable for PREZISTA co-administered with ritonavir)   |



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| <b>ANTIEMETICS</b>   |  |  |
| Domperidone  | Not studied.   | Co-administration of domperidone with boosted PREZISTA is contraindicated.   |
| <b>ANTIFUNGALS</b>   |  |  |
| Voriconazole   | <p>Not studied. Ritonavir may decrease plasma concentrations of voriconazole. (induction of CYP450 enzymes)</p> <p>Concentrations of voriconazole may increase or decrease when co-administered with PREZISTA co-administered with cobicistat. (inhibition of CYP450 enzymes)</p>  | Voriconazole should not be combined with boosted PREZISTA unless an assessment of the benefit/risk ratio justifies the use of voriconazole.  |
| Fluconazole<br>Isavuconazole<br>Itraconazole<br>Posaconazole<br><br>Clotrimazole | <p>Not studied. Boosted PREZISTA may increase antifungal plasma concentrations and posaconazole, isavuconazole, itraconazole or fluconazole may increase darunavir concentrations. (CYP3A and/or P-gp inhibition)</p> <p>Not studied. Concomitant systemic use of clotrimazole and boosted PREZISTA may increase plasma concentrations of darunavir and/or clotrimazole. darunavir AUC<sub>24h</sub> ↑ 33% (based on population pharmacokinetic model)</p> | <p>Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of itraconazole should not exceed 200 mg.</p>  |
| <b>ANTIGOUT MEDICINES</b>  |  |  |
| Colchicine   | Not studied. Concomitant use of colchicine and boosted PREZISTA may increase the exposure to colchicine. (CYP3A and/ or P-gp inhibition)   | A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with boosted PREZISTA is required. For patients with renal or hepatic impairment colchicine with boosted PREZISTA is contraindicated (see sections 4.3 and 4.4). |
| <b>ANTIMALARIALS</b>   |  |  |
| Artemether/Lumefantrine<br>80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours  | artemether AUC ↓ 16%<br>artemether C <sub>min</sub> ↔<br>artemether C <sub>max</sub> ↓ 18%<br>dihydroartemisinin AUC ↓ 18%<br>dihydroartemisinin C <sub>min</sub> ↔<br>dihydroartemisinin C <sub>max</sub> ↓ 18%<br>lumefantrine AUC ↑ 175%<br>lumefantrine C <sub>min</sub> ↑ 126%<br>lumefantrine C <sub>max</sub> ↑ 65%<br>darunavir AUC ↔<br>darunavir C <sub>min</sub> ↓ 13%<br>darunavir C <sub>max</sub> ↔  | The combination of boosted PREZISTA and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.  |

| ANTIMYCOBACTERIALS                                   |  |  |
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| Rifampicin<br>Rifapentine                            | Not studied. Rifapentine and rifampicin are strong CYP3A inducers and have been shown to cause profound decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction). During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with low dose ritonavir, a high frequency of liver reactions was seen with rifampicin.  | <p>The combination of rifapentine and boosted PREZISTA is not recommended.</p> <p>The combination of rifampicin and boosted PREZISTA is contraindicated (see section 4.3).</p>   |
| Rifabutin<br>150 mg once every other day             | <p>rifabutin AUC<sup>**</sup> ↑ 55%<br/> rifabutin C<sub>min</sub><sup>**</sup> ↑ ND<br/> rifabutin C<sub>max</sub><sup>**</sup> ↔<br/> darunavir AUC ↑ 53%<br/> darunavir C<sub>min</sub> ↑ 68%<br/> darunavir C<sub>max</sub> ↑ 39%<br/> <sup>**</sup> sum of active moieties of rifabutin (parent drug + 25-<i>O</i>-desacetyl metabolite)</p> <p>The interaction trial showed a comparable daily systemic exposure for rifabutin between treatment at 300 mg once daily alone and 150 mg once every other day in combination with PREZISTA/ritonavir (600/100 mg twice daily) with an about 10-fold increase in the daily exposure to the active metabolite 25-<i>O</i>-desacetyl rifabutin. Furthermore, AUC of the sum of active moieties of rifabutin (parent drug + 25-<i>O</i>-desacetyl metabolite) was increased 1.6-fold, while C<sub>max</sub> remained comparable.</p> <p>Data on comparison with a 150 mg once daily reference dose is lacking.</p> <p>(Rifabutin is an inducer and substrate of CYP3A.) An increase of systemic exposure to darunavir was observed when PREZISTA co-administered with 100 mg ritonavir was co-administered with rifabutin (150 mg once every other day).</p> | <p>A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg once every other day) and increased monitoring for rifabutin related adverse events is warranted in patients receiving the combination with PREZISTA co-administered with ritonavir. In case of safety issues, a further increase of the dosing interval for rifabutin and/or monitoring of rifabutin levels should be considered.</p> <p>Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients.</p> <p>Based upon the safety profile of PREZISTA/ritonavir, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for PREZISTA/ritonavir.</p> <p>Based on pharmacokinetic modeling, this dosage reduction of 75% is also applicable if patients receive rifabutin at doses other than 300 mg/day.</p> <p>Co-administration of PREZISTA co-administered with cobicistat and rifabutin is not recommended.</p> |
| ANTINEOPLASTICS                                      |  |  |
| Dasatinib<br>Nilotinib<br>Vinblastine<br>Vincristine | Not studied. Boosted PREZISTA is expected to increase these antineoplastic plasma concentrations. (CYP3A inhibition)   | <p>Concentrations of these medicinal products may be increased when co-administered with boosted PREZISTA resulting in the potential for increased adverse events usually associated with these agents.</p> <p>Caution should be exercised when combining one of these antineoplastic agents with boosted PREZISTA.</p>  |
| Everolimus<br>Irinotecan                             |  | Concomitant use of everolimus or irinotecan and boosted PREZISTA is not recommended.   |

| <b>ANTIPSYCHOTICS/NEUROLEPTICS</b>   |   |  |
|--|---|--|
| Quetiapine   | Not studied. Boosted PREZISTA is expected to increase these antipsychotic plasma concentrations.<br>(CYP3A inhibition)  | Concomitant administration of boosted PREZISTA and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased concentrations of quetiapine may lead to coma (see section 4.3).  |
| Perphenazine<br>Risperidone<br>Thioridazine<br><br>Lurasidone<br>Pimozide<br>Sertindole  | Not studied. Boosted PREZISTA is expected to increase these antipsychotic plasma concentrations.<br>(CYP3A, CYP2D6 and/or P-gp inhibition)  | A dose decrease may be needed for these drugs when co-administered with boosted PREZISTA.<br><br>Concomitant administration of boosted PREZISTA and lurasidone, pimozide or sertindole is contraindicated (see section 4.3).   |
| <b>β-BLOCKERS</b>  |   |  |
| Carvedilol<br>Metoprolol<br>Timolol  | Not studied. Boosted PREZISTA is expected to increase these β-blocker plasma concentrations.<br>(CYP2D6 inhibition)   | Clinical monitoring is recommended when co-administering boosted PREZISTA with β-blockers. A lower dose of the β-blocker should be considered.   |
| <b>CALCIUM CHANNEL BLOCKERS</b>  |   |  |
| Amlodipine<br>Diltiazem<br>Felodipine<br>Nicardipine<br>Nifedipine<br>Verapamil  | Not studied. Boosted PREZISTA can be expected to increase the plasma concentrations of calcium channel blockers.<br>(CYP3A and/or CYP2D6 inhibition)  | Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with boosted PREZISTA.   |
| <b>CORTICOSTEROIDS</b>   |   |  |
| Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone) | Fluticasone: in a clinical study where ritonavir 100 mg capsules twice daily 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% CI 82-89%). Greater effects may be expected when fluticasone 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. The effects of high fluticasone systemic exposure on ritonavir plasma levels are unknown.<br><br>Other corticosteroids: interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with boosted PREZISTA, resulting in reduced serum cortisol concentrations. | Concomitant use of boosted PREZISTA and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.<br>Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects.<br>Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long term use. |
| Dexamethasone (systemic)   | Not studied. Dexamethasone may decrease plasma concentrations of darunavir.<br>(CYP3A induction)  | Systemic dexamethasone should be used with caution when combined with boosted PREZISTA.  |

| <b>ENDOTHELIN RECEPTOR ANTAGONISTS</b>                  |   |  |
|---|---|--|
| Bosentan  | Not studied. Concomitant use of bosentan and boosted PREZISTA may increase plasma concentrations of bosentan. Bosentan is expected to decrease plasma concentrations of darunavir and/or its pharmacoenhancer. (CYP3A induction)  | When administered concomitantly with PREZISTA and low dose ritonavir, the patient's tolerability of bosentan should be monitored.<br><br>Co-administration of PREZISTA co-administered with cobicistat and bosentan is not recommended.  |
| <b>HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS</b> |   |  |
| <b>NS3-4A protease inhibitors</b>                       |   |  |
| Elbasvir/grazoprevir                                    | Boosted PREZISTA may increase the exposure to grazoprevir. (CYP3A and OATP1B inhibition)  | Concomitant use of boosted PREZISTA and elbasvir/grazoprevir is contraindicated (see section 4.3).   |
| Boceprevir<br>800 mg three times daily                  | boceprevir AUC ↓ 32%<br>boceprevir C <sub>min</sub> ↓ 35%<br>boceprevir C <sub>max</sub> ↓ 25%<br>darunavir AUC ↓ 44%<br>darunavir C <sub>min</sub> ↓ 59%<br>darunavir C <sub>max</sub> ↓ 36%   | It is not recommended to co-administer boosted PREZISTA and boceprevir.  |
| Glecaprevir/pibrentasvir                                | Based on theoretical considerations boosted PREZISTA may increase the exposure to glecaprevir and pibrentasvir. (P-gp, BCRP and/or OATP1B1/3 inhibition)  | It is not recommended to co-administer boosted PREZISTA with glecaprevir/pibrentasvir.   |
| Simeprevir  | simeprevir AUC ↑ 159%<br>simeprevir C <sub>min</sub> ↑ 358%<br>simeprevir C <sub>max</sub> ↑ 79%<br>darunavir AUC ↑ 18%<br>darunavir C <sub>min</sub> ↑ 31%<br>darunavir C <sub>max</sub> ↔<br><br>The dose of simeprevir in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir, compared to 150 mg in the simeprevir alone treatment group. | It is not recommended to co-administer boosted PREZISTA and simeprevir.  |
| <b>HERBAL PRODUCTS</b>                                  |   |  |
| St John's wort<br>( <i>Hypericum perforatum</i> )       | Not studied. St John's wort is expected to decrease the plasma concentrations of darunavir or its pharmacoenhancers. (CYP450 induction)   | Boosted PREZISTA must not be used concomitantly with products containing St John's wort ( <i>Hypericum perforatum</i> ) (see section 4.3). 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. |
| <b>HMG CO-A REDUCTASE INHIBITORS</b>                    |   |  |
| Lovastatin<br>Simvastatin                               | Not studied. Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with boosted PREZISTA. (CYP3A inhibition)  | Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of boosted PREZISTA with lovastatin and simvastatin is therefore contraindicated (see section 4.3).   |

|  |  |   |
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| Atorvastatin<br>10 mg once daily                         | atorvastatin AUC ↑ 3-4 fold<br>atorvastatin C <sub>min</sub> ↑ ≈5.5-10 fold<br>atorvastatin C <sub>max</sub> ↑ ≈2 fold<br># darunavir/ritonavir<br><br>atorvastatin AUC ↑ 290% <sup>Ω</sup><br>atorvastatin C <sub>max</sub> ↑ 319% <sup>Ω</sup><br>atorvastatin C <sub>min</sub> ND <sup>Ω</sup><br><sup>Ω</sup> with darunavir/cobicistat 800/150 mg             | When administration of atorvastatin and boosted PREZISTA is desired, it is recommended to start with an atorvastatin dose of 10 mg once daily. A gradual dose increase of atorvastatin may be tailored to the clinical response.    |
| Pravastatin<br>40 mg single dose                         | pravastatin AUC ↑ 81% <sup>¶</sup><br>pravastatin C <sub>min</sub> ND<br>pravastatin C <sub>max</sub> ↑ 63%<br><sup>¶</sup> an up to five-fold increase was seen in a limited subset of subjects   | When administration of pravastatin and boosted PREZISTA is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effect while monitoring for safety.             |
| Rosuvastatin<br>10 mg once daily                         | rosuvastatin AUC ↑ 48% <sup>  </sup><br>rosuvastatin C <sub>max</sub> ↑ 144% <sup>  </sup><br><sup>  </sup> based on published data with darunavir/ritonavir<br><br>rosuvastatin AUC ↑ 93% <sup>§</sup><br>rosuvastatin C <sub>max</sub> ↑ 277% <sup>§</sup><br>rosuvastatin C <sub>min</sub> ND <sup>§</sup><br><sup>§</sup> with darunavir/cobicistat 800/150 mg | When administration of rosuvastatin and boosted PREZISTA is required, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.           |
| <b>OTHER LIPID MODIFYING AGENTS</b>                      |  |   |
| Lomitapide   | Based on theoretical considerations boosted PREZISTA is expected to increase the exposure of lomitapide when co-administered.<br>(CYP3A inhibition)  | Co-administration is contraindicated (see section 4.3)  |
| <b>H<sub>2</sub>-RECEPTOR ANTAGONISTS</b>                |  |   |
| Ranitidine<br>150 mg twice daily                         | # darunavir AUC ↔<br># darunavir C <sub>min</sub> ↔<br># darunavir C <sub>max</sub> ↔  | Boosted PREZISTA can be co-administered with H <sub>2</sub> -receptor antagonists without dose adjustments.   |
| <b>IMMUNOSUPPRESSANTS</b>                                |  |   |
| Cyclosporin<br>Sirolimus<br>Tacrolimus<br><br>Everolimus | Not studied. Exposure to these immunosuppressants will be increased when co-administered with boosted PREZISTA.<br>(CYP3A inhibition)  | Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs.<br><br>Concomitant use of everolimus and boosted PREZISTA is not recommended.  |
| <b>INHALED BETA AGONISTS</b>                             |  |   |
| Salmeterol   | Not studied. Concomitant use of salmeterol and boosted darunavir may increase plasma concentrations of salmeterol.   | Concomitant use of salmeterol and boosted PREZISTA is not recommended. The combination may result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia. |

| <b>NARCOTIC ANALGESICS / TREATMENT OF OPIOID DEPENDENCE</b>                |  |  |
|--|--|--|
| Methadone<br>individual dose ranging<br>from 55 mg to 150 mg<br>once daily | R(-) methadone AUC ↓ 16%<br>R(-) methadone C <sub>min</sub> ↓ 15%<br>R(-) methadone C <sub>max</sub> ↓ 24%<br><br>PREZISTA/cobicistat may, in contrast,<br>increase methadone plasma<br>concentrations (see cobicistat SmPC).  | No adjustment of methadone<br>dosage is required when initiating<br>co-administration with boosted<br>PREZISTA. However, adjustment<br>of the methadone dose may be<br>necessary when concomitantly<br>administered for a longer period of<br>time. Therefore, clinical<br>monitoring is recommended, as<br>maintenance therapy may need to<br>be adjusted in some patients. |
| Buprenorphine/naloxone<br>8/2 mg–16/4 mg once<br>daily                     | buprenorphine AUC ↓ 11%<br>buprenorphine C <sub>min</sub> ↔<br>buprenorphine C <sub>max</sub> ↓ 8%<br>norbuprenorphine AUC ↑ 46%<br>norbuprenorphine C <sub>min</sub> ↑ 71%<br>norbuprenorphine C <sub>max</sub> ↑ 36%<br>naloxone AUC ↔<br>naloxone C <sub>min</sub> ND<br>naloxone C <sub>max</sub> ↔  | The clinical relevance of the<br>increase in norbuprenorphine<br>pharmacokinetic parameters has<br>not been established. Dose<br>adjustment for buprenorphine may<br>not be necessary when<br>co-administered with boosted<br>PREZISTA but a careful clinical<br>monitoring for signs of opiate<br>toxicity is recommended.  |
| Fentanyl<br>Oxycodone<br>Tramadol  | Based on theoretical considerations<br>boosted PREZISTA may increase plasma<br>concentrations of these analgesics.<br>(CYP2D6 and/or CYP3A inhibition)   | Clinical monitoring is<br>recommended when<br>co-administering boosted<br>PREZISTA with these analgesics.  |
| <b>OESTROGEN-BASED CONTRACEPTIVES</b>                                      |  |  |
| Drospirenone<br>Ethinylestradiol<br>(3 mg/0.02 mg once<br>daily)           | drospirenone AUC ↑ 58% <sup>ε</sup><br>drospirenone C <sub>min</sub> ND <sup>ε</sup><br>drospirenone C <sub>max</sub> ↑ 15% <sup>ε</sup><br>ethinylestradiol AUC ↓ 30% <sup>ε</sup><br>ethinylestradiol C <sub>min</sub> ND <sup>ε</sup><br>ethinylestradiol C <sub>max</sub> ↓ 14% <sup>ε</sup><br><sup>ε</sup> with darunavir/cobicistat     | When PREZISTA is co-<br>administered with a drospirenone-<br>containing product, clinical<br>monitoring is recommended due to<br>the potential for hyperkalaemia.  |
| Ethinylestradiol<br>Norethindrone<br>35 µg/1 mg once daily                 | ethinylestradiol AUC ↓ 44% <sup>β</sup><br>ethinylestradiol C <sub>min</sub> ↓ 62% <sup>β</sup><br>ethinylestradiol C <sub>max</sub> ↓ 32% <sup>β</sup><br>norethindrone AUC ↓ 14% <sup>β</sup><br>norethindrone C <sub>min</sub> ↓ 30% <sup>β</sup><br>norethindrone C <sub>max</sub> ↔ <sup>β</sup><br><sup>β</sup> with darunavir/ritonavir | Alternative or additional<br>contraceptive measures are<br>recommended when<br>oestrogen-based contraceptives are<br>co-administered with boosted<br>PREZISTA. Patients using<br>oestrogens as hormone<br>replacement therapy should be<br>clinically monitored for signs of<br>oestrogen deficiency.  |
| <b>OPIOID ANTAGONIST</b>   |  |  |
| Naloxegol  | Not studied.   | Co-administration of boosted<br>PREZISTA and naloxegol is<br>contraindicated.  |

| <b>PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS</b>  |   |  |
|--|---|--|
| For the treatment of erectile dysfunction<br>Avanafil<br>Sildenafil<br>Tadalafil<br>Vardenafil | In an interaction study <sup>#</sup> , 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 and low dose ritonavir. | The combination of avanafil and boosted PREZISTA is contraindicated (see section 4.3). Concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with boosted PREZISTA should be done with caution. If concomitant use of boosted PREZISTA with sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended.  |
| For the treatment of pulmonary arterial hypertension<br>Sildenafil<br>Tadalafil                | Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and boosted PREZISTA may increase plasma concentrations of sildenafil or tadalafil. (CYP3A inhibition)                           | A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with boosted PREZISTA has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope). Therefore, co-administration of boosted PREZISTA and sildenafil when used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3). Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with boosted PREZISTA is not recommended. |
| <b>PROTON PUMP INHIBITORS</b>  |   |  |
| Omeprazole<br>20 mg once daily   | <sup>#</sup> darunavir AUC ↔<br><sup>#</sup> darunavir C <sub>min</sub> ↔<br><sup>#</sup> darunavir C <sub>max</sub> ↔  | Boosted PREZISTA can be co-administered with proton pump inhibitors without dose adjustments.  |





during pregnancy, and women who become pregnant during therapy with PREZISTA/cobicistat should be switched to an alternative regimen (see sections 4.2 and 4.4).

#### Breast-feeding

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 (1,000 mg/kg/day) resulted in toxicity. Because of both the potential for HIV transmission and the potential for adverse reactions in breast-fed infants, mothers should be instructed not to breast-feed under any circumstances 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**

PREZISTA in combination with cobicistat or ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing PREZISTA co-administered with cobicistat or low dose 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**

#### Summary of the safety profile

During the clinical development program (N=2,613 treatment-experienced subjects who initiated therapy with PREZISTA/ritonavir 600/100 mg twice daily), 51.3% of subjects experienced at least one adverse reaction. The total mean treatment duration for subjects was 95.3 weeks. The most frequent adverse reactions reported in clinical trials and as spontaneous reports are diarrhoea, nausea, rash, headache and vomiting. The most frequent serious reactions are acute renal failure, myocardial infarction, immune reconstitution inflammatory syndrome, thrombocytopenia, osteonecrosis, diarrhoea, hepatitis and pyrexia.

In the 96 week analysis, the safety profile of PREZISTA/ritonavir 800/100 mg once daily in treatment-naïve subjects was similar to that seen with PREZISTA/ritonavir 600/100 mg twice daily in treatment-experienced subjects except for nausea which was observed more frequently in treatment-naïve subjects. This was driven by mild intensity nausea. No new safety findings were identified in the 192 week analysis of the treatment-naïve subjects in which the mean treatment duration of PREZISTA/ritonavir 800/100 mg once daily was 162.5 weeks.

During the Phase III clinical trial GS-US-216-130 with darunavir/cobicistat (N=313 treatment-naïve and treatment-experienced subjects), 66.5% of subjects experienced at least one adverse reaction. The mean treatment duration was 58.4 weeks. The most frequent adverse reactions reported were diarrhoea (28%), nausea (23%), and rash (16%). Serious adverse reactions are diabetes mellitus, (drug) hypersensitivity, immune reconstitution inflammatory syndrome, rash and vomiting.

For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

#### Tabulated list of adverse reactions

Adverse reactions are listed by system organ class (SOC) and frequency category. Within each frequency category, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as follows: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and not known (frequency cannot be estimated from the available data).

*Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing*

| MedDRA system organ class<br>Frequency category | Adverse reaction  |
|---|---|
| <i>Infections and infestations</i>              |   |
| uncommon  | herpes simplex  |
| <i>Blood and lymphatic system disorders</i>     |   |
| uncommon  | thrombocytopenia, neutropenia, anaemia, leukopenia  |
| rare  | increased eosinophil count  |
| <i>Immune system disorders</i>                  |   |
| uncommon  | immune reconstitution inflammatory syndrome, (drug) hypersensitivity  |
| <i>Endocrine disorders</i>                      |   |
| uncommon  | hypothyroidism, increased blood thyroid stimulating hormone   |
| <i>Metabolism and nutrition disorders</i>       |   |
| common  | diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia  |
| uncommon  | gout, anorexia, decreased appetite, decreased weight, increased weight, hyperglycaemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase |
| <i>Psychiatric disorders</i>                    |   |
| common  | insomnia  |
| uncommon  | depression, disorientation, anxiety, sleep disorder, abnormal dreams, nightmare, decreased libido   |
| rare  | confusional state, altered mood, restlessness   |
| <i>Nervous system disorders</i>                 |   |
| common  | headache, peripheral neuropathy, dizziness  |
| uncommon  | lethargy, paraesthesia, hypoaesthesia, dysgeusia, disturbance in attention, memory impairment, somnolence   |
| rare  | syncope, convulsion, ageusia, sleep phase rhythm disturbance  |
| <i>Eye disorders</i>                            |   |
| uncommon  | conjunctival hyperaemia, dry eye  |
| rare  | visual disturbance  |
| <i>Ear and labyrinth disorders</i>              |   |
| uncommon  | vertigo   |
| <i>Cardiac disorders</i>                        |   |
| uncommon  | myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia   |
| rare  | acute myocardial infarction, sinus bradycardia, palpitations  |

|  |   |
|--|---|
| <i>Vascular disorders</i>                              |   |
| uncommon   | hypertension, flushing  |
| <i>Respiratory, thoracic and mediastinal disorders</i> |   |
| uncommon   | dyspnoea, cough, epistaxis, throat irritation   |
| rare   | rhinorrhoea   |
| <i>Gastrointestinal disorders</i>                      |   |
| very common  | diarrhoea   |
| common   | vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence  |
| uncommon   | pancreatitis, gastritis, gastrooesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia  |
| rare   | stomatitis, haematemesis, cheilitis, dry lip, coated tongue   |
| <i>Hepatobiliary disorders</i>                         |   |
| common   | increased alanine aminotransferase  |
| uncommon   | hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-glutamyltransferase |
| <i>Skin and subcutaneous tissue disorders</i>          |   |
| common   | rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus  |
| uncommon   | angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation  |
| rare   | DRESS, Stevens-Johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma  |
| not known  | toxic epidermal necrolysis, acute generalised exanthematous pustulosis  |
| <i>Musculoskeletal and connective tissue disorders</i> |   |
| uncommon   | myalgia, osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphokinase   |
| rare   | musculoskeletal stiffness, arthritis, joint stiffness   |
| <i>Renal and urinary disorders</i>                     |   |
| uncommon   | acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria   |
| rare   | decreased creatinine renal clearance  |

|   |  |
|---|--|
| <i>Reproductive system and breast disorders</i>             |  |
| uncommon  | erectile dysfunction, gynaecomastia  |
| <i>General disorders and administration site conditions</i> |  |
| common  | asthenia, fatigue  |
| uncommon  | pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain |
| rare  | chills, abnormal feeling, xerosis  |

*Adverse reactions observed with darunavir/cobicistat in adult patients*

| MedDRA system organ class<br>Frequency category        | Adverse reaction   |
|--|--|
| <i>Immune system disorders</i>                         |  |
| common   | (drug) hypersensitivity  |
| uncommon   | immune reconstitution inflammatory syndrome  |
| <i>Metabolism and nutrition disorders</i>              |  |
| common   | anorexia, diabetes mellitus, hypercholesterolaemia, hypertriglyceridaemia, hyperlipidaemia                               |
| <i>Psychiatric disorders</i>                           |  |
| common   | abnormal dreams  |
| <i>Nervous system disorders</i>                        |  |
| very common  | headache   |
| <i>Gastrointestinal disorders</i>                      |  |
| very common  | diarrhoea, nausea  |
| common   | vomiting, abdominal pain, abdominal distension, dyspepsia, flatulence, pancreatic enzymes increased                      |
| uncommon   | pancreatitis acute   |
| <i>Hepatobiliary disorders</i>                         |  |
| common   | hepatic enzyme increased   |
| uncommon   | hepatitis*, cytolytic hepatitis*   |
| <i>Skin and subcutaneous tissue disorders</i>          |  |
| very common  | rash (including macular, maculopapular, papular, erythematous, pruritic rash, generalised rash, and allergic dermatitis) |
| common   | angioedema, pruritus, urticaria  |
| rare   | drug reaction with eosinophilia and systemic symptoms*, Stevens-Johnson syndrome*  |
| not known  | toxic epidermal necrolysis*, acute generalised exanthematous pustulosis*   |
| <i>Musculoskeletal and connective tissue disorders</i> |  |
| common   | myalgia  |
| uncommon   | osteonecrosis*   |
| <i>Reproductive system and breast disorders</i>        |  |
| uncommon   | gynaecomastia*   |

|   |                            |
|---|----------------------------|
| <i>General disorders and administration site conditions</i> |                            |
| common  | fatigue                    |
| uncommon  | asthenia                   |
| <i>Investigations</i>                                       |                            |
| common  | increased blood creatinine |

\* these adverse drug reactions have not been reported in clinical trial experience with darunavir/cobicistat but have been noted with darunavir/ritonavir treatment and could be expected with darunavir/cobicistat too.

### Description of selected adverse reactions

#### *Rash*

In clinical trials, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In cases of severe skin reaction see the warning in section 4.4. In a single arm trial investigating darunavir 800 mg once daily in combination with cobicistat 150 mg once daily and other antiretrovirals 2.2% of patients discontinued treatment due to rash.

During the clinical development program of raltegravir in treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing PREZISTA/ritonavir + raltegravir compared to those containing PREZISTA/ritonavir without raltegravir or raltegravir without PREZISTA/ritonavir. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR), respectively; and for drug-related rash were 2.4, 1.1, and 2.3 per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy (see section 4.4).

#### *Metabolic parameters*

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

#### *Musculoskeletal abnormalities*

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).

#### *Immune reconstitution inflammatory syndrome*

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

#### *Bleeding in haemophiliac patients*

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

### Paediatric population

The safety assessment in paediatric patients is based on the 48-week analysis of safety data from three Phase II trials. The following patient populations were evaluated (see section 5.1):

- 80 ART-experienced HIV-1 infected paediatric patients aged from 6 to 17 years and weighing at least 20 kg who received PREZISTA tablets with low dose ritonavir twice daily in combination with other antiretroviral agents.

- 21 ART-experienced HIV-1 infected paediatric patients aged from 3 to < 6 years and weighing 10 kg to < 20 kg (16 participants from 15 kg to < 20 kg) who received PREZISTA oral suspension with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 12 ART-naïve HIV-1 infected paediatric patients aged from 12 to 17 years and weighing at least 40 kg who received PREZISTA tablets with low dose ritonavir once daily in combination with other antiretroviral agents (see section 5.1).

Overall, the safety profile in these paediatric patients was similar to that observed in the adult population.

#### Other special populations

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

Among 1,968 treatment-experienced patients receiving PREZISTA co-administered with ritonavir 600/100 mg twice daily, 236 patients were co-infected with 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).

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

## **4.9 Overdose**

Human experience of acute overdose with PREZISTA co-administered with cobicistat or low dose ritonavir is limited. Single doses up to 3,200 mg of darunavir as oral solution alone and up to 1,600 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. 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: Antivirals for systemic use, protease inhibitors, ATC code: J05AE10.

#### Mechanism of action

Darunavir is an inhibitor of the dimerisation and of the catalytic activity 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.

## Resistance

*In vitro* selection of darunavir-resistant virus from wild type HIV-1 was lengthy (> 3 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23-50-fold) harboured 2 to 4 amino acid substitutions in the protease gene. The decreased susceptibility to darunavir of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations.

The clinical trial data from ART-experienced patients (*TITAN* trial and the pooled analysis of the *POWER* 1, 2 and 3 and *DUET* 1 and 2 trials) showed that virologic response to PREZISTA co-administered with low dose ritonavir was decreased when 3 or more darunavir RAMs (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) were present at baseline or when these mutations developed during treatment.

Increasing baseline darunavir fold change in EC<sub>50</sub> (FC) was associated with decreasing virologic response. A lower and upper clinical cut-off of 10 and 40 were identified. Isolates with baseline FC ≤ 10 are susceptible; isolates with FC > 10 to 40 have decreased susceptibility; isolates with FC > 40 are resistant (see Clinical results).

Viruses isolated from patients on PREZISTA/ritonavir 600/100 mg twice daily experiencing virologic failure by rebound that were susceptible to tipranavir at baseline remained susceptible to tipranavir after treatment in the vast majority of cases.

The lowest rates of developing resistant HIV virus are observed in ART-naïve patients who are treated for the first time with darunavir in combination with other ART.

The table below shows the development of HIV-1 protease mutations and loss of susceptibility to PIs in virologic failures at endpoint in the *ARTEMIS*, *ODIN* and *TITAN* trials.

|   | ARTEMIS<br>Week 192   | ODIN<br>Week 48   |  | TITAN<br>Week 48   |
|---|---|---|--|--|
|   | PREZISTA/<br>ritonavir<br>800/100 mg<br>once daily<br>N=343 | PREZISTA/<br>ritonavir<br>800/100 mg<br>once daily<br>N=294 | PREZISTA/<br>ritonavir<br>600/100 mg<br>twice daily<br>N=296 | PREZISTA/<br>ritonavir<br>600/100 mg<br>twice daily<br>N=298 |
| Total number of<br>virologic failures <sup>a</sup> , n<br>(%)   | 55 (16.0%)  | 65 (22.1%)  | 54 (18.2%)   | 31 (10.4%)   |
| Rebounders  | 39 (11.4%)  | 11 (3.7%)   | 11 (3.7%)  | 16 (5.4%)  |
| Never suppressed<br>subjects  | 16 (4.7%)   | 54 (18.4%)  | 43 (14.5%)   | 15 (5.0%)  |
| Number of subjects with virologic failure and paired baseline/endpoint genotypes, developing mutations <sup>b</sup> at<br>endpoint, n/N                           |   |   |  |  |
| Primary (major) PI<br>mutations   | 0/43  | 1/60  | 0/42   | 6/28   |
| PI RAMs   | 4/43  | 7/60  | 4/42   | 10/28  |
| Number of subjects with virologic failure and paired baseline/endpoint phenotypes, showing loss of<br>susceptibility to PIs at endpoint compared to baseline, n/N |   |   |  |  |
| PI  |   |   |  |  |
| darunavir   | 0/39  | 1/58  | 0/41   | 3/26   |
| amprenavir  | 0/39  | 1/58  | 0/40   | 0/22   |
| atazanavir  | 0/39  | 2/56  | 0/40   | 0/22   |
| indinavir   | 0/39  | 2/57  | 0/40   | 1/24   |
| lopinavir   | 0/39  | 1/58  | 0/40   | 0/23   |
| saquinavir  | 0/39  | 0/56  | 0/40   | 0/22   |
| tipranavir  | 0/39  | 0/58  | 0/41   | 1/25   |

<sup>a</sup> TLOVR non-VF censored algorithm based on HIV-1 RNA < 50 copies/ml, except for *TITAN* (HIV-1 RNA < 400 copies/ml)

<sup>b</sup> IAS-USA lists

Low rates of developing resistant HIV-1 virus were observed in ART-naïve patients who are treated for the first time with darunavir/cobicistat once daily in combination with other ART, and in ART-experienced patients with no darunavir RAMs receiving darunavir/cobicistat in combination with other ART. The table below shows the development of HIV-1 protease mutations and resistance to PIs in virologic failures at endpoint in the GS-US-216-130 trial.

|  | GS-US-216-130<br>Week 48  |  |
|--|---|--|
|  | Treatment-naïve<br>darunavir/cobicistat 800/150 mg<br>once daily<br>N=295 | Treatment-experienced<br>darunavir/cobicistat 800/150 mg<br>once daily<br>N=18 |
| Number of subjects with virologic failure <sup>a</sup> and genotype data that develop mutations <sup>b</sup> at endpoint, n/N        |   |  |
| Primary (major) PI mutations   | 0/8   | 1/7  |
| PI RAMs  | 2/8   | 1/7  |
| Number of subjects with virologic failure <sup>a</sup> and phenotype data that show resistance to PIs at endpoint <sup>c</sup> , n/N |   |  |
| HIV PI   |   |  |
| darunavir  | 0/8   | 0/7  |
| amprenavir   | 0/8   | 0/7  |
| atazanavir   | 0/8   | 0/7  |
| indinavir  | 0/8   | 0/7  |
| lopinavir  | 0/8   | 0/7  |
| saquinavir   | 0/8   | 0/7  |
| tipranavir   | 0/8   | 0/7  |

<sup>a</sup> Virologic failures were defined as: never suppressed: confirmed HIV-1 RNA < 1 log<sub>10</sub> reduction from baseline and ≥ 50 copies/ml at the week-8; rebound: HIV-1 RNA < 50 copies/ml followed by confirmed HIV-1 RNA to ≥ 400 copies/ml or confirmed > 1 log<sub>10</sub> HIV-1 RNA increase from the nadir; discontinuations with HIV-1 RNA ≥ 400 copies/ml at last visit

<sup>b</sup> IAS-USA lists

<sup>c</sup> In GS-US216-130 baseline phenotype was not available

### Cross-resistance

Darunavir FC was less than 10 for 90% of 3,309 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.

In the virologic failures of the *ARTEMIS* trial no cross-resistance with other PIs was observed. In the virologic failures of the GS-US-216-130 trial no cross-resistance with other HIV PIs was observed.

### Clinical results

The pharmacokinetic enhancing effect of cobicistat on darunavir was evaluated in a Phase I study in healthy subjects that were administered darunavir 800 mg with either cobicistat at 150 mg or ritonavir at 100 mg once daily. The steady-state pharmacokinetic parameters of darunavir were comparable when boosted with cobicistat versus ritonavir. For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

### Adult patients

#### *Efficacy of darunavir 800 mg once daily co-administered with 150 mg cobicistat once daily in ART-naïve and ART-experienced patients*

GS-US-216-130 is a single arm, open-label, Phase III trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with cobicistat in 313 HIV-1 infected adult patients (295 treatment-naïve and 18 treatment-experienced). These patients received darunavir 800 mg once daily in combination with cobicistat 150 mg once daily with an investigator selected background regimen consisting of 2 active NRTIs.



HIV-1 infected patients who were eligible for this trial had a screening genotype showing no darunavir RAMs and plasma HIV-1 RNA  $\geq 1,000$  copies/ml. The table below shows the efficacy data of the 48 week analyses from the GS-US-216-130 trial:

| <i>Outcomes at Week 48</i>  | GS-US-216-130   |  |  |
|---|---|--|--|
|   | Treatment-naïve darunavir/cobicistat 800/150 mg once daily + OBR<br>N=295 | Treatment-experienced darunavir/cobicistat 800/150 mg once daily + OBR<br>N=18 | All subjects darunavir/cobicistat 800/150 mg once daily + OBR<br>N=313 |
| HIV-1 RNA < 50 copies/ml <sup>a</sup>                                 | 245 (83.1%)   | 8 (44.4%)  | 253 (80.8%)  |
| mean HIV-1 RNA log change from baseline (log <sub>10</sub> copies/ml) | -3.01   | -2.39  | -2.97  |
| CD4 <sup>+</sup> cell count mean change from baseline <sup>b</sup>    | +174  | +102   | +170   |

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

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

*Efficacy of PREZISTA 800 mg once daily co-administered with 100 mg ritonavir once daily in ART-naïve patients*

The evidence of efficacy of PREZISTA/ritonavir 800/100 mg once daily is based on the analyses of 192 week data from the randomised, controlled, open-label Phase III trial *ARTEMIS* in antiretroviral treatment-naïve HIV-1 infected patients comparing PREZISTA/ritonavir 800/100 mg once daily with lopinavir/ritonavir 800/200 mg per day (given as a twice-daily or as a once-daily regimen). Both arms used a fixed background regimen consisting of tenofovir disoproxil fumarate 300 mg once daily and emtricitabine 200 mg once daily.

The table below shows the efficacy data of the 48 week and 96 week analyses from the *ARTEMIS* trial:

| ARTEMIS   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| <i>Outcomes</i>   | Week 48 <sup>a</sup>                              |   |   | Week 96 <sup>b</sup>                              |   |   |
|   | PREZISTA/ritonavir 800/100 mg once daily<br>N=343 | Lopinavir/ritonavir 800/200 mg per day<br>N=346 | Treatment difference (95% CI of difference) | PREZISTA/ritonavir 800/100 mg once daily<br>N=343 | Lopinavir/ritonavir 800/200 mg per day<br>N=346 | Treatment difference (95% CI of difference) |
| HIV-1 RNA < 50 copies/ml <sup>c</sup><br>All patients                                       | 83.7%<br>(287)                                    | 78.3%<br>(271)                                  | 5.3%<br>(-0.5; 11.2) <sup>d</sup>           | 79.0%<br>(271)                                    | 70.8%<br>(245)                                  | 8.2%<br>(1.7; 14.7) <sup>d</sup>            |
| With baseline HIV-RNA < 100,000   | 85.8%<br>(194/226)                                | 84.5%<br>(191/226)                              | 1.3%<br>(-5.2; 7.9) <sup>d</sup>            | 80.5%<br>(182/226)                                | 75.2%<br>(170/226)                              | 5.3%<br>(-2.3; 13.0) <sup>d</sup>           |
| With baseline HIV-RNA $\geq 100,000$  | 79.5%<br>(93/117)                                 | 66.7%<br>(80/120)                               | 12.8%<br>(1.6; 24.1) <sup>d</sup>           | 76.1%<br>(89/117)                                 | 62.5%<br>(75/120)                               | 13.6%<br>(1.9; 25.3) <sup>d</sup>           |
| With baseline CD4 <sup>+</sup> cell count < 200   | 79.4%<br>(112/141)                                | 70.3%<br>(104/148)                              | 9.2%<br>(-0.8; 19.2) <sup>d</sup>           | 78.7%<br>(111/141)                                | 64.9%<br>(96/148)                               | 13.9%<br>(3.5; 24.2) <sup>d</sup>           |
| With baseline CD4 <sup>+</sup> cell count $\geq 200$  | 86.6%<br>(175/202)                                | 84.3%<br>(167/198)                              | 2.3%<br>(-4.6; 9.2) <sup>d</sup>            | 79.2%<br>(160/202)                                | 75.3%<br>(149/198)                              | 4.0%<br>(-4.3; 12.2) <sup>d</sup>           |
| median CD4 <sup>+</sup> cell count change from baseline (x 10 <sup>6</sup> /l) <sup>c</sup> | 137   | 141   |   | 171   | 188   |   |

- <sup>a</sup> Data based on analyses at week 48  
<sup>b</sup> Data based on analyses at week 96  
<sup>c</sup> Imputations according to the TLOVR algorithm  
<sup>d</sup> Based on normal approximation to the difference in % response  
<sup>e</sup> Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0

Non-inferiority in virologic response to the PREZISTA/ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/ml, was demonstrated (at the pre-defined 12% non-inferiority margin) for both Intent-To-Treat (ITT) and On Protocol (OP) populations in the 48 week analysis. These results were confirmed in the analyses of data at 96 weeks of treatment in the ARTEMIS trial. These results were sustained up to 192 weeks of treatment in the ARTEMIS trial.

**Efficacy of PREZISTA 800 mg once daily co-administered with 100 mg ritonavir once daily in ART-experienced patients**

**ODIN** is a Phase III, randomised, open-label trial comparing PREZISTA/ritonavir 800/100 mg once daily versus PREZISTA/ritonavir 600/100 mg twice daily in ART-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a screening HIV-1 RNA > 1,000 copies/ml. Efficacy analysis is based on 48 weeks of treatment (see table below). Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs.

| ODIN  |   |  |  |
|---|---|--|--|
| Outcomes  | PREZISTA/ritonavir<br>800/100 mg once daily +<br>OBR<br>N=294 | PREZISTA/ritonavir<br>600/100 mg twice daily +<br>OBR<br>N=296 | Treatment difference<br>(95% CI of difference) |
| HIV-1 RNA<br>< 50 copies/ml <sup>a</sup>  | 72.1% (212)   | 70.9% (210)  | 1.2% (-6.1; 8.5) <sup>b</sup>                  |
| With Baseline HIV-1<br>RNA (copies/ml)  |   |  |  |
| < 100,000   | 77.6% (198/255)   | 73.2% (194/265)  | 4.4% (-3.0; 11.9)                              |
| ≥ 100,000   | 35.9% (14/39)   | 51.6% (16/31)  | -15.7% (-39.2; 7.7)                            |
| With Baseline CD4+<br>cell count (x 10 <sup>6</sup> /l)                             |   |  |  |
| ≥ 100   | 75.1% (184/245)   | 72.5% (187/258)  | 2.6% (-5.1; 10.3)                              |
| < 100   | 57.1% (28/49)   | 60.5% (23/38)  | -3.4% (-24.5; 17.8)                            |
| With HIV-1 clade  |   |  |  |
| Type B  | 70.4% (126/179)   | 64.3% (128/199)  | 6.1% (-3.4; 15.6)                              |
| Type AE   | 90.5% (38/42)   | 91.2% (31/34)  | -0.7% (-14.0; 12.6)                            |
| Type C  | 72.7% (32/44)   | 78.8% (26/33)  | -6.1% (-2.6; 13.7)                             |
| Other <sup>c</sup>  | 55.2% (16/29)   | 83.3% (25/30)  | -28.2% (-51.0; -5.3)                           |
| mean CD4+ cell count<br>change from baseline<br>(x 10 <sup>6</sup> /l) <sup>e</sup> | 108   | 112  | -5 <sup>d</sup> (-25; 16)                      |

- <sup>a</sup> Imputations according to the TLOVR algorithm  
<sup>b</sup> Based on a normal approximation of the difference in % response  
<sup>c</sup> Clades A1, D, F1, G, K, CRF02\_AG, CRF12\_BF, and CRF06\_CPX  
<sup>d</sup> Difference in means  
<sup>e</sup> Last Observation Carried Forward imputation

At 48 weeks, virologic response, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/ml, with PREZISTA/ritonavir 800/100 mg once daily treatment was demonstrated to be non-inferior (at the pre-defined 12% non-inferiority margin) compared to PREZISTA/ritonavir 600/100 mg twice daily for both ITT and OP populations.

PREZISTA/ritonavir 800/100 mg once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10<sup>6</sup>/l (see section 4.2 and 4.4). Limited data is available in patients with HIV-1 clades other than B.

## Paediatric patients

*ART-naïve paediatric patients from the age of 12 years to < 18 years, and weighing at least 40 kg*  
**DIONE** is an open-label, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of PREZISTA with low dose ritonavir in 12 ART-naïve HIV-1 infected paediatric patients aged 12 to less than 18 years and weighing at least 40 kg. These patients received PREZISTA/ritonavir 800/100 mg once daily in combination with other antiretroviral agents. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 log<sub>10</sub> versus baseline.

| DIONE   |                            |
|---|----------------------------|
| Outcomes at week 48   | PREZISTA/ritonavir<br>N=12 |
| HIV-1 RNA < 50 copies/ml <sup>a</sup>                               | 83.3% (10)                 |
| CD4+ percent change from baseline <sup>b</sup>                      | 14                         |
| CD4+ cell count mean change from baseline <sup>b</sup>              | 221                        |
| ≥ 1.0 log <sub>10</sub> decrease from baseline in plasma viral load | 100%                       |

<sup>a</sup> Imputations according to the TLOVR algorithm.

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

For additional clinical study results in ART-experienced adults and paediatric patients, refer to the Summary of Product Characteristics for PREZISTA 75 mg, 150 mg, 300 mg or 600 mg tablets and 100 mg/ml oral suspension.

### *Pregnancy and postpartum*

Darunavir/ritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 36 pregnant women (18 in each arm) during the second and third trimesters, and postpartum. Virologic response was preserved throughout the study period in both arms. No mother to child transmission occurred in the infants born to the 31 subjects who stayed on the antiretroviral treatment through delivery. There were no new clinically relevant safety findings compared with the known safety profile of darunavir/ritonavir in HIV-1 infected adults (see sections 4.2, 4.4 and 5.2).

## **5.2 Pharmacokinetic properties**

The pharmacokinetic properties of darunavir, co-administered with cobicistat or 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. Cobicistat and ritonavir inhibit CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

For information on cobicistat pharmacokinetic properties, consult the cobicistat Summary of Product Characteristics.

### 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 twice daily ritonavir. The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily (see section 4.4).

When administered without food, the relative bioavailability of darunavir in the presence of cobicistat or low dose ritonavir is lower as compared to intake with food. Therefore, PREZISTA tablets should be taken with cobicistat or 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.

### Biotransformation

*In vitro* experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolised by the hepatic CYP system and almost exclusively by isozyme CYP3A4. A  $^{14}$ C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir 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  $^{14}$ C-darunavir with ritonavir dose, approximately 79.5% and 13.9% of the administered dose of  $^{14}$ C-darunavir could be retrieved in faeces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in faeces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir.

The intravenous clearance of darunavir alone (150 mg) and in the presence of low dose ritonavir was 32.8 l/h and 5.9 l/h, respectively.

### Special populations

#### *Paediatric population*

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 74 treatment-experienced paediatric patients, aged 6 to 17 years and weighing at least 20 kg, showed that the administered weight-based doses of PREZISTA/ritonavir resulted in darunavir exposure comparable to that in adults receiving PREZISTA/ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 14 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 15 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving PREZISTA/ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 12 ART-naïve paediatric patients, aged 12 to < 18 years and weighing at least 40 kg, showed that PREZISTA/ritonavir 800/100 mg once daily results in darunavir exposure that was comparable to that achieved in adults receiving PREZISTA/ritonavir 800/100 mg once daily. Therefore the same once daily dosage may be used in treatment-experienced adolescents aged 12 to < 18 years and weighing at least 40 kg without darunavir resistance associated mutations (DRV-RAMs)\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100$  cells  $\times 10^6$ /l (see section 4.2).

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 10 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 14 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that

achieved in adults receiving PREZISTA/ritonavir 800/100 mg once daily (see section 4.2). In addition, pharmacokinetic modeling and simulation of darunavir exposures in paediatric patients across the ages of 3 to < 18 years confirmed the darunavir exposures as observed in the clinical studies and allowed the identification of weight-based PREZISTA/ritonavir once daily dosing regimens for paediatric patients weighing at least 15 kg that are either ART-naïve or treatment-experienced paediatric patients without DRV-RAMs\* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count  $\geq 100 \text{ cells} \times 10^6/\text{l}$  (see section 4.2).

\* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

### *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 total plasma concentrations of darunavir in subjects with mild (Child-Pugh Class A, n=8) and moderate (Child-Pugh Class B, n=8) hepatic impairment were comparable with those in healthy subjects. However, unbound darunavir concentrations were approximately 55% (Child-Pugh Class A) and 100% (Child-Pugh Class B) higher, respectively. The clinical relevance of this increase is unknown therefore, PREZISTA should be used with caution. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see sections 4.2, 4.3 and 4.4).

### *Pregnancy and postpartum*

The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 600/100 mg twice daily and darunavir/ritonavir 800/100 mg once daily as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum. However, for unbound (i.e. active) darunavir, the pharmacokinetic parameters were less reduced during pregnancy compared to postpartum, due to an increase in the unbound fraction of darunavir during pregnancy compared to postpartum.

| <b>Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 600/100 mg twice daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum</b> |   |  |                                       |
|---|---|--|---------------------------------------|
| <b>Pharmacokinetics of total darunavir (mean <math>\pm</math> SD)</b>   | <b>Second trimester of pregnancy (n=12)<sup>a</sup></b> | <b>Third trimester of pregnancy (n=12)</b> | <b>Postpartum (6-12 weeks) (n=12)</b> |
| $C_{\text{max}}$ , ng/ml  | 4,668 $\pm$ 1,097                                       | 5,328 $\pm$ 1,631                          | 6,659 $\pm$ 2,364                     |
| $\text{AUC}_{12\text{h}}$ , ng.h/ml   | 39,370 $\pm$ 9,597                                      | 45,880 $\pm$ 17,360                        | 56,890 $\pm$ 26,340                   |
| $C_{\text{min}}$ , ng/ml  | 1,922 $\pm$ 825   | 2,661 $\pm$ 1,269                          | 2,851 $\pm$ 2,216                     |

<sup>a</sup> n=11 for  $\text{AUC}_{12\text{h}}$

| <b>Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 800/100 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum</b> |   |  |                                       |
|--|---|--|---------------------------------------|
| <b>Pharmacokinetics of total darunavir (mean ± SD)</b>   | <b>Second trimester of pregnancy (n=17)</b> | <b>Third Trimester of pregnancy (n=15)</b> | <b>Postpartum (6-12 weeks) (n=16)</b> |
| $C_{max}$ , ng/ml  | 4,964 ± 1,505                               | 5,132 ± 1,198                              | 7,310 ± 1,704                         |
| $AUC_{24h}$ , ng.h/ml  | 62,289 ± 16,234                             | 61,112 ± 13,790                            | 92,116 ± 29,241                       |
| $C_{min}$ , ng/ml  | 1,248 ± 542                                 | 1,075 ± 594                                | 1,473 ± 1,141                         |

In women receiving darunavir/ritonavir 600/100 mg twice daily during the second trimester of pregnancy, mean intra-individual values for total darunavir  $C_{max}$ ,  $AUC_{12h}$  and  $C_{min}$  were 28%, 26% and 26% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir  $C_{max}$ ,  $AUC_{12h}$  and  $C_{min}$  values were 18%, 16% lower and 2% higher, respectively, as compared with postpartum.

In women receiving darunavir/ritonavir 800/100 mg once daily during the second trimester of pregnancy, mean intra-individual values for total darunavir  $C_{max}$ ,  $AUC_{24h}$  and  $C_{min}$  were 33%, 31% and 30% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir  $C_{max}$ ,  $AUC_{24h}$  and  $C_{min}$  values were 29%, 32% and 50% lower, respectively, as compared with postpartum.

Treatment with darunavir/cobicistat 800/150 mg once daily during pregnancy results in low darunavir exposure. In women receiving darunavir/cobicistat during the second trimester of pregnancy, mean intra-individual values for total darunavir  $C_{max}$ ,  $AUC_{24h}$  and  $C_{min}$  were 49%, 56% and 92% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir  $C_{max}$ ,  $AUC_{24h}$  and  $C_{min}$  values were 37%, 50% and 89% lower, respectively, as compared with postpartum. The unbound fraction was also substantially reduced, including around 90% reductions of  $C_{min}$  levels. The main cause of these low exposures is a marked reduction in cobicistat exposure as a consequence of pregnancy-associated enzyme induction (see below).

| <b>Pharmacokinetic results of total darunavir after administration of darunavir/cobicistat 800/150 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy, and postpartum</b> |  |   |                                      |
|---|--|---|--------------------------------------|
| <b>Pharmacokinetics of total darunavir (mean ± SD)</b>  | <b>Second trimester of pregnancy (n=7)</b> | <b>Third trimester of pregnancy (n=6)</b> | <b>Postpartum (6-12 weeks) (n=6)</b> |
| $C_{max}$ , ng/mL   | 4,340 ± 1,616                              | 4,910 ± 970                               | 7,918 ± 2,199                        |
| $AUC_{24h}$ , ng.h/mL   | 47,293 ± 19,058                            | 47,991 ± 9,879                            | 99,613 ± 34,862                      |
| $C_{min}$ , ng/mL   | 168 ± 149                                  | 184 ± 99                                  | 1,538 ± 1,344                        |

The exposure to cobicistat was lower during pregnancy, potentially leading to suboptimal boosting of darunavir. During the second trimester of pregnancy, cobicistat  $C_{max}$ ,  $AUC_{24h}$ , and  $C_{min}$  were 50%, 63%, and 83% lower, respectively, as compared with postpartum. During the third trimester of pregnancy, cobicistat  $C_{max}$ ,  $AUC_{24h}$ , and  $C_{min}$ , were 27%, 49%, and 83% lower, respectively, as compared with postpartum.

### 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 1,000 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 receiving darunavir up to days 23-26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher than in adult rats after comparable doses in mg/kg between days 5 and 11 of age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals. No treatment related mortalities were noted in juvenile rats dosed at 1,000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats.

Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, PREZISTA with low dose ritonavir should not be used in paediatric patients below 3 years of age.

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1,000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumours in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

After 2 years administration of darunavir at exposures at or below the human exposure, kidney changes were observed in mice (nephrosis) and rats (chronic progressive nephropathy).

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### PREZISTA 400 mg film-coated tablets

##### Tablet core

Microcrystalline cellulose  
Colloidal anhydrous silica  
Crospovidone  
Magnesium stearate

##### Tablet film-coat

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

#### PREZISTA 800 mg film-coated tablets

##### Tablet core

Microcrystalline cellulose  
Colloidal anhydrous silica  
Crospovidone  
Magnesium stearate  
Hypromellose

##### Tablet film-coat

Poly(vinyl alcohol) – partially hydrolysed  
Macrogol 3350  
Titanium dioxide (E171)  
Talc  
Iron oxide red (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

#### PREZISTA 400 mg film-coated tablets

3 years

#### PREZISTA 800 mg film-coated tablets

3 years

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

This medicinal product does not require any special storage conditions.

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

#### PREZISTA 400 mg film-coated tablets

Opaque, white, high density polyethylene (HDPE) plastic, 160 ml bottle containing 60 tablets, fitted with polypropylene (PP) child resistant closure.  
Pack size of one bottle.

#### PREZISTA 800 mg film-coated tablets



Opaque, white, high density polyethylene (HDPE) plastic, 75 ml bottle containing 30 tablets, fitted with polypropylene (PP) child resistant closure.  
Pack size of one bottle or three bottles per carton.

#### **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)**

PREZISTA 400 mg film-coated tablets  
EU/1/06/380/003

PREZISTA 800 mg film-coated tablets  
EU/1/06/380/007 - 30 film-coated tablets  
EU/1/06/380/008 - 90 film-coated tablets (3 x 30)

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

Date of first authorisation: 12 February 2007  
Date of latest renewal: 19 September 2013

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

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

PREZISTA oral suspension

Janssen Pharmaceutica NV  
Turnhoutseweg 30  
B-2340 Beerse  
Belgium

PREZISTA tablets

Janssen-Cilag SpA  
Via C. Janssen  
Borgo San Michele  
04100 Latina  
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

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

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON FOR ORAL SUSPENSION****1. NAME OF THE MEDICINAL PRODUCT**

PREZISTA 100 mg/ml oral suspension  
darunavir

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

Each ml of suspension contains 100 mg darunavir (as ethanolate).

**3. LIST OF EXCIPIENTS**

Contains sodium methyl parahydroxybenzoate (E219).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Oral suspension  
200 ml bottle  
Pack includes a 6 ml dosing pipette with 0.2 ml gradations.

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

Read the package leaflet before use.  
Oral use  
Shake bottle vigorously before use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.  
Do not refrigerate or freeze. Avoid exposure to excessive heat.

Store in the original container.

|  |
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| <b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b> |
|--|

|   |
|---|
| <b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b> |
|---|

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

|  |
|--|
| <b>12. MARKETING AUTHORISATION NUMBER(S)</b> |
|--|

EU/1/06/380/006

|                         |
|-------------------------|
| <b>13. BATCH NUMBER</b> |
|-------------------------|

Lot

|  |
|--|
| <b>14. GENERAL CLASSIFICATION FOR SUPPLY</b> |
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|                                |
|--------------------------------|
| <b>15. INSTRUCTIONS ON USE</b> |
|--------------------------------|

|                                   |
|-----------------------------------|
| <b>16. INFORMATION IN BRAILLE</b> |
|-----------------------------------|

prezista 100 mg/ml

|   |
|---|
| <b>17. UNIQUE IDENTIFIER – 2D BARCODE</b> |
|---|

2D barcode carrying the unique identifier included.

|  |
|--|
| <b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b> |
|--|

PC:  
SN:  
NN:

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING****BOTTLE LABEL FOR ORAL SUSPENSION****1. NAME OF THE MEDICINAL PRODUCT**

PREZISTA 100 mg/ml oral suspension  
darunavir

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

Each ml of suspension contains 100 mg darunavir (as ethanolate).

**3. LIST OF EXCIPIENTS**

Contains sodium methyl parahydroxybenzoate (E219).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Oral suspension  
200 ml

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

Read the package leaflet before use.  
Oral use  
Shake bottle vigorously before use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.  
Do not refrigerate or freeze. Avoid exposure to excessive heat.  
Store in the original container.



**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/1/06/380/006

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

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

**OUTER CARTON / BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

PREZISTA 75 mg film-coated tablets  
darunavir

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

Each film-coated tablet contains 75 mg darunavir (as ethanolate).

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

480 film-coated tablets

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

Read the package leaflet before use.  
Oral use

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

Keep out of the sight and reach 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/1/06/380/005

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

prezista 75 mg *(this is only applicable to the outer pack)*

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

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

**OUTER CARTON / BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

PREZISTA 150 mg film-coated tablets  
darunavir

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

Each film-coated tablet contains 150 mg darunavir (as ethanolate).

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

240 film-coated tablets

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

Read the package leaflet before use.  
Oral use

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

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

|  |
|--|
| <b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b> |
|--|

|   |
|---|
| <b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b> |
|---|

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

|  |
|--|
| <b>12. MARKETING AUTHORISATION NUMBER(S)</b> |
|--|

EU/1/06/380/004

|                         |
|-------------------------|
| <b>13. BATCH NUMBER</b> |
|-------------------------|

Lot

|  |
|--|
| <b>14. GENERAL CLASSIFICATION FOR SUPPLY</b> |
|--|

|                                |
|--------------------------------|
| <b>15. INSTRUCTIONS ON USE</b> |
|--------------------------------|

|                                   |
|-----------------------------------|
| <b>16. INFORMATION IN BRAILLE</b> |
|-----------------------------------|

pezista 150 mg *(this is only applicable to the outer pack)*

|   |
|---|
| <b>17. UNIQUE IDENTIFIER – 2D BARCODE</b> |
|---|

2D barcode carrying the unique identifier included.

|  |
|--|
| <b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b> |
|--|

PC:  
SN:  
NN:

**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**

Read the package leaflet before use.  
Oral use

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

Keep out of the sight and reach 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/1/06/380/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

pezista 300 mg *(this is only applicable to the outer pack)*

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

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

**OUTER CARTON / BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

PREZISTA 400 mg film-coated tablets  
darunavir

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

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

**3. LIST OF EXCIPIENTS**

Also contains sunset yellow FCF (E110).

**4. PHARMACEUTICAL FORM AND CONTENTS**

60 film-coated tablets

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

Read the package leaflet before use.  
Oral use

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

Keep out of the sight and reach 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/1/06/380/003

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

pezista 400 mg *(this is only applicable to the outer pack)*

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

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

**OUTER CARTON / BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

PREZISTA 600 mg film-coated tablets  
darunavir

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

Each film-coated tablet contains 600 mg darunavir (as ethanolate).

**3. LIST OF EXCIPIENTS**

Also contains sunset yellow FCF (E110).

**4. PHARMACEUTICAL FORM AND CONTENTS**

60 film-coated tablets

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

Read the package leaflet before use.  
Oral use

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

Keep out of the sight and reach 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/1/06/380/002

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

pezista 600 mg *(this is only applicable to the outer pack)*

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

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

**OUTER CARTON / BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

PREZISTA 800 mg film-coated tablets  
darunavir

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

Each film-coated tablet contains 800 mg darunavir (as ethanolate).

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

30 film-coated tablets  
90 film-coated tablets (3 bottles containing 30 tablets each)  
The bottles are not to be distributed individually.

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

Read the package leaflet before use.  
Oral use

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

Keep out of the sight and reach 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/1/06/380/007 - 30 film-coated tablets  
EU/1/06/380/008 - 90 film-coated tablets (3 x 30)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

pezista 800 mg (*this is only applicable to the outer pack*)

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

## **B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

### PREZISTA 100 mg/ml oral suspension darunavir

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

1. What PREZISTA is and what it is used for
2. What you need to know before you take PREZISTA
3. How to take PREZISTA
4. Possible side effects
5. How to store PREZISTA
6. Contents of the pack and other information

#### 1. What PREZISTA is and what it is used for

##### What is PREZISTA?

PREZISTA contains the active substance darunavir. 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 HIV infected adults as well as HIV infected children of 3 years of age and above, and at least 15 kilogram body weight (see **How to take PREZISTA**).

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

#### 2. What you need to know before you take PREZISTA

##### Do not take PREZISTA

- if you are **allergic** to darunavir or any of the other ingredients of this medicine (listed in section 6) or to cobicistat or 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

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

| Medicine   | Purpose of the medicine                       |
|--|---|
| <i>Avanafil</i>  | to treat erectile dysfunction                 |
| <i>Astemizole</i> or <i>terfenadine</i>                            | to treat allergy symptoms                     |
| <i>Triazolam</i> and <i>oral</i> (taken by mouth) <i>midazolam</i> | to help you sleep and/or relieve anxiety      |
| <i>Cisapride</i>   | to treat some stomach conditions              |
| <i>Colchicine</i> (if you have kidney and/or liver problems)       | to treat gout or familial Mediterranean fever |

|   |  |
|---|--|
| <i>Lurasidone, pimozone, quetiapine or sertindole</i>                                       | to treat psychiatric conditions  |
| <i>Ergot alkaloids like ergotamine, dihydroergotamine, ergometrine and methylergonovine</i> | to treat migraine headaches  |
| <i>Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine</i>                 | to treat certain heart disorders e.g. abnormal heart beat  |
| <i>Lovastatin, simvastatin and lomitapide</i>   | to lower cholesterol levels  |
| <i>Rifampicin</i>   | to treat some infections such as tuberculosis  |
| The combination product <i>lopinavir/ritonavir</i>  | this anti-HIV medicine belongs to the same class as PREZISTA   |
| <i>Elbasvir/grazoprevir</i>   | to treat hepatitis C infection   |
| <i>Alfuzosin</i>  | to treat enlarged prostate   |
| <i>Sildenafil</i>   | to treat high blood pressure in the pulmonary circulation  |
| <i>Dabigatran, ticagrelor</i>   | to help stop the clumping of platelets in the treatment of patients with a history of a heart attack |
| <i>Naloxegol</i>  | to treat opioid induced constipation   |
| <i>Dapoxetine</i>   | to treat premature ejaculation   |
| <i>Domperidone</i>  | to treat nausea and vomiting   |

Do not combine PREZISTA with products that contain St John's wort (*Hypericum perforatum*).

### Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking PREZISTA.

PREZISTA is not a cure for HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

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

People taking PREZISTA may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking PREZISTA and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

### Tell your doctor about your situation BEFORE and DURING your treatment

Make sure that you check the following 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 infection. 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** (for example enlarged lymph nodes and fever). 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.
- In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of



the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- 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.

### **Elderly**

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.

### **Children**

PREZISTA is not for use in children younger than 3 years of age or weighing less than 15 kilograms.

### **Other medicines and PREZISTA**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

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 medicines:'

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), CCR5 antagonists and FIs (fusion inhibitors)]. PREZISTA with cobicistat or ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. In some cases dosage of other medicines might need to be changed. 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* (to prevent seizures)
- *Dexamethasone* (corticosteroid)
- *Efavirenz* (HIV infection)
- *Boceprevir* (hepatitis C infection)
- *Rifapentine, rifabutin* (medicines to treat some infections such as tuberculosis)
- *Saquinavir* (HIV infection).

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

- *Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nicardipine, propafenone, timolol, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Apixaban, edoxaban, rivaroxaban, warfarin* (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. PREZISTA might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.
- *Ethinylestradiol/drospirenone*. PREZISTA might increase the risk for elevated potassium levels by drospirenone.

- *Atorvastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Clarithromycin* (antibiotic)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased. Your doctor might want to do some additional tests.
- *Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone*. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone* (medicines to treat opioid dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria)
- *Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine* (to treat cancer)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension)
- *Glecaprevir/pibrentasvir, simeprevir* (to treat hepatitis C infection)
- *Fentanyl, oxycodone, tramadol* (to treat pain)
- *Fesoterodine, solifenacin* (to treat urologic disorders).

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

Tell your doctor if you take:

- *Alfentanil* (injectable strong and short-acting painkiller that is used for surgical procedures)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Itraconazole, isavuconazole, fluconazole, posaconazole, clotrimazole* (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- *Rifabutin* (against bacterial infections)
- *Sildenafil, vardenafil, tadalafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Maraviroc* (to treat HIV infection)
- *Methadone* (to treat opiate dependence)
- *Carbamazepine, clonazepam* (to prevent seizures or to treat certain types of nerve pain)
- *Colchicine* (to treat gout or familial Mediterranean fever)
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam when used as injection, zolpidem* (sedative agents)
- *Perphenazine, risperidone, thioridazine* (to treat psychiatric conditions)
- *Metformin* (to treat type 2 diabetes).

This is **not** a complete list of medicines. Tell your healthcare provider about **all** medicines that you are taking.

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

See section 3 'How to take PREZISTA.'

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

Tell your doctor immediately if you are pregnant, planning to become pregnant or if you are breast-feeding. Pregnant or breast-feeding mothers should not take PREZISTA with ritonavir unless specifically directed by the doctor. Pregnant or breast-feeding mothers should not take PREZISTA with cobicistat.

It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of your baby becoming infected with HIV through your breast milk and because of the unknown effects of the medicine on your baby.

### **Driving and using machines**

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

**PREZISTA oral suspension contains sodium methyl parahydroxybenzoate.** This ingredient may cause allergic reactions (sometimes delayed).

### **3. How to take PREZISTA**

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

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

After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

#### **Dose for children of 3 years of age and above, weighing at least 15 kilograms who have not taken antiretroviral medicines before (your child's doctor will determine this)**

The doctor will work out the right once daily dose based on the weight of the child (see table below). This dose must not exceed the recommended adult dose, which is 800 milligram PREZISTA together with 100 milligram ritonavir once a day.

The doctor will inform you on how much PREZISTA oral suspension and how much ritonavir (capsules, tablets or solution) the child must take.

| <b>Weight</b>               | <b>One PREZISTA dose is</b>    | <b>One ritonavir<sup>a</sup> dose is</b> |
|-----------------------------|--------------------------------|--|
| between 15 and 30 kilograms | 600 milligram (6 milliliter)   | 100 milligram (1.2 milliliter)           |
| between 30 and 40 kilograms | 675 milligram (6.8 milliliter) | 100 milligram (1.2 milliliter)           |
| more than 40 kilograms      | 800 milligram (8 milliliter)   | 100 milligram (1.2 milliliter)           |

<sup>a</sup> ritonavir oral solution: 80 milligram per milliliter

The child must take PREZISTA every day and always in combination with 100 milligram of ritonavir and with food. PREZISTA cannot work properly without ritonavir and food. The child must eat a meal or a snack within 30 minutes prior to taking PREZISTA and ritonavir. The type of food is not important.

#### **Dose for children of 3 years of age and above, weighing at least 15 kilograms who have taken antiretroviral medicines before (your child's doctor will determine this)**

The doctor will work out the right dose based on the weight of the child (see table below). The doctor will determine if once daily dosing or twice daily dosing is appropriate for the child. This dose must not exceed the recommended adult dose, which is 600 milligram PREZISTA together with 100 milligram ritonavir two times per day or 800 milligram PREZISTA together with 100 milligram ritonavir once a day.

The doctor will inform you on how much PREZISTA oral suspension and how much ritonavir (capsules, tablets or solution) the child must take.

#### **Twice daily dosing**

| <b>Weight</b>               | <b>One PREZISTA dose is</b>    | <b>One ritonavir<sup>a</sup> dose is</b> |
|-----------------------------|--------------------------------|--|
| between 15 and 30 kilograms | 380 milligram (3.8 milliliter) | 50 milligram (0.6 milliliter)            |
| between 30 and 40 kilograms | 460 milligram (4.6 milliliter) | 60 milligram (0.8 milliliter)            |
| more than 40 kilograms      | 600 milligram (6 milliliter)   | 100 milligram (1.2 milliliter)           |

<sup>a</sup> ritonavir oral solution: 80 milligram per milliliter

Once daily dosing

| Weight                      | One PREZISTA dose is           | One ritonavir <sup>a</sup> dose is |
|-----------------------------|--------------------------------|------------------------------------|
| between 15 and 30 kilograms | 600 milligram (6 milliliter)   | 100 milligram (1.2 milliliter)     |
| between 30 and 40 kilograms | 675 milligram (6.8 milliliter) | 100 milligram (1.2 milliliter)     |
| more than 40 kilograms      | 800 milligram (8 milliliter)   | 100 milligram (1.2 milliliter)     |

<sup>a</sup> ritonavir oral solution: 80 milligram per milliliter

### ***Instructions for children***

- The child must take PREZISTA always together with ritonavir. PREZISTA cannot work properly without ritonavir.
- The child must take the appropriate doses of PREZISTA and ritonavir two times per day or once a day. If prescribed PREZISTA twice daily the child must take one dose in the morning, and one dose in the evening. Your child's doctor will determine the appropriate dosing regimen for your child.
- The child must take PREZISTA with food. PREZISTA cannot work properly without food. The type of food is not important.

### **Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this)**

The usual dose of PREZISTA is 800 milligram once daily.

You must take PREZISTA every day and always in combination with 150 milligram of cobicistat or 100 milligram of ritonavir and with food. PREZISTA cannot work properly without cobicistat or ritonavir and food. You must eat a meal or a snack within 30 minutes prior to taking your PREZISTA and cobicistat or ritonavir. The type of food is not important. Even if you feel better, do not stop taking PREZISTA and cobicistat or ritonavir without talking to your doctor.

### **Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)**

The dose is either:

- 600 milligram PREZISTA together with 100 milligram ritonavir twice daily.  
OR
- 800 milligram PREZISTA together with 150 milligram cobicistat or 100 milligram ritonavir once daily.

Please discuss with your doctor which dose is right for you.

### ***Instructions for adults***

- Take PREZISTA always together with cobicistat or ritonavir. PREZISTA cannot work properly without cobicistat or ritonavir.
- Take PREZISTA with food. PREZISTA cannot work properly without food. The type of food is not important.

### ***Instructions for use***

Use the dosing pipette supplied with the pack to measure your dose accurately:

1. Shake the bottle well before each use.
2. Open the bottle of PREZISTA oral suspension by pushing downward on the cap and twisting it counter-clockwise.



3. Insert the supplied oral dosing pipette all the way into the bottle.

4. Pull the plunger until the top of the barrel meets the line that matches the dose prescribed by your health care provider.
5. Take the dose of PREZISTA. Place the tip of the oral dosing pipette in the mouth. Press on the plunger of the pipette towards the mouth, then swallow.
6. Close the bottle with the cap after use, and store PREZISTA oral suspension as directed in section 5 below.
7. Remove the plunger from the barrel of the pipette, rinse both with water and allow to air dry after each use.
8. Put the oral dosing pipette back together after air drying and store with the PREZISTA bottle.

Do not use the dosing pipette for any other medicines.

**If you take more PREZISTA than you should**

Contact your doctor, pharmacist or nurse immediately.

**If you forget to take PREZISTA**

If you take PREZISTA two times a day and if you notice **within 6 hours**, you must take the oral suspension 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.

If you take PREZISTA once a day and if you notice within **12 hours**, you must take the oral suspension immediately. Always take with cobicistat or ritonavir and food. If you notice **after 12 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 taking PREZISTA without talking to your doctor first**

Anti-HIV medicines may make you feel better. 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 medicine, ask your doctor, pharmacist or nurse.

#### **4. Possible side effects**

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor if you develop any of the following side effects.**

Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start PREZISTA. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or pain and discomfort on your right side below your ribs.

Skin rash (more often when used in combination with raltegravir), itching. The rash is usually mild to moderate. A skin rash might also be a symptom of a rare severe situation. It is important to talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether PREZISTA must be stopped.

Other severe side effects were diabetes (common) and inflammation of the pancreas (uncommon).

Very common side effects (may affect more than 1 in 10 people)

- diarrhoea.

Common side effects (may affect up to 1 in 10 people)

- vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

Uncommon side effects (may affect up to 1 in 100 people)

- chest pain, changes in electrocardiogram, rapid heart beating
- decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory, problems with your balance
- difficulty breathing, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching
- kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of urine, sometimes at night
- urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails
- muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis
- slowing down of the thyroid gland function. This can be seen in a blood test.
- high blood pressure, flushing
- red or dry eyes
- fever, swelling of lower limbs due to fluids, malaise, irritability, pain
- symptoms of infection, herpes simplex
- erectile dysfunction, enlargement of breasts
- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive

Rare side effects (may affect up to 1 in 1,000 people)

- a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung]
- heart attack, slow heart beating, palpitations
- visual disturbance
- chills, feeling abnormal
- a feeling of confusion or disorientation, altered mood, restlessness
- fainting, epileptic fits, changes or loss of taste
- mouth sores, vomiting blood, inflammation of the lips, dry lips, coated tongue
- running nose
- skin lesions, dry skin
- stiffness of muscles or joints, joint pain with or without inflammation
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.

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

- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.

### **Reporting of side effects**

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store PREZISTA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not refrigerate or freeze. Avoid exposure to excessive heat.

Store in the original container.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What PREZISTA contains

- The active substance is darunavir. Each milliliter contains 100 milligram of darunavir (as ethanolate).
- The other ingredients are hydroxypropylcellulose, microcrystalline cellulose and carmellose sodium, citric acid monohydrate, sucralose, strawberry cream flavour, masking flavour, sodium methyl parahydroxybenzoate (E219), hydrochloric acid (for pH adjustment), purified water.
- This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

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

White to off-white opaque oral suspension. Provided in a 200 ml amber glass bottle with polypropylene child resistant closure and a 6 ml low density polyethylene (LDPE) oral dosing pipette with 0.2 ml gradations. The bottle neck is filled with a low density polyethylene (LDPE) insert that accommodates the dosing pipette. Do not use the oral dosing pipette for any other medicines. PREZISTA is also available as 75 milligram, 150 milligram, 300 milligram, 400 milligram, 600 milligram and 800 milligram film-coated tablets.

### Marketing Authorisation Holder

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

### Manufacturer

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**This leaflet was last revised in {MM/YYYY}.**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

## Package leaflet: Information for the user

### PREZISTA 75 mg film-coated tablets darunavir

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What PREZISTA is and what it is used for
2. What you need to know before you take PREZISTA
3. How to take PREZISTA
4. Possible side effects
5. How to store PREZISTA
6. Contents of the pack and other information

#### **1. What PREZISTA is and what it is used for**

##### **What is PREZISTA?**

PREZISTA contains the active substance darunavir. 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 and children of 3 years of age and above, and at least 15 kilogram body weight who are infected by HIV and who have already used 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. What you need to know before you take PREZISTA**

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

- if you are **allergic** to darunavir or any of the other ingredients of this medicine (listed in section 6) 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**

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

| Medicine   | Purpose of the medicine                       |
|--|---|
| <i>Avanafil</i>  | to treat erectile dysfunction                 |
| <i>Astemizole</i> or <i>terfenadine</i>                            | to treat allergy symptoms                     |
| <i>Triazolam</i> and <i>oral</i> (taken by mouth) <i>midazolam</i> | to help you sleep and/or relieve anxiety      |
| <i>Cisapride</i>   | to treat some stomach conditions              |
| <i>Colchicine</i> (if you have kidney and/or liver problems)       | to treat gout or familial Mediterranean fever |

|   |  |
|---|--|
| <i>Lurasidone, pimozone, quetiapine or sertindole</i>                                       | to treat psychiatric conditions  |
| <i>Ergot alkaloids like ergotamine, dihydroergotamine, ergometrine and methylergonovine</i> | to treat migraine headaches  |
| <i>Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine</i>                 | to treat certain heart disorders e.g. abnormal heart beat  |
| <i>Lovastatin, simvastatin and lomitapide</i>   | to lower cholesterol levels  |
| <i>Rifampicin</i>   | to treat some infections such as tuberculosis  |
| The combination product <i>lopinavir/ritonavir</i>  | this anti-HIV medicine belongs to the same class as PREZISTA   |
| <i>Elbasvir/grazoprevir</i>   | to treat hepatitis C infection   |
| <i>Alfuzosin</i>  | to treat enlarged prostate   |
| <i>Sildenafil</i>   | to treat high blood pressure in the pulmonary circulation  |
| <i>Dabigatran, ticagrelor</i>   | to help stop the clumping of platelets in the treatment of patients with a history of a heart attack |
| <i>Naloxegol</i>  | to treat opioid induced constipation   |
| <i>Dapoxetine</i>   | to treat premature ejaculation   |
| <i>Domperidone</i>  | to treat nausea and vomiting   |

Do not combine PREZISTA with products that contain St John's wort (*Hypericum perforatum*).

### Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking PREZISTA.

PREZISTA is not a cure for HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

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

People taking PREZISTA may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking PREZISTA and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

### Tell your doctor about your situation BEFORE and DURING your treatment

Make sure that you check the following 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 infection. 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** (for example enlarged lymph nodes and fever). 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.
- In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of

the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- 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.

### **Elderly**

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.

### **Children**

PREZISTA is not for use in children younger than 3 years of age or weighing less than 15 kilograms.

### **Other medicines and PREZISTA**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

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 medicines:'

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), CCR5 antagonists and FIs (fusion inhibitors)]. PREZISTA with ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. In some cases dosage of other medicines might need to be changed. 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* (to prevent seizures)
- *Dexamethasone* (corticosteroid)
- *Efavirenz* (HIV infection)
- *Boceprevir* (hepatitis C infection)
- *Rifapentine, rifabutin* (medicines to treat some infections such as tuberculosis)
- *Saquinavir* (HIV infection).

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

- *Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nicardipine, propafenone, timolol, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Apixaban, edoxaban, rivaroxaban, warfarin* (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. PREZISTA might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.
- *Ethinylestradiol/drospirenone*. PREZISTA might increase the risk for elevated potassium levels by drospirenone.

- *Atorvastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Clarithromycin* (antibiotic)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased. Your doctor might want to do some additional tests.
- *Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone*. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone* (medicines to treat opioid dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria)
- *Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine* (to treat cancer)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension)
- *Glecaprevir/pibrentasvir, simeprevir* (to treat hepatitis C infection)
- *Fentanyl, oxycodone, tramadol* (to treat pain)
- *Fesoterodine, solifenacin* (to treat urologic disorders).

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

Tell your doctor if you take:

- *Alfentanil* (injectable strong and short-acting painkiller that is used for surgical procedures)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Itraconazole, isavuconazole, fluconazole, posaconazole, clotrimazole* (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- *Rifabutin* (against bacterial infections)
- *Sildenafil, vardenafil, tadalafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Maraviroc* (to treat HIV infection)
- *Methadone* (to treat opiate dependence)
- *Carbamazepine, clonazepam* (to prevent seizures or to treat certain types of nerve pain)
- *Colchicine* (to treat gout or familial Mediterranean fever)
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam when used as injection, zolpidem* (sedative agents)
- *Perphenazine, risperidone, thioridazine* (to treat psychiatric conditions).

This is **not** a complete list of medicines. Tell your healthcare provider about **all** medicines that you are taking.

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

See section 3 'How to take PREZISTA.'

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

Tell your doctor immediately if you are pregnant, planning to become pregnant or if you are breast-feeding. Pregnant or breast-feeding mothers should not take PREZISTA with ritonavir unless specifically directed by the doctor. Pregnant or breast-feeding mothers should not take PREZISTA with cobicistat.

It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of your baby becoming infected with HIV through your breast milk and because of the unknown effects of the medicine on your baby.

### **Driving and using machines**

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

### **3. How to take PREZISTA**

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

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

After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

#### **Dose for children of 3 years of age and above, weighing at least 15 kilograms who have not taken antiretroviral medicines before (your child's doctor will determine this)**

The doctor will work out the right once daily dose based on the weight of the child (see table below). This dose must not exceed the recommended adult dose, which is 800 milligram PREZISTA together with 100 milligram ritonavir once a day.

The doctor will inform you on how much PREZISTA tablets and how much ritonavir (capsules, tablets or solution) the child must take.

| <b>Weight</b>               | <b>One PREZISTA dose is</b> | <b>One ritonavir<sup>a</sup> dose is</b> |
|-----------------------------|-----------------------------|--|
| between 15 and 30 kilograms | 600 milligram               | 100 milligram                            |
| between 30 and 40 kilograms | 675 milligram               | 100 milligram                            |
| more than 40 kilograms      | 800 milligram               | 100 milligram                            |

<sup>a</sup> ritonavir oral solution: 80 milligram per milliliter

#### **Dose for children of 3 years of age and above, weighing at least 15 kilograms who have taken antiretroviral medicines before (your child's doctor will determine this)**

The doctor will work out the right dose based on the weight of the child (see table below). The doctor will determine if once daily dosing or twice daily dosing is appropriate for the child. This dose must not exceed the recommended adult dose, which is 600 milligram PREZISTA together with 100 milligram ritonavir two times per day or 800 milligram PREZISTA together with 100 milligram ritonavir once a day.

The doctor will inform you on how many PREZISTA tablets and how much ritonavir (capsules, tablets or solution) the child must take. Tablets of other strengths are available and your doctor may have prescribed a certain combination of tablets to construct the appropriate dosing regimen. PREZISTA oral suspension is also available. Your doctor will determine whether PREZISTA tablets or oral suspension is right for the child.

#### **Twice daily dosing**

| <b>Weight</b>               | <b>One dose is</b>   |
|-----------------------------|--|
| between 15 and 30 kilograms | 375 milligram PREZISTA + 50 milligram ritonavir twice a day  |
| between 30 and 40 kilograms | 450 milligram PREZISTA + 60 milligram ritonavir twice a day  |
| more than 40 kilograms*     | 600 milligram PREZISTA + 100 milligram ritonavir twice a day |

\* For children aged 12 or more and weighing at least 40 kilograms, your child's doctor will determine if PREZISTA 800 milligram once daily dosing may be used. This cannot be administered with these 75 milligram tablets. Other strengths of PREZISTA are available.

#### **Once daily dosing**

| <b>Weight</b>               | <b>One PREZISTA dose is</b> | <b>One ritonavir<sup>a</sup> dose is</b> |
|-----------------------------|-----------------------------|--|
| between 15 and 30 kilograms | 600 milligram               | 100 milligram                            |
| between 30 and 40 kilograms | 675 milligram               | 100 milligram                            |

|                        |               |               |
|------------------------|---------------|---------------|
| more than 40 kilograms | 800 milligram | 100 milligram |
|------------------------|---------------|---------------|

<sup>a</sup> ritonavir oral solution: 80 milligram per milliliter

### **Instructions for children**

- The child must take PREZISTA always together with ritonavir. PREZISTA cannot work properly without ritonavir.
- The child must take the appropriate doses of PREZISTA and ritonavir two times per day or once a day. If prescribed PREZISTA twice daily the child must take one dose in the morning, and one dose in the evening. Your child's doctor will determine the appropriate dosing regimen for your child.
- The child must take PREZISTA with food. PREZISTA cannot work properly without food. The type of food is not important.
- The child must swallow the tablets with a drink such as water or milk.

### **Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this)**

You will require a different dose of PREZISTA which cannot be administered with these 75 milligram tablets. Other strengths of PREZISTA are available.

### **Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)**

The dose is either:

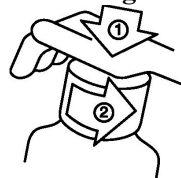
- 600 milligram PREZISTA (2 tablets containing 300 milligram of PREZISTA or 1 tablet containing 600 milligram of PREZISTA) together with 100 milligram ritonavir twice daily.  
OR
- 800 milligram PREZISTA (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) together with 100 milligram ritonavir once daily. PREZISTA 400 milligram and 800 milligram tablets are only to be used to construct the once daily 800 milligram regimen.

Please discuss with your doctor which dose is right for you.

### **Instructions for adults**

- Take PREZISTA always together with ritonavir. PREZISTA cannot work properly without ritonavir.
- In the morning, take 600 milligram PREZISTA together with 100 milligram ritonavir.
- In the evening, take 600 milligram PREZISTA 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.
- PREZISTA 75 milligram and 150 milligram tablets and 100 milligram per milliliter oral suspension have been developed for use in children, but can also be used in adults in some cases.

### **Removing the child resistant cap**



The plastic bottle comes with a child resistant cap and must 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, pharmacist or nurse 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 taking PREZISTA without talking to your doctor first**

Anti-HIV medicines may make you feel better. 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 medicine, ask your doctor, pharmacist or nurse.

**4. Possible side effects**

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor if you develop any of the following side effects.**

Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start PREZISTA. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or pain and discomfort on your right side below your ribs.

Skin rash (more often when used in combination with raltegravir), itching. 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 talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether PREZISTA must be stopped.

Other severe side effects were diabetes (common) and inflammation of the pancreas (uncommon).

Very common side effects (may affect more than 1 in 10 people)

- diarrhoea.

Common side effects (may affect up to 1 in 10 people)

- vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

Uncommon side effects (may affect up to 1 in 100 people)

- chest pain, changes in electrocardiogram, rapid heart beating
- decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory, problems with your balance
- difficulty breathing, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching
- kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of urine, sometimes at night
- urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails
- muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis
- slowing down of the thyroid gland function. This can be seen in a blood test.
- high blood pressure, flushing
- red or dry eyes
- fever, swelling of lower limbs due to fluids, malaise, irritability, pain



- symptoms of infection, herpes simplex
- erectile dysfunction, enlargement of breasts
- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive

Rare side effects (may affect up to 1 in 1,000 people)

- a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung]
- heart attack, slow heart beating, palpitations
- visual disturbance
- chills, feeling abnormal
- a feeling of confusion or disorientation, altered mood, restlessness
- fainting, epileptic fits, changes or loss of taste
- mouth sores, vomiting blood, inflammation of the lips, dry lips, coated tongue
- running nose
- skin lesions, dry skin
- stiffness of muscles or joints, joint pain with or without inflammation
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.

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

- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.

### **Reporting of side effects**

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store PREZISTA**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after EXP. The expiry date refers to the last day of that month.

PREZISTA does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What PREZISTA contains**

- The active substance is darunavir. Each tablet contains 75 milligram of darunavir (as ethanolate).
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate. The film-coating contains poly(vinyl alcohol) - partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc.
- This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

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

Film-coated, white, caplet shaped tablet, mentioning TMC on one side, 75 on the other side.  
480 tablets in a plastic bottle.

PREZISTA is also available as 150 milligram, 300 milligram, 400 milligram, 600 milligram and 800 milligram film-coated tablets and 100 milligram per milliliter oral suspension.

**Marketing Authorisation Holder**

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

**Manufacturer**

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**This leaflet was last revised in {MM/YYYY}.**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

## Package leaflet: Information for the user

### PREZISTA 150 mg film-coated tablets darunavir

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What PREZISTA is and what it is used for
2. What you need to know before you take PREZISTA
3. How to take PREZISTA
4. Possible side effects
5. How to store PREZISTA
6. Contents of the pack and other information

#### **1. What PREZISTA is and what it is used for**

##### **What is PREZISTA?**

PREZISTA contains the active substance darunavir. 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 and children of 3 years of age and above, and at least 15 kilogram body weight who are infected by HIV and who have already used 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. What you need to know before you take PREZISTA**

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

- if you are **allergic** to darunavir or any of the other ingredients of this medicine (listed in section 6) 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**

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

| Medicine   | Purpose of the medicine                       |
|--|---|
| <i>Avanafil</i>  | to treat erectile dysfunction                 |
| <i>Astemizole</i> or <i>terfenadine</i>                            | to treat allergy symptoms                     |
| <i>Triazolam</i> and <i>oral</i> (taken by mouth) <i>midazolam</i> | to help you sleep and/or relieve anxiety      |
| <i>Cisapride</i>   | to treat some stomach conditions              |
| <i>Colchicine</i> (if you have kidney and/or liver problems)       | to treat gout or familial Mediterranean fever |

|   |  |
|---|--|
| <i>Lurasidone, pimozone, quetiapine or sertindole</i>                                       | to treat psychiatric conditions  |
| <i>Ergot alkaloids like ergotamine, dihydroergotamine, ergometrine and methylergonovine</i> | to treat migraine headaches  |
| <i>Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine</i>                 | to treat certain heart disorders e.g. abnormal heart beat  |
| <i>Lovastatin, simvastatin and lomitapide</i>   | to lower cholesterol levels  |
| <i>Rifampicin</i>   | to treat some infections such as tuberculosis  |
| The combination product <i>lopinavir/ritonavir</i>  | this anti-HIV medicine belongs to the same class as PREZISTA   |
| <i>Elbasvir/grazoprevir</i>   | to treat hepatitis C infection   |
| <i>Alfuzosin</i>  | to treat enlarged prostate   |
| <i>Sildenafil</i>   | to treat high blood pressure in the pulmonary circulation  |
| <i>Dabigatran, ticagrelor</i>   | to help stop the clumping of platelets in the treatment of patients with a history of a heart attack |
| <i>Naloxegol</i>  | to treat opioid induced constipation   |
| <i>Dapoxetine</i>   | to treat premature ejaculation   |
| <i>Domperidone</i>  | to treat nausea and vomiting   |

Do not combine PREZISTA with products that contain St John's wort (*Hypericum perforatum*).

### Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking PREZISTA.

PREZISTA is not a cure for HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

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

People taking PREZISTA may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking PREZISTA and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

### Tell your doctor about your situation BEFORE and DURING your treatment

Make sure that you check the following 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 infection. 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** (for example enlarged lymph nodes and fever). 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.
- In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of

the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- 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.

### **Elderly**

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.

### **Children**

PREZISTA is not for use in children younger than 3 years of age or weighing less than 15 kilograms.

### **Other medicines and PREZISTA**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

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 medicines:'

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), CCR5 antagonists and FIs (fusion inhibitors)]. PREZISTA with ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. In some cases dosage of other medicines might need to be changed. 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* (to prevent seizures)
- *Dexamethasone* (corticosteroid)
- *Efavirenz* (HIV infection)
- *Boceprevir* (hepatitis C infection)
- *Rifapentine, rifabutin* (medicines to treat some infections such as tuberculosis)
- *Saquinavir* (HIV infection).

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

- *Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nicardipine, propafenone, timolol, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Apixaban, edoxaban, rivaroxaban, warfarin* (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. PREZISTA might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.
- *Ethinylestradiol/drospirenone*. PREZISTA might increase the risk for elevated potassium levels by drospirenone.

- *Atorvastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Clarithromycin* (antibiotic)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased. Your doctor might want to do some additional tests.
- *Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone*. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone* (medicines to treat opioid dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria)
- *Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine* (to treat cancer)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension)
- *Glecaprevir/pibrentasvir, simeprevir* (to treat hepatitis C infection)
- *Fentanyl, oxycodone, tramadol* (to treat pain)
- *Fesoterodine, solifenacin* (to treat urologic disorders).

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

Tell your doctor if you take:

- *Alfentanil* (injectable strong and short-acting painkiller that is used for surgical procedures)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Itraconazole, isavuconazole, fluconazole, posaconazole, clotrimazole* (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- *Rifabutin* (against bacterial infections)
- *Sildenafil, vardenafil, tadalafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Maraviroc* (to treat HIV infection)
- *Methadone* (to treat opiate dependence)
- *Carbamazepine, clonazepam* (to prevent seizures or to treat certain types of nerve pain)
- *Colchicine* (to treat gout or familial Mediterranean fever)
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam when used as injection, zolpidem* (sedative agents)
- *Perphenazine, risperidone, thioridazine* (to treat psychiatric conditions).

This is **not** a complete list of medicines. Tell your healthcare provider about **all** medicines that you are taking.

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

See section 3 'How to take PREZISTA.'

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

Tell your doctor immediately if you are pregnant, planning to become pregnant or if you are breast-feeding. Pregnant or breast-feeding mothers should not take PREZISTA with ritonavir unless specifically directed by the doctor. Pregnant or breast-feeding mothers should not take PREZISTA with cobicistat.

It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of your baby becoming infected with HIV through your breast milk and because of the unknown effects of the medicine on your baby.

### **Driving and using machines**

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

### **3. How to take PREZISTA**

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

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

After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

#### **Dose for children of 3 years of age and above, weighing at least 15 kilograms who have not taken antiretroviral medicines before (your child's doctor will determine this)**

The doctor will work out the right once daily dose based on the weight of the child (see table below). This dose must not exceed the recommended adult dose, which is 800 milligram PREZISTA together with 100 milligram ritonavir once a day.

The doctor will inform you on how much PREZISTA tablets and how much ritonavir (capsules, tablets or solution) the child must take.

| <b>Weight</b>               | <b>One PREZISTA dose is</b> | <b>One ritonavir<sup>a</sup> dose is</b> |
|-----------------------------|-----------------------------|--|
| between 15 and 30 kilograms | 600 milligram               | 100 milligram                            |
| between 30 and 40 kilograms | 675 milligram               | 100 milligram                            |
| more than 40 kilograms      | 800 milligram               | 100 milligram                            |

<sup>a</sup> ritonavir oral solution: 80 milligram per milliliter

#### **Dose for children of 3 years of age and above, weighing at least 15 kilograms who have taken antiretroviral medicines before (your child's doctor will determine this)**

The doctor will work out the right dose based on the weight of the child (see table below). The doctor will determine if once daily dosing or twice daily dosing is appropriate for the child. This dose must not exceed the recommended adult dose, which is 600 milligram PREZISTA together with 100 milligram ritonavir two times per day or 800 milligram PREZISTA together with 100 milligram ritonavir once a day.

The doctor will inform you on how many PREZISTA tablets and how much ritonavir (capsules, tablets or solution) the child must take. Tablets of other strengths are available and your doctor may have prescribed a certain combination of tablets to construct the appropriate dosing regimen. PREZISTA oral suspension is also available. Your doctor will determine whether PREZISTA tablets or oral suspension is right for the child.

#### **Twice daily dosing**

| <b>Weight</b>               | <b>One dose is</b>   |
|-----------------------------|--|
| between 15 and 30 kilograms | 375 milligram PREZISTA + 50 milligram ritonavir twice a day  |
| between 30 and 40 kilograms | 450 milligram PREZISTA + 60 milligram ritonavir twice a day  |
| more than 40 kilograms*     | 600 milligram PREZISTA + 100 milligram ritonavir twice a day |

\* For children aged 12 or more and weighing at least 40 kilograms, your child's doctor will determine if PREZISTA 800 milligram once daily dosing may be used. This cannot be administered with these 150 milligram tablets. Other strengths of PREZISTA are available.

#### **Once daily dosing**

| <b>Weight</b>               | <b>One PREZISTA dose is</b> | <b>One ritonavir<sup>a</sup> dose is</b> |
|-----------------------------|-----------------------------|--|
| between 15 and 30 kilograms | 600 milligram               | 100 milligram                            |
| between 30 and 40 kilograms | 675 milligram               | 100 milligram                            |



|                        |               |               |
|------------------------|---------------|---------------|
| more than 40 kilograms | 800 milligram | 100 milligram |
|------------------------|---------------|---------------|

<sup>a</sup> ritonavir oral solution: 80 milligram per milliliter

### **Instructions for children**

- The child must take PREZISTA always together with ritonavir. PREZISTA cannot work properly without ritonavir.
- The child must take the appropriate doses of PREZISTA and ritonavir two times per day or once a day. If prescribed PREZISTA twice daily the child must take one dose in the morning, and one dose in the evening. Your child's doctor will determine the appropriate dosing regimen for your child.
- The child must take PREZISTA with food. PREZISTA cannot work properly without food. The type of food is not important.
- The child must swallow the tablets with a drink such as water or milk.

### **Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this)**

You will require a different dose of PREZISTA which cannot be administered with these 150 milligram tablets. Other strengths of PREZISTA are available.

### **Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)**

The dose is either:

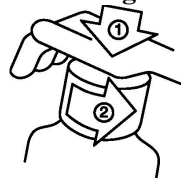
- 600 milligram PREZISTA (2 tablets containing 300 milligram of PREZISTA or 1 tablet containing 600 milligram of PREZISTA) together with 100 milligram ritonavir twice daily.  
OR
- 800 milligram PREZISTA (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) together with 100 milligram ritonavir once daily. PREZISTA 400 milligram and 800 milligram tablets are only to be used to construct the once daily 800 milligram regimen.

Please discuss with your doctor which dose is right for you.

### **Instructions for adults**

- Take PREZISTA always together with ritonavir. PREZISTA cannot work properly without ritonavir.
- In the morning, take 600 milligram PREZISTA together with 100 milligram ritonavir.
- In the evening, take 600 milligram PREZISTA 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.
- PREZISTA 75 milligram and 150 milligram tablets and 100 milligram per milliliter oral suspension have been developed for use in children, but can also be used in adults in some cases.

### **Removing the child resistant cap**



The plastic bottle comes with a child resistant cap and must 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, pharmacist or nurse 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 taking PREZISTA without talking to your doctor first**

Anti-HIV medicines may make you feel better. 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 medicine, ask your doctor, pharmacist or nurse.

**4. Possible side effects**

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor if you develop any of the following side effects.**

Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start PREZISTA. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or pain and discomfort on your right side below your ribs.

Skin rash (more often when used in combination with raltegravir), itching. 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 talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether PREZISTA must be stopped.

Other severe side effects were diabetes (common) and inflammation of the pancreas (uncommon).

Very common side effects (may affect more than 1 in 10 people)

- diarrhoea.

Common side effects (may affect up to 1 in 10 people)

- vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

Uncommon side effects (may affect up to 1 in 100 people)

- chest pain, changes in electrocardiogram, rapid heart beating
- decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory, problems with your balance
- difficulty breathing, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching
- kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of urine, sometimes at night
- urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails
- muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis
- slowing down of the thyroid gland function. This can be seen in a blood test.
- high blood pressure, flushing
- red or dry eyes
- fever, swelling of lower limbs due to fluids, malaise, irritability, pain

- symptoms of infection, herpes simplex
- erectile dysfunction, enlargement of breasts
- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive

Rare side effects (may affect up to 1 in 1,000 people)

- a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung]
- heart attack, slow heart beating, palpitations
- visual disturbance
- chills, feeling abnormal
- a feeling of confusion or disorientation, altered mood, restlessness
- fainting, epileptic fits, changes or loss of taste
- mouth sores, vomiting blood, inflammation of the lips, dry lips, coated tongue
- running nose
- skin lesions, dry skin
- stiffness of muscles or joints, joint pain with or without inflammation
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.

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

- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.

### **Reporting of side effects**

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store PREZISTA**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after EXP. The expiry date refers to the last day of that month.

PREZISTA does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What PREZISTA contains**

- The active substance is darunavir. Each tablet contains 150 milligram of darunavir (as ethanolate).
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate. The film-coating contains poly(vinyl alcohol) - partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc.
- This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

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

Film-coated, white, oval shaped tablet, mentioning TMC on one side, 150 on the other side.

240 tablets in a plastic bottle.

PREZISTA is also available as 75 milligram, 300 milligram, 400 milligram, 600 milligram and 800 milligram film-coated tablets and 100 milligram per milliliter oral suspension.

**Marketing Authorisation Holder**

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**Manufacturer**

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**This leaflet was last revised in {MM/YYYY}.**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

## 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 because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

1. What PREZISTA is and what it is used for
2. What you need to know before you take PREZISTA
3. How to take PREZISTA
4. Possible side effects
5. How to store PREZISTA
6. Contents of the pack and other information

#### 1. What PREZISTA is and what it is used for

##### What is PREZISTA?

PREZISTA contains the active substance darunavir. 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 and children of 3 years of age and above, and at least 15 kilogram body weight who are infected by HIV and who have already used 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. What you need to know before you take PREZISTA

##### Do not take PREZISTA

- if you are **allergic** to darunavir or any of the other ingredients of this medicine (listed in section 6) 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

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

| Medicine   | Purpose of the medicine                       |
|--|---|
| <i>Avanafil</i>  | to treat erectile dysfunction                 |
| <i>Astemizole</i> or <i>terfenadine</i>                            | to treat allergy symptoms                     |
| <i>Triazolam</i> and <i>oral</i> (taken by mouth) <i>midazolam</i> | to help you sleep and/or relieve anxiety      |
| <i>Cisapride</i>   | to treat some stomach conditions              |
| <i>Colchicine</i> (if you have kidney and/or liver problems)       | to treat gout or familial Mediterranean fever |

|   |  |
|---|--|
| <i>Lurasidone, pimozone, quetiapine or sertindole</i>                                       | to treat psychiatric conditions  |
| <i>Ergot alkaloids like ergotamine, dihydroergotamine, ergometrine and methylergonovine</i> | to treat migraine headaches  |
| <i>Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine</i>                 | to treat certain heart disorders e.g. abnormal heart beat  |
| <i>Lovastatin, simvastatin and lomitapide</i>   | to lower cholesterol levels  |
| <i>Rifampicin</i>   | to treat some infections such as tuberculosis  |
| The combination product <i>lopinavir/ritonavir</i>  | this anti-HIV medicine belongs to the same class as PREZISTA   |
| <i>Elbasvir/grazoprevir</i>   | to treat hepatitis C infection   |
| <i>Alfuzosin</i>  | to treat enlarged prostate   |
| <i>Sildenafil</i>   | to treat high blood pressure in the pulmonary circulation  |
| <i>Dabigatran, ticagrelor</i>   | to help stop the clumping of platelets in the treatment of patients with a history of a heart attack |
| <i>Naloxegol</i>  | to treat opioid induced constipation   |
| <i>Dapoxetine</i>   | to treat premature ejaculation   |
| <i>Domperidone</i>  | to treat nausea and vomiting   |

Do not combine PREZISTA with products that contain St John's wort (*Hypericum perforatum*).

### Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking PREZISTA.

PREZISTA is not a cure for HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

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

People taking PREZISTA may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking PREZISTA and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

### Tell your doctor about your situation BEFORE and DURING your treatment

Make sure that you check the following 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 infection. 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** (for example enlarged lymph nodes and fever). 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.
- In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of

the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- 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.

### **Elderly**

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.

### **Children**

PREZISTA is not for use in children younger than 3 years of age or weighing less than 15 kilograms.

### **Other medicines and PREZISTA**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

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 medicines:'

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), CCR5 antagonists and FIs (fusion inhibitors)]. PREZISTA with ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. In some cases dosage of other medicines might need to be changed. 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* (to prevent seizures)
- *Dexamethasone* (corticosteroid)
- *Efavirenz* (HIV infection)
- *Boceprevir* (hepatitis C infection)
- *Rifapentine, rifabutin* (medicines to treat some infections such as tuberculosis)
- *Saquinavir* (HIV infection).

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

- *Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nicardipine, propafenone, timolol, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Apixaban, edoxaban, rivaroxaban, warfarin* (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. PREZISTA might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.
- *Ethinylestradiol/drospirenone*. PREZISTA might increase the risk for elevated potassium levels by drospirenone.



- *Atorvastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Clarithromycin* (antibiotic)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased. Your doctor might want to do some additional tests.
- *Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone*. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone* (medicines to treat opioid dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria)
- *Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine* (to treat cancer)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension)
- *Glecaprevir/pibrentasvir, simeprevir* (to treat hepatitis C infection)
- *Fentanyl, oxycodone, tramadol* (to treat pain)
- *Fesoterodine, solifenacin* (to treat urologic disorders).

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

Tell your doctor if you take:

- *Alfentanil* (injectable strong and short-acting painkiller that is used for surgical procedures)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Itraconazole, isavuconazole, fluconazole, posaconazole, clotrimazole* (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- *Rifabutin* (against bacterial infections)
- *Sildenafil, vardenafil, tadalafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Maraviroc* (to treat HIV infection)
- *Methadone* (to treat opiate dependence)
- *Carbamazepine, clonazepam* (to prevent seizures or to treat certain types of nerve pain)
- *Colchicine* (to treat gout or familial Mediterranean fever)
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam when used as injection, zolpidem* (sedative agents)
- *Perphenazine, risperidone, thioridazine* (to treat psychiatric conditions).

This is **not** a complete list of medicines. Tell your healthcare provider about **all** medicines that you are taking.

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

See section 3 'How to take PREZISTA.'

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

Tell your doctor immediately if you are pregnant, planning to become pregnant or if you are breast-feeding. Pregnant or breast-feeding mothers should not take PREZISTA with ritonavir unless specifically directed by the doctor. Pregnant or breast-feeding mothers should not take PREZISTA with cobicistat.

It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of your baby becoming infected with HIV through your breast milk and because of the unknown effects of the medicine on your baby.

### **Driving and using machines**

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

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

### **3. How to take PREZISTA**

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

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

After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

#### **Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this)**

You will require a different dose of PREZISTA which cannot be administered with these 300 milligram tablets. Other strengths of PREZISTA are available.

#### **Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)**

The dose is either:

- 600 milligram PREZISTA (2 tablets containing 300 milligram of PREZISTA or 1 tablet containing 600 milligram of PREZISTA) together with 100 milligram ritonavir twice daily.  
OR
- 800 milligram PREZISTA (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) together with 100 milligram ritonavir once daily. PREZISTA 400 milligram and 800 milligram tablets are only to be used to construct the once daily 800 milligram regimen.

Please discuss with your doctor which dose is right for you.

#### **Instructions for adults**

- 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.
- PREZISTA 75 milligram and 150 milligram tablets and 100 milligram per milliliter oral suspension have been developed for use in children, but can also be used in adults in some cases.

#### **Dose for children of 3 years of age and above, weighing at least 15 kilograms who have not taken antiretroviral medicines before (your child's doctor will determine this)**

The doctor will work out the right once daily dose based on the weight of the child (see table below). This dose must not exceed the recommended adult dose, which is 800 milligram PREZISTA together with 100 milligram ritonavir once a day.

The doctor will inform you on how much PREZISTA tablets and how much ritonavir (capsules, tablets or solution) the child must take.

| Weight                      | One PREZISTA dose is | One ritonavir <sup>a</sup> dose is |
|-----------------------------|----------------------|------------------------------------|
| between 15 and 30 kilograms | 600 milligram        | 100 milligram                      |
| between 30 and 40 kilograms | 675 milligram        | 100 milligram                      |
| more than 40 kilograms      | 800 milligram        | 100 milligram                      |

<sup>a</sup> ritonavir oral solution: 80 milligram per milliliter

**Dose for children of 3 years of age and above, weighing at least 15 kilograms who have taken antiretroviral medicines before (your child's doctor will determine this)**

The doctor will work out the right dose based on the weight of the child (see table below). The doctor will determine if once daily dosing or twice daily dosing is appropriate for the child. This dose must not exceed the recommended adult dose, which is 600 milligram PREZISTA together with 100 milligram of ritonavir two times per day or 800 milligram PREZISTA together with 100 milligram ritonavir once a day. The doctor will inform you on how many PREZISTA tablets and how much ritonavir (capsules, tablets or solution) the child must take. Tablets of lower strengths are available and your doctor may have prescribed a certain combination of tablets to construct the appropriate dosing regimen. PREZISTA oral suspension is also available. Your doctor will determine whether PREZISTA tablets or oral suspension is right for the child.

**Twice daily dosing**

| Weight                      | One dose is  |
|-----------------------------|--|
| between 15 and 30 kilograms | 375 milligram PREZISTA + 50 milligram ritonavir twice a day  |
| between 30 and 40 kilograms | 450 milligram PREZISTA + 60 milligram ritonavir twice a day  |
| more than 40 kilograms*     | 600 milligram PREZISTA + 100 milligram ritonavir twice a day |

\* For children aged 12 or more and weighing at least 40 kilograms, your child's doctor will determine if PREZISTA 800 milligram once daily dosing may be used. This cannot be administered with these 300 milligram tablets. Other strengths of PREZISTA are available.

**Once daily dosing**

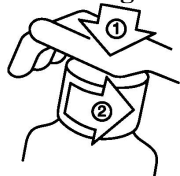
| Weight                      | One PREZISTA dose is | One ritonavir <sup>a</sup> dose is |
|-----------------------------|----------------------|------------------------------------|
| between 15 and 30 kilograms | 600 milligram        | 100 milligram                      |
| between 30 and 40 kilograms | 675 milligram        | 100 milligram                      |
| more than 40 kilograms      | 800 milligram        | 100 milligram                      |

<sup>a</sup> ritonavir oral solution: 80 milligram per milliliter

**Instructions for children**

- The child must take PREZISTA always together with ritonavir. PREZISTA cannot work properly without ritonavir.
- The child must take the appropriate doses of PREZISTA and ritonavir two times per day or once a day. If prescribed PREZISTA twice daily the child must take one dose in the morning, and one dose in the evening. Your child's doctor will determine the appropriate dosing regimen for your child.
- The child must take PREZISTA with food. PREZISTA cannot work properly without food. The type of food is not important.
- The child must 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 must 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, pharmacist or nurse 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 taking PREZISTA without talking to your doctor first**

Anti-HIV medicines may make you feel better. 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 medicine, ask your doctor, pharmacist or nurse.

**4. Possible side effects**

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor if you develop any of the following side effects.**

Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start PREZISTA. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or pain and discomfort on your right side below your ribs.

Skin rash (more often when used in combination with raltegravir), itching. The rash is usually mild to moderate. A skin rash might also be a symptom of a rare severe situation. It is important to talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether PREZISTA must be stopped.

Other severe side effects were diabetes (common) and inflammation of the pancreas (uncommon).

Very common side effects (may affect more than 1 in 10 people)

- diarrhoea.

Common side effects (may affect up to 1 in 10 people)

- vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

Uncommon side effects (may affect up to 1 in 100 people)

- chest pain, changes in electrocardiogram, rapid heart beating
- decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory, problems with your balance
- difficulty breathing, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching
- kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of urine, sometimes at night
- urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails
- muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis

- slowing down of the thyroid gland function. This can be seen in a blood test.
- high blood pressure, flushing
- red or dry eyes
- fever, swelling of lower limbs due to fluids, malaise, irritability, pain
- symptoms of infection, herpes simplex
- erectile dysfunction, enlargement of breasts
- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive

Rare side effects (may affect up to 1 in 1,000 people)

- a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung]
- heart attack, slow heart beating, palpitations
- visual disturbance
- chills, feeling abnormal
- a feeling of confusion or disorientation, altered mood, restlessness
- fainting, epileptic fits, changes or loss of taste
- mouth sores, vomiting blood, inflammation of the lips, dry lips, coated tongue
- running nose
- skin lesions, dry skin
- stiffness of muscles or joints, joint pain with or without inflammation
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.

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

- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.

### **Reporting of side effects**

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store PREZISTA**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after EXP. The expiry date refers to the last day of that month.

PREZISTA does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What PREZISTA contains**

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

- This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

### **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.

PREZISTA is also available as 75 milligram, 150 milligram, 400 milligram, 600 milligram and 800 milligram film-coated tablets and 100 milligram per milliliter oral suspension.

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### **Manufacturer**

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**This leaflet was last revised in {MM/YYYY}.**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

## Package leaflet: Information for the user

### PREZISTA 400 mg film-coated tablets darunavir

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What PREZISTA is and what it is used for
2. What you need to know before you take PREZISTA
3. How to take PREZISTA
4. Possible side effects
5. How to store PREZISTA
6. Contents of the pack and other information

#### **1. What PREZISTA is and what it is used for**

##### **What is PREZISTA?**

PREZISTA contains the active substance darunavir. 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?**

The PREZISTA 400 milligram tablet is used to treat adults and children (3 years of age and above, at least 40 kilograms body weight) who are infected by HIV and

- who have not used antiretroviral medicines before.
- in certain patients who have used antiretroviral medicines before (your doctor will determine this).

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

#### **2. What you need to know before you take PREZISTA**

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

- if you are **allergic** to darunavir or any of the other ingredients of this medicine (listed in section 6) or to cobicistat or 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**

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

| Medicine   | Purpose of the medicine                  |
|--|--|
| <i>Avanafil</i>  | to treat erectile dysfunction            |
| <i>Astemizole</i> or <i>terfenadine</i>                            | to treat allergy symptoms                |
| <i>Triazolam</i> and <i>oral</i> (taken by mouth) <i>midazolam</i> | to help you sleep and/or relieve anxiety |



|   |  |
|---|--|
| <i>Cisapride</i>  | to treat some stomach conditions   |
| <i>Colchicine</i> (if you have kidney and/or liver problems)  | to treat gout or familial Mediterranean fever  |
| <i>Lurasidone, pimozide, quetiapine</i> or <i>sertindole</i>  | to treat psychiatric conditions  |
| <i>Ergot alkaloids</i> like <i>ergotamine</i> , <i>dihydroergotamine</i> , <i>ergometrine</i> and <i>methylergonovine</i> | to treat migraine headaches  |
| <i>Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine</i>   | to treat certain heart disorders e.g. abnormal heart beat  |
| <i>Lovastatin, simvastatin</i> and <i>lomitapide</i>  | to lower cholesterol levels  |
| <i>Rifampicin</i>   | to treat some infections such as tuberculosis  |
| The combination product <i>lopinavir/ritonavir</i>  | this anti-HIV medicine belongs to the same class as PREZISTA   |
| <i>Elbasvir/grazoprevir</i>   | to treat hepatitis C infection   |
| <i>Alfuzosin</i>  | to treat enlarged prostate   |
| <i>Sildenafil</i>   | to treat high blood pressure in the pulmonary circulation  |
| <i>Dabigatran, ticagrelor</i>   | to help stop the clumping of platelets in the treatment of patients with a history of a heart attack |
| <i>Naloxegol</i>  | to treat opioid induced constipation   |
| <i>Dapoxetine</i>   | to treat premature ejaculation   |
| <i>Domperidone</i>  | to treat nausea and vomiting   |

Do not combine PREZISTA with products that contain St John's wort (*Hypericum perforatum*).

### Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking PREZISTA.

PREZISTA is not a cure for HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

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

People taking PREZISTA may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking PREZISTA and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

### Tell your doctor about your situation BEFORE and DURING your treatment

Make sure that you check the following 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 infection. 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** (for example enlarged lymph nodes and fever). 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.
- In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines

for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- 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.

### **Elderly**

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.

### **Children and adolescents**

The PREZISTA 400 milligram tablet is not for use in children younger than 3 years of age or weighing less than 40 kilograms.

### **Other medicines and PREZISTA**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

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 medicines:'

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), CCR5 antagonists and FIs (fusion inhibitors)]. PREZISTA with cobicistat or ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. In some cases dosage of other medicines might need to be changed. 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* (to prevent seizures)
- *Dexamethasone* (corticosteroid)
- *Efavirenz* (HIV infection)
- *Boceprevir* (hepatitis C infection)
- *Rifapentine, rifabutin* (medicines to treat some infections such as tuberculosis)
- *Saquinavir* (HIV infection).

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

- *Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nicardipine, propafenone, timolol, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Apixaban, edoxaban, rivaroxaban, warfarin* (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. PREZISTA might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.

- *Ethinylestradiol/drospirenone*. PREZISTA might increase the risk for elevated potassium levels by drospirenone.
- *Atorvastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Clarithromycin* (antibiotic)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased. Your doctor might want to do some additional tests.
- *Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone*. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone* (medicines to treat opioid dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria)
- *Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine* (to treat cancer)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension)
- *Glecaprevir/pibrentasvir, simeprevir* (to treat hepatitis C infection)
- *Fentanyl, oxycodone, tramadol* (to treat pain)
- *Fesoterodine, solifenacin* (to treat urologic disorders).

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

Tell your doctor if you take:

- *Alfentanil* (injectable strong and short-acting painkiller that is used for surgical procedures)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Itraconazole, isavuconazole, fluconazole, posaconazole, clotrimazole* (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- *Rifabutin* (against bacterial infections)
- *Sildenafil, vardenafil, tadalafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Maraviroc* (to treat HIV infection)
- *Methadone* (to treat opiate dependence)
- *Carbamazepine, clonazepam* (to prevent seizures or to treat certain types of nerve pain)
- *Colchicine* (to treat gout or familial Mediterranean fever)
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam when used as injection, zolpidem* (sedative agents)
- *Perphenazine, risperidone, thioridazine* (to treat psychiatric conditions)
- *Metformin* (to treat type 2 diabetes).

This is **not** a complete list of medicines. Tell your healthcare provider about **all** medicines that you are taking.

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

See section 3 'How to take PREZISTA.'

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

Tell your doctor immediately if you are pregnant, planning to become pregnant or if you are breast-feeding. Pregnant or breast-feeding mothers should not take PREZISTA with ritonavir unless

specifically directed by the doctor. Pregnant or breast-feeding mothers should not take PREZISTA with cobicistat.

It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of your baby becoming infected with HIV through your breast milk and because of the unknown effects of the medicine on your baby.

### **Driving and using machines**

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

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

## **3. How to take PREZISTA**

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

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

After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

PREZISTA 400 milligram tablets are only to be used to construct the once daily 800 milligram regimen.

### **Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this)**

The usual dose of PREZISTA is 800 milligram (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) once daily.

You must take PREZISTA every day and always in combination with 150 milligram of cobicistat or 100 milligram of ritonavir and with food. PREZISTA cannot work properly without cobicistat or ritonavir and food. You must eat a meal or a snack within 30 minutes prior to taking your PREZISTA and cobicistat or ritonavir. The type of food is not important. Even if you feel better, do not stop taking PREZISTA and cobicistat or ritonavir without talking to your doctor.

### **Instructions for adults**

- Take two 400 milligram tablets at the same time, once a day, every day.
- Take PREZISTA always together with 150 milligram of cobicistat or 100 milligram of ritonavir.
- Take PREZISTA with food.
- Swallow the tablets with a drink such as water or milk.
- Take your other HIV medicines used in combination with PREZISTA and cobicistat or ritonavir as recommended by your doctor.
- PREZISTA 100 milligram per milliliter oral suspension has been developed for use in children, but can also be used in adults in some cases.

### **Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)**

The dose is either:

- 800 milligram PREZISTA (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) together with 150 milligram cobicistat or 100 milligram ritonavir once daily.  
OR
- 600 milligram PREZISTA (2 tablets containing 300 milligram of PREZISTA or 1 tablet containing 600 milligram of PREZISTA) together with 100 milligram ritonavir twice daily.

Please discuss with your doctor which dose is right for you.

**Dose for children 3 years of age and above, weighing more than 40 kilograms who have not taken antiretroviral medicines before (your child's doctor will determine this)**

- The usual dose of PREZISTA is 800 milligram (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) together with 100 milligram ritonavir once daily.

**Dose for children 3 years of age and above, weighing more than 40 kilograms who have taken antiretroviral medicines before (your child's doctor will determine this)**

The dose is either:

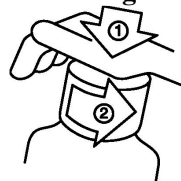
- 800 milligram PREZISTA (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) together with 100 milligram ritonavir once daily.  
OR
- 600 milligram PREZISTA (2 tablets containing 300 milligram of PREZISTA or 1 tablet containing 600 milligram of PREZISTA) together with 100 milligram ritonavir twice daily.

Please discuss with your doctor which dose is right for you.

**Instructions for children 3 years of age and above, weighing more than 40 kilograms**

- Take 800 milligram PREZISTA (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) at the same time, once a day, every day.
- Take PREZISTA always together with 100 milligram of ritonavir.
- Take PREZISTA with food.
- Swallow the tablets with a drink such as water or milk.
- Take your other HIV medicines used in combination with PREZISTA and ritonavir as recommended by your doctor.

**Removing the child resistant cap**



The plastic bottle comes with a child resistant cap and must 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, pharmacist or nurse immediately.

**If you forget to take PREZISTA**

If you notice **within 12 hours**, you must take the tablets immediately. Always take with cobicistat or ritonavir and food. If you notice **after 12 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 taking PREZISTA without talking to your doctor first**

Anti-HIV medicines may make you feel better. 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 medicine, ask your doctor, pharmacist or nurse.

**4. Possible side effects**

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor if you develop any of the following side effects.**

Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start PREZISTA. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or pain and discomfort on your right side below your ribs.

Skin rash (more often when used in combination with raltegravir), itching. The rash is usually mild to moderate. A skin rash might also be a symptom of a rare severe situation. It is important to talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether PREZISTA must be stopped.

Other severe side effects were diabetes (common) and inflammation of the pancreas (uncommon).

Very common side effects (may affect more than 1 in 10 people)

- diarrhoea.

Common side effects (may affect up to 1 in 10 people)

- vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

Uncommon side effects (may affect up to 1 in 100 people)

- chest pain, changes in electrocardiogram, rapid heart beating
- decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory, problems with your balance
- difficulty breathing, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching
- kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of urine, sometimes at night
- urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails
- muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis
- slowing down of the thyroid gland function. This can be seen in a blood test.
- high blood pressure, flushing
- red or dry eyes
- fever, swelling of lower limbs due to fluids, malaise, irritability, pain
- symptoms of infection, herpes simplex
- erectile dysfunction, enlargement of breasts
- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive

Rare side effects (may affect up to 1 in 1,000 people)

- a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung]
- heart attack, slow heart beating, palpitations
- visual disturbance
- chills, feeling abnormal
- a feeling of confusion or disorientation, altered mood, restlessness
- fainting, epileptic fits, changes or loss of taste
- mouth sores, vomiting blood, inflammation of the lips, dry lips, coated tongue
- running nose
- skin lesions, dry skin

- stiffness of muscles or joints, joint pain with or without inflammation
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.

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

- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.

### **Reporting of side effects**

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store PREZISTA**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after EXP. The expiry date refers to the last day of that month.

PREZISTA does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What PREZISTA contains**

- The active substance is darunavir. Each tablet contains 400 milligram of darunavir (as ethanolate).
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate. The film-coating contains poly(vinyl alcohol) - partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc, sunset yellow FCF (E110).
- This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

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

Film-coated, light orange, oval shaped tablet, mentioning TMC on one side, 400MG on the other side. 60 tablets in a plastic bottle.

PREZISTA is also available as 75 milligram, 150 milligram, 300 milligram, 600 milligram and 800 milligram film-coated tablets and 100 milligram per milliliter oral suspension.

### **Marketing Authorisation Holder**

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

### **Manufacturer**

Janssen-Cilag SpA, Via C. Janssen, Borgo San Michele, 04100 Latina, Italy

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**This leaflet was last revised in {MM/YYYY}.**

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

## Package leaflet: Information for the user

### PREZISTA 600 mg film-coated tablets darunavir

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What PREZISTA is and what it is used for
2. What you need to know before you take PREZISTA
3. How to take PREZISTA
4. Possible side effects
5. How to store PREZISTA
6. Contents of the pack and other information

#### **1. What PREZISTA is and what it is used for**

##### **What is PREZISTA?**

PREZISTA contains the active substance darunavir. 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 and children of 3 years of age and above, and at least 15 kilogram body weight who are infected by HIV and who have already used 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. What you need to know before you take PREZISTA**

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

- if you are **allergic** to darunavir or any of the other ingredients of this medicine (listed in section 6) 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**

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

| Medicine   | Purpose of the medicine                       |
|--|---|
| <i>Avanafil</i>  | to treat erectile dysfunction                 |
| <i>Astemizole</i> or <i>terfenadine</i>                            | to treat allergy symptoms                     |
| <i>Triazolam</i> and <i>oral</i> (taken by mouth) <i>midazolam</i> | to help you sleep and/or relieve anxiety      |
| <i>Cisapride</i>   | to treat some stomach conditions              |
| <i>Colchicine</i> (if you have kidney and/or liver problems)       | to treat gout or familial Mediterranean fever |

|   |  |
|---|--|
| <i>Lurasidone, pimozone, quetiapine or sertindole</i>                                       | to treat psychiatric conditions  |
| <i>Ergot alkaloids like ergotamine, dihydroergotamine, ergometrine and methylergonovine</i> | to treat migraine headaches  |
| <i>Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine</i>                 | to treat certain heart disorders e.g. abnormal heart beat  |
| <i>Lovastatin, simvastatin and lomitapide</i>   | to lower cholesterol levels  |
| <i>Rifampicin</i>   | to treat some infections such as tuberculosis  |
| The combination product <i>lopinavir/ritonavir</i>  | this anti-HIV medicine belongs to the same class as PREZISTA   |
| <i>Elbasvir/grazoprevir</i>   | to treat hepatitis C infection   |
| <i>Alfuzosin</i>  | to treat enlarged prostate   |
| <i>Sildenafil</i>   | to treat high blood pressure in the pulmonary circulation  |
| <i>Dabigatran, ticagrelor</i>   | to help stop the clumping of platelets in the treatment of patients with a history of a heart attack |
| <i>Naloxegol</i>  | to treat opioid induced constipation   |
| <i>Dapoxetine</i>   | to treat premature ejaculation   |
| <i>Domperidone</i>  | to treat nausea and vomiting   |

Do not combine PREZISTA with products that contain St John's wort (*Hypericum perforatum*).

### Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking PREZISTA.

PREZISTA is not a cure for HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

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

People taking PREZISTA may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking PREZISTA and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

### Tell your doctor about your situation BEFORE and DURING your treatment

Make sure that you check the following 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 infection. 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** (for example enlarged lymph nodes and fever). 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.
- In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of

the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- 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.

### **Elderly**

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.

### **Children**

PREZISTA is not for use in children younger than 3 years of age or weighing less than 15 kilograms.

### **Other medicines and PREZISTA**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

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 medicines:'

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), CCR5 antagonists and FIs (fusion inhibitors)]. PREZISTA with ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. In some cases dosage of other medicines might need to be changed. 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* (to prevent seizures)
- *Dexamethasone* (corticosteroid)
- *Efavirenz* (HIV infection)
- *Boceprevir* (hepatitis C infection)
- *Rifapentine, rifabutin* (medicines to treat some infections such as tuberculosis)
- *Saquinavir* (HIV infection).

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

- *Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nicardipine, propafenone, timolol, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Apixaban, edoxaban, rivaroxaban, warfarin* (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. PREZISTA might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.
- *Ethinylestradiol/drospirenone*. PREZISTA might increase the risk for elevated potassium levels by drospirenone.

- *Atorvastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Clarithromycin* (antibiotic)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased. Your doctor might want to do some additional tests.
- *Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone*. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone* (medicines to treat opioid dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria)
- *Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine* (to treat cancer)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension)
- *Glecaprevir/pibrentasvir, simeprevir* (to treat hepatitis C infection)
- *Fentanyl, oxycodone, tramadol* (to treat pain)
- *Fesoterodine, solifenacin* (to treat urologic disorders).

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

Tell your doctor if you take:

- *Alfentanil* (injectable strong and short-acting painkiller that is used for surgical procedures)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Itraconazole, isavuconazole, fluconazole, posaconazole, clotrimazole* (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- *Rifabutin* (against bacterial infections)
- *Sildenafil, vardenafil, tadalafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Maraviroc* (to treat HIV infection)
- *Methadone* (to treat opiate dependence)
- *Carbamazepine, clonazepam* (to prevent seizures or to treat certain types of nerve pain)
- *Colchicine* (to treat gout or familial Mediterranean fever)
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam when used as injection, zolpidem* (sedative agents)
- *Perphenazine, risperidone, thioridazine* (to treat psychiatric conditions).

This is **not** a complete list of medicines. Tell your healthcare provider about **all** medicines that you are taking.

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

See section 3 'How to take PREZISTA.'

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

Tell your doctor immediately if you are pregnant, planning to become pregnant or if you are breast-feeding. Pregnant or breast-feeding mothers should not take PREZISTA with ritonavir unless specifically directed by the doctor. Pregnant or breast-feeding mothers should not take PREZISTA with cobicistat.

It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of your baby becoming infected with HIV through your breast milk and because of the unknown effects of the medicine on your baby.

### **Driving and using machines**

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

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

## **3. How to take PREZISTA**

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

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

After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

### **Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this)**

You will require a different dose of PREZISTA which cannot be administered with these 600 milligram tablets. Other strengths of PREZISTA are available.

### **Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)**

The dose is either:

- 600 milligram PREZISTA (2 tablets containing 300 milligram of PREZISTA or 1 tablet containing 600 milligram of PREZISTA) together with 100 milligram ritonavir twice daily.  
OR
- 800 milligram PREZISTA (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) together with 100 milligram ritonavir once daily.  
PREZISTA 400 milligram and 800 milligram tablets are only to be used to construct the once daily 800 milligram regimen.

Please discuss with your doctor which dose is right for you.

### **Instructions for adults**

- Take PREZISTA always together with ritonavir. PREZISTA cannot work properly without ritonavir.
- In the morning, take one 600 milligram PREZISTA tablet together with 100 milligram ritonavir.
- In the evening, take one 600 milligram PREZISTA tablet 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.
- PREZISTA 75 milligram and 150 milligram tablets and 100 milligram per milliliter oral suspension have been developed for use in children, but can also be used in adults in some cases.

### **Dose for children of 3 years of age and above, weighing at least 15 kilograms who have not taken antiretroviral medicines before (your child's doctor will determine this)**

The doctor will work out the right once daily dose based on the weight of the child (see table below). This dose must not exceed the recommended adult dose, which is 800 milligram PREZISTA together with 100 milligram ritonavir once a day.

The doctor will inform you on how much PREZISTA tablets and how much ritonavir (capsules, tablets or solution) the child must take.

| Weight                      | One PREZISTA dose is | One ritonavir <sup>a</sup> dose is |
|-----------------------------|----------------------|------------------------------------|
| between 15 and 30 kilograms | 600 milligram        | 100 milligram                      |
| between 30 and 40 kilograms | 675 milligram        | 100 milligram                      |
| more than 40 kilograms      | 800 milligram        | 100 milligram                      |

<sup>a</sup> ritonavir oral solution: 80 milligram per milliliter

**Dose for children of 3 years of age and above, weighing at least 15 kilograms who have taken antiretroviral medicines before (your child's doctor will determine this)**

The doctor will work out the right dose based on the weight of the child (see table below). The doctor will determine if once daily dosing or twice daily dosing is appropriate for the child. This dose must not exceed the recommended adult dose, which is 600 milligram PREZISTA together with 100 milligram of ritonavir two times per day or 800 milligram PREZISTA together with 100 milligram ritonavir once a day. The doctor will inform you on how many PREZISTA tablets and how much ritonavir (capsules, tablets or solution) the child must take. Tablets of lower strengths are available to construct the appropriate dosing regimen. PREZISTA oral suspension is also available. Your doctor will determine whether PREZISTA tablets or oral suspension is right for the child.

**Twice daily dosing**

| Weight                      | One dose is  |
|-----------------------------|--|
| between 15 and 30 kilograms | 375 milligram PREZISTA + 50 milligram ritonavir twice a day  |
| between 30 and 40 kilograms | 450 milligram PREZISTA + 60 milligram ritonavir twice a day  |
| more than 40 kilograms*     | 600 milligram PREZISTA + 100 milligram ritonavir twice a day |

\* For children aged 12 or more and weighing at least 40 kilograms, your child's doctor will determine if PREZISTA 800 milligram once daily dosing may be used. This cannot be administered with these 600 milligram tablets. Other strengths of PREZISTA are available.

**Once daily dosing**

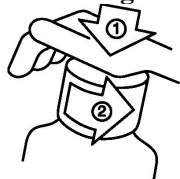
| Weight                      | One PREZISTA dose is | One ritonavir <sup>a</sup> dose is |
|-----------------------------|----------------------|------------------------------------|
| between 15 and 30 kilograms | 600 milligram        | 100 milligram                      |
| between 30 and 40 kilograms | 675 milligram        | 100 milligram                      |
| more than 40 kilograms      | 800 milligram        | 100 milligram                      |

<sup>a</sup> ritonavir oral solution: 80 milligram per milliliter

**Instructions for children**

- The child must take PREZISTA always together with ritonavir. PREZISTA cannot work properly without ritonavir.
- The child must take the appropriate doses of PREZISTA and ritonavir two times per day or once a day. If prescribed PREZISTA twice daily the child must take one dose in the morning, and one dose in the evening. Your child's doctor will determine the appropriate dosing regimen for your child.
- The child must take PREZISTA with food. PREZISTA cannot work properly without food. The type of food is not important.
- The child must swallow the tablets with a drink such as water or milk.
- PREZISTA 75 milligram and 150 milligram tablets and 100 milligram per milliliter oral suspension have been developed for use in children weighing less than 40 kilograms, but can also be used in some cases.

**Removing the child resistant cap**



The plastic bottle comes with a child resistant cap and must 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, pharmacist or nurse immediately.

**If you forget to take PREZISTA**

If you notice **within 6 hours**, you must take your missed dose 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 taking PREZISTA without talking to your doctor first**

Anti-HIV medicine may make you feel better. 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 medicine, ask your doctor, pharmacist or nurse.

**4. Possible side effects**

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor if you develop any of the following side effects.**

Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start PREZISTA. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or pain and discomfort on your right side below your ribs.

Skin rash (more often when used in combination with raltegravir), itching. 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 talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether PREZISTA must be stopped.

Other severe side effects were diabetes (common) and inflammation of the pancreas (uncommon).

Very common side effects (may affect more than 1 in 10 people)

- diarrhoea.

Common side effects (may affect up to 1 in 10 people)

- vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

Uncommon side effects (may affect up to 1 in 100 people)

- chest pain, changes in electrocardiogram, rapid heart beating
- decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory, problems with your balance
- difficulty breathing, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching
- kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of urine, sometimes at night
- urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails
- muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis



- slowing down of the thyroid gland function. This can be seen in a blood test.
- high blood pressure, flushing
- red or dry eyes
- fever, swelling of lower limbs due to fluids, malaise, irritability, pain
- symptoms of infection, herpes simplex
- erectile dysfunction, enlargement of breasts
- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive

Rare side effects (may affect up to 1 in 1,000 people)

- a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung]
- heart attack, slow heart beating, palpitations
- visual disturbance
- chills, feeling abnormal
- a feeling of confusion or disorientation, altered mood, restlessness
- fainting, epileptic fits, changes or loss of taste
- mouth sores, vomiting blood, inflammation of the lips, dry lips, coated tongue
- running nose
- skin lesions, dry skin
- stiffness of muscles or joints, joint pain with or without inflammation
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.

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

- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.

### **Reporting of side effects**

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store PREZISTA**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after EXP. The expiry date refers to the last day of that month.

PREZISTA does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What PREZISTA contains**

- The active substance is darunavir. Each tablet contains 600 milligram of darunavir (as ethanolate).
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate. The film-coating contains poly(vinyl alcohol) - partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc, sunset yellow FCF (E110).

- This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

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

Film-coated, orange, oval shaped tablet, mentioning TMC on one side, 600MG on the other side. 60 tablets in a plastic bottle.

PREZISTA is also available as 75 milligram, 150 milligram, 300 milligram, 400 milligram and 800 milligram film-coated tablets and 100 milligram per milliliter oral suspension.

### **Marketing Authorisation Holder**

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### **Manufacturer**

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**This leaflet was last revised in {MM/YYYY}.**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

## Package leaflet: Information for the user

### PREZISTA 800 mg film-coated tablets darunavir

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What PREZISTA is and what it is used for
2. What you need to know before you take PREZISTA
3. How to take PREZISTA
4. Possible side effects
5. How to store PREZISTA
6. Contents of the pack and other information

#### **1. What PREZISTA is and what it is used for**

##### **What is PREZISTA?**

PREZISTA contains the active substance darunavir. 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?**

The PREZISTA 800 milligram tablet is used to treat adults and children (3 years of age and above, at least 40 kilograms body weight) who are infected by HIV and

- who have not used antiretroviral medicines before.
- in certain patients who have used antiretroviral medicines before (your doctor will determine this).

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

#### **2. What you need to know before you take PREZISTA**

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

- if you are **allergic** to darunavir or any of the other ingredients of this medicine (listed in section 6) or to cobicistat or 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**

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

| Medicine   | Purpose of the medicine                  |
|--|--|
| <i>Avanafil</i>  | to treat erectile dysfunction            |
| <i>Astemizole</i> or <i>terfenadine</i>                            | to treat allergy symptoms                |
| <i>Triazolam</i> and <i>oral</i> (taken by mouth) <i>midazolam</i> | to help you sleep and/or relieve anxiety |

|   |  |
|---|--|
| <i>Cisapride</i>  | to treat some stomach conditions   |
| <i>Colchicine</i> (if you have kidney and/or liver problems)  | to treat gout or familial Mediterranean fever  |
| <i>Lurasidone, pimozide, quetiapine</i> or <i>sertindole</i>  | to treat psychiatric conditions  |
| <i>Ergot alkaloids</i> like <i>ergotamine</i> , <i>dihydroergotamine</i> , <i>ergometrine</i> and <i>methylergonovine</i> | to treat migraine headaches  |
| <i>Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine</i>   | to treat certain heart disorders e.g. abnormal heart beat  |
| <i>Lovastatin, simvastatin</i> and <i>lomitapide</i>  | to lower cholesterol levels  |
| <i>Rifampicin</i>   | to treat some infections such as tuberculosis  |
| The combination product <i>lopinavir/ritonavir</i>  | this anti-HIV medicine belongs to the same class as PREZISTA   |
| <i>Elbasvir/grazoprevir</i>   | to treat hepatitis C infection   |
| <i>Alfuzosin</i>  | to treat enlarged prostate   |
| <i>Sildenafil</i>   | to treat high blood pressure in the pulmonary circulation  |
| <i>Dabigatran, ticagrelor</i>   | to help stop the clumping of platelets in the treatment of patients with a history of a heart attack |
| <i>Naloxegol</i>  | to treat opioid induced constipation   |
| <i>Dapoxetine</i>   | to treat premature ejaculation   |
| <i>Domperidone</i>  | to treat nausea and vomiting   |

Do not combine PREZISTA with products that contain St John's wort (*Hypericum perforatum*).

### Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking PREZISTA.

PREZISTA is not a cure for HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

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

People taking PREZISTA may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking PREZISTA and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

### Tell your doctor about your situation BEFORE and DURING your treatment

Make sure that you check the following 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 infection. 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** (for example enlarged lymph nodes and fever). 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.
- In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines

for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- 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.

### **Elderly**

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.

### **Children and adolescents**

The PREZISTA 800 milligram tablet is not for use in children younger than 3 years of age or weighing less than 40 kilograms.

### **Other medicines and PREZISTA**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

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 medicines:'

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), CCR5 antagonists and FIs (fusion inhibitors)]. PREZISTA with cobicistat or ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. In some cases dosage of other medicines might need to be changed. 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* (to prevent seizures)
- *Dexamethasone* (corticosteroid)
- *Efavirenz* (HIV infection)
- *Boceprevir* (hepatitis C infection)
- *Rifapentine, rifabutin* (medicines to treat some infections such as tuberculosis)
- *Saquinavir* (HIV infection).

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

- *Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nicardipine, propafenone, timolol, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Apixaban, edoxaban, rivaroxaban, warfarin* (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. PREZISTA might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.

- *Ethinylestradiol/drospirenone*. PREZISTA might increase the risk for elevated potassium levels by drospirenone.
- *Atorvastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Clarithromycin* (antibiotic)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased. Your doctor might want to do some additional tests.
- *Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone*. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone* (medicines to treat opioid dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria)
- *Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine* (to treat cancer)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension)
- *Glecaprevir/pibrentasvir, simeprevir* (to treat hepatitis C infection)
- *Fentanyl, oxycodone, tramadol* (to treat pain)
- *Fesoterodine, solifenacin* (to treat urologic disorders).

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

Tell your doctor if you take:

- *Alfentanil* (injectable strong and short-acting painkiller that is used for surgical procedures)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Itraconazole, isavuconazole, fluconazole, posaconazole, clotrimazole* (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- *Rifabutin* (against bacterial infections)
- *Sildenafil, vardenafil, tadalafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Maraviroc* (to treat HIV infection)
- *Methadone* (to treat opiate dependence)
- *Carbamazepine, clonazepam* (to prevent seizures or to treat certain types of nerve pain)
- *Colchicine* (to treat gout or familial Mediterranean fever)
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam when used as injection, zolpidem* (sedative agents)
- *Perphenazine, risperidone, thioridazine* (to treat psychiatric conditions)
- *Metformin* (to treat type 2 diabetes).

This is **not** a complete list of medicines. Tell your healthcare provider about **all** medicines that you are taking.

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

See section 3 'How to take PREZISTA.'

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

Tell your doctor immediately if you are pregnant, planning to become pregnant or if you are breast-feeding. Pregnant or breast-feeding mothers should not take PREZISTA with ritonavir unless

specifically directed by the doctor. Pregnant or breast-feeding mothers should not take PREZISTA with cobicistat.

It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of your baby becoming infected with HIV through your breast milk and because of the unknown effects of the medicine on your baby.

### **Driving and using machines**

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

## **3. How to take PREZISTA**

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

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

After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

PREZISTA 800 milligram tablets are intended for once daily use only.

### **Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this)**

The usual dose of PREZISTA is 800 milligram (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) once daily.

You must take PREZISTA every day and always in combination with 150 milligram of cobicistat or 100 milligram of ritonavir and with food. PREZISTA cannot work properly without cobicistat or ritonavir and food. You must eat a meal or a snack within 30 minutes prior to taking your PREZISTA and cobicistat or ritonavir. The type of food is not important. Even if you feel better, do not stop taking PREZISTA and cobicistat or ritonavir without talking to your doctor.

### **Instructions for adults**

- Take one 800 milligram tablet at the same time, once a day, every day.
- Take PREZISTA always together with 150 milligram of cobicistat or 100 milligram of ritonavir.
- Take PREZISTA with food.
- Swallow the tablet with a drink such as water or milk.
- Take your other HIV medicines used in combination with PREZISTA and cobicistat or ritonavir as recommended by your doctor.
- PREZISTA 100 milligram per milliliter oral suspension has been developed for use in children, but can also be used in adults in some cases.

### **Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)**

The dose is either:

- 800 milligram PREZISTA (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) together with 150 milligram cobicistat or 100 milligram ritonavir once daily.  
OR
- 600 milligram PREZISTA (2 tablets containing 300 milligram of PREZISTA or 1 tablet containing 600 milligram of PREZISTA) together with 100 milligram ritonavir twice daily.

Please discuss with your doctor which dose is right for you.



**Dose for children 3 years of age and above, weighing more than 40 kilograms who have not taken antiretroviral medicines before (your child's doctor will determine this)**

- The usual dose of PREZISTA is 800 milligram (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) together with 100 milligram ritonavir once daily.

**Dose for children 3 years of age and above, weighing more than 40 kilograms who have taken antiretroviral medicines before (your child's doctor will determine this)**

The dose is either:

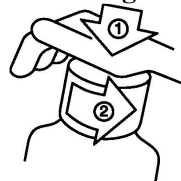
- 800 milligram PREZISTA (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) together with 100 milligram ritonavir once daily.  
OR
- 600 milligram PREZISTA (2 tablets containing 300 milligram of PREZISTA or 1 tablet containing 600 milligram of PREZISTA) together with 100 milligram ritonavir twice daily.

Please discuss with your doctor which dose is right for you.

**Instructions for children 3 years of age and above, weighing more than 40 kilograms**

- Take 800 milligram PREZISTA (2 tablets containing 400 milligram of PREZISTA or 1 tablet containing 800 milligram of PREZISTA) at the same time, once a day, every day.
- Take PREZISTA always together with 100 milligram of ritonavir.
- Take PREZISTA with food.
- Swallow the tablets with a drink such as water or milk.
- Take your other HIV medicines used in combination with PREZISTA and ritonavir as recommended by your doctor

**Removing the child resistant cap**



The plastic bottle comes with a child resistant cap and must 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, pharmacist or nurse immediately.

**If you forget to take PREZISTA**

If you notice **within 12 hours**, you must take the tablets immediately. Always take with cobicistat or ritonavir and food. If you notice **after 12 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 taking PREZISTA without talking to your doctor first**

Anti-HIV medicines may make you feel better. 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 medicine, ask your doctor, pharmacist or nurse.

**4. Possible side effects**

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor if you develop any of the following side effects.**

Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start PREZISTA. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or pain and discomfort on your right side below your ribs.

Skin rash (more often when used in combination with raltegravir), itching. 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 talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether PREZISTA must be stopped.

Other severe side effects were diabetes (common) and inflammation of the pancreas (uncommon).

Very common side effects (may affect more than 1 in 10 people)

- diarrhoea.

Common side effects (may affect up to 1 in 10 people)

- vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

Uncommon side effects (may affect up to 1 in 100 people)

- chest pain, changes in electrocardiogram, rapid heart beating
- decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory, problems with your balance
- difficulty breathing, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching
- kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of urine, sometimes at night
- urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails
- muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis
- slowing down of the thyroid gland function. This can be seen in a blood test.
- high blood pressure, flushing
- red or dry eyes
- fever, swelling of lower limbs due to fluids, malaise, irritability, pain
- symptoms of infection, herpes simplex
- erectile dysfunction, enlargement of breasts
- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive

Rare side effects (may affect up to 1 in 1,000 people)

- a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung]
- heart attack, slow heart beating, palpitations
- visual disturbance
- chills, feeling abnormal
- a feeling of confusion or disorientation, altered mood, restlessness
- fainting, epileptic fits, changes or loss of taste
- mouth sores, vomiting blood, inflammation of the lips, dry lips, coated tongue
- running nose
- skin lesions, dry skin

- stiffness of muscles or joints, joint pain with or without inflammation
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.

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

- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.

### **Reporting of side effects**

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store PREZISTA**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after EXP. The expiry date refers to the last day of that month.

PREZISTA does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What PREZISTA contains**

- The active substance is darunavir. Each tablet contains 800 milligram of darunavir (as ethanolate).
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate, hypromellose. The film-coating contains poly(vinyl alcohol) - partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc, iron oxide red (E172).
- This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

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

Film-coated, dark red, oval shaped tablet, mentioning T on one side, 800 on the other side. 30 tablets in a plastic bottle. The PREZISTA 800 milligram tablets are available in packs containing one bottle or three bottles per carton.

Not all pack sizes may be marketed.

PREZISTA is also available as 75 milligram, 150 milligram, 300 milligram, 400 milligram and 600 milligram film-coated tablets and 100 milligram per milliliter oral suspension.

### **Marketing Authorisation Holder**

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### **Manufacturer**

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Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.