1. NAME OF THE MEDICINAL PRODUCT

Darunavir (as ethanolate) 400mg Tablets[1]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 433.648 mg darunavir ethanolate equivalent to 400 mg darunavir**.**

Excipient with known effect

Each tablet contains 1.152 mg of FD&C yellow #6/Sunset yellow FCF Aluminium Lake.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Light orange coloured, oval shaped, biconvex, film coated tablet, debossed with 'DNV' on one side & '400' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Darunavir (as ethanolate) 400mg Tablets, co-administered with low dose ritonavir, is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV) infection in adult and adolescent patients weighing at least 40 kg who are:

- Protease inhibitor (PI) naïve (see section 4.2)
- When HIV-1 genotype testing is available: protease inhibitor-experienced with no darunavir resistance associated mutations (DRV-RAMs*) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106 /l. (see sections 4.4 and 5.1).

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

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).

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 Darunavir (as ethanolate) 400mg Tablets has been initiated, patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their health care provider.

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory agency's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Posology

Darunavir (as ethanolate) 400mg Tablets must always be given orally with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The product information of ritonavir must therefore be consulted prior to initiation of therapy with Darunavir (as ethanolate) 400mg Tablets.

Patients weighing at least 40 kg

The recommended dose regimen is 800 mg (2 tablets of Darunavir (as ethanolate) 400mg Tablets) once daily with ritonavir 100 mg once daily, taken with food.

Advice on missed doses

If a dose of darunavir and/or ritonavir is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of darunavir and 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, darunavir 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, darunavir 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, darunavir 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).

Paediatric population

Dose adjustments cannot be achieved with Darunavir (as ethanolate) 400mg Tablets. Other formulations/tablet strengths of darunavir are required.

Darunavir/ritonavir should not be used in children below 3 years of age or weighing less than 15 kg (see section 5.3)

Pregnancy and postpartum

No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. (see sections 4.6 and 5.2).

Method of administration

Patients should be instructed to take darunavir with low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir (see section 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 darunavir 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 darunavir 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 (alpha 1-adrenoreceptor antagonist)
- amiodarone, bepridil, dronedarone, quinidine, ranolazine, systemic lidocaine (antiarrhythmics/antianginals)
- astemizole, terfenadine (antihistamines)
- colchicine when used in patients with renal and/or hepatic impairment (antigout) (see section 4.5)
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- cisapride (gastrointestinal motility agent)
- pimozide, quetiapine, sertindole (antipsychotics/neuroleptics) (see section 4.5)
- triazolam, midazolam administered orally (sedatives/hypnotics) (for caution on parenterally administered midazolam, see section 4.5)
- sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil (PDE-5 inhibitors)
- simvastatin and lovastatin (HMG-CoA reductase inhibitors) (see section 4.5)
- ticagrelor (antiplatelets) (see section 4.5).

4.4 Special warnings and precautions for use

PI-experienced patients

When genotypic testing is not feasible, a twice daily dosing regimen is recommended in HIV protease inhibitor-experienced patients. Other formulations should be used.

Transmission

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 relevant guidelines.

Severe skin reactions

Severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been uncommonly reported. 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. Symptoms 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 (see also section 4.8).Darunavir should be discontinued immediately if signs or symptoms of severe skin reactions develop.

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

Hepatotoxicity

Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported in 0.5% of patients receiving combination antiretroviral therapy with darunavir /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 darunavir/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 darunavir/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 darunavir/ritonavir, interruption or discontinuation of treatment should be considered promptly.

Hepatic impairment

The safety and efficacy of darunavir have not been established in patients with severe underlying liver disorders and darunavir is therefore contraindicated in patients with severe hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, this medicine 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

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

Opportunistic infections

Patients receiving darunavir or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

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 darunavir co-administered with low dose ritonavir.

Autoimmune disorders (such as Graves' disease) 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

Efavirenz in combination with darunavir/ritonavir 800/100 mg once daily may result in sub-optimal darunavir Cmin. If efavirenz is to be used in combination with darunavir/ritonavir a twice daily dosing regimen is recommended in HIV protease inhibitor-experienced patients. Other formulations should be used.

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).

Excipients

Each tablet contains 1.152 mg of FD&C yellow #6/Sunset yellow FCF Aluminium Lake, a colouring agent which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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 low dose ritonavir as a pharmacokinetic enhancer (see section 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 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 these compounds and consequently that of darunavir, leading to loss of therapeutic effect and possible development of resistance (see sections 4.3). 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, systemic azoles like ketoconazole and clotrimazole).

Interaction table

Interactions between darunavir/ritonavir and antiretroviral and non-antiretroviral medicinal products are listed in the table below (not determined as "ND"). The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 80-125% range.
Several of the interaction studies (indicated by # 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.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
HIV ANTIRETROVIRALS		
Integrase strand transfer inhibitors		
Dolutegravir	darunavir ↔ dolutegravir AUC ↓ C_{max} ↓	Darunavir co-administered with low dose ritonavir and dolutegravir can be used without dose adjustment.
Elvitegravir	darunavir AUC ↔ C_{max} ↔ elvitegravir AUC ↔ C_{min} ↔ C_{max} ↔	When darunavir co-administered with low dose ritonavir (600/100 mg twice daily) is used in combination with elvitegravir, the dose of elvitegravir should be 150 mg once daily. The pharmacokinetics and dosing recommendations for other doses of darunavir or with elvitegravir/cobicistat have not been established. Therefore, co-administration of darunavir with low dose ritonavir in doses other than 600/100 mg twice daily and elvitegravir is not recommended. Co-administration of darunavir with low dose ritonavir and elvitegravir in the presence of cobicistat is not recommended.
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. Darunavir co-administered with low dose ritonavir and raltegravir can be used without dose adjustments.
Nucleo(s/t)ide reverse transcriptase inhibitors (NRTIs)		
Didanosine	darunavir AUC ↔ C_{min} ↔ C_{max} ↔ didanosine AUC ↓ C_{max} ↓	Darunavir co-administered with low dose ritonavir and didanosine can be used without dose adjustments. Didanosine is to be administered on an empty stomach, thus it should be administered 1 hour before or 2 hours after darunavir/ritonavir given with food.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
Tenofovir disoproxil fumarate	#darunavir AUC ↑ C_{min} ↑ C_{max} ↑ tenofovir AUC ↑ C_{min} ↑ C_{max} ↑ (↑ tenofovir from effect on MDR-1 transport in the renal tubules)	Monitoring of renal function may be indicated when darunavir co-administered with low dose ritonavir is given in combination with tenofovir, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.
Abacavir Emtricitabine Lamivudine Stavudine 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 darunavir co-administered with low dose ritonavir.	Darunavir co-administered with low dose ritonavir can be used with these NRTIs without dose adjustment.
Non-nucleo(s/t)ide reverse transcriptase inhibitors (NNRTIs)		
Efavirenz	#darunavir AUC ↓ C_{min} ↓ C_{max} ↓ efavirenz AUC ↑ C_{min} ↑ C_{max} ↑ (↑ efavirenz from CYP3A inhibition) (↓ darunavir from CYP3A induction)	Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when darunavir co-administered with low dose ritonavir is given in combination with efavirenz. Efavirenz in combination with darunavir/ritonavir 800/100 mg once daily may result in sub-optimal darunavir C_{min}. If efavirenz is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used (see section 4.4).

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
Etravirine	darunavir AUC ↑ C_{min} ↔ C_{max} ↔ etravirine AUC ↓ C_{min} ↓ C_{max} ↓	Darunavir co-administered with low dose ritonavir and etravirine 200 mg twice daily can be used without dose adjustments.
Nevirapine	#darunavir: concentrations were consistent with historical data nevirapine AUC ↑ C_{min} ↑ C_{max} ↑ (↑ nevirapine from CYP3A inhibition)	Darunavir co-administered with low dose ritonavir and nevirapine can be used without dose adjustments.
Rilpivirine	darunavir AUC ↔ C_{min} ↓ C_{max} ↔ rilpivirine AUC ↑ C_{min} ↑ C_{max} ↑	Darunavir co-administered with low dose ritonavir and rilpivirine can be used without dose adjustments.
HIV Protease inhibitors (PIs) - without additional co-administration of low dose ritonavir†		
Atazanavir	#darunavir AUC ↔ C_{min} ↔ C_{max} ↔ atazanavir AUC ↔ C_{min} ↑ C_{max} ↓	Darunavir co-administered with low dose ritonavir and atazanavir can be used without dose adjustments.
Indinavir	#darunavir AUC ↑ C_{min} ↑ C_{max} ↑ indinavir AUC ↑ C_{min} ↑ C_{max} ↔	When used in combination with darunavir 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.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
Saquinavir	#darunavir AUC ↓ C_{min} ↓ C_{max} ↓ saquinavir AUC ↓ C_{min} ↓ C_{max} ↓	It is not recommended to combine darunavir co-administered with low dose ritonavir with saquinavir.
HIV Protease inhibitors (PIs) - with co-administration of low dose ritonavir†		
Lopinavir/ritonavir	darunavir AUC ↓ C_{min} ↓ C_{max} ↓ lopinavir AUC ↑ 9% lopinavir C_{min} ↑ 23% lopinavir C_{max} ↓ 2%	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 darunavir co-administered with low dose ritonavir and the combination product lopinavir/ritonavir is contraindicated (see section 4.3).
CCR5 ANTAGONIST		
Maraviroc	darunavir, ritonavir concentrations were consistent with historical data maraviroc AUC ↑ C_{max} ↑	The maraviroc dose should be 150 mg twice daily when co-administered with darunavir co-administered with low dose ritonavir
ANAESTHETIC		
Alfentanil	Not studied The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by darunavir co-administered with low dose ritonavir	The concomitant use with darunavir co-administered with 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 Flecainide Mexiletine Propafenone	Not studied. Darunavir is expected to increase these antiarrhythmic plasma concentrations. (CYP3A inhibition)	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with darunavir co-administered with low dose ritonavir.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
Amiodarone Bepridil Dronedarone Lidocaine (systemic) Quinidine Ranolazine		Darunavir co-administered with low dose ritonavir and amiodarone, bepridil, dronedarone, systemic lidocaine, quinidine, or ranolazine is contraindicated (see section 4.3).
Digoxin	digoxin AUC ↑ C_{max} ↑ (↑ 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.
ANTIBIOTIC		
Clarithromycin	#darunavir AUC ↓ C_{min} ↑ C_{max} ↓ clarithromycin AUC ↑ C_{min} ↑ C_{max} ↑ (↑ clarithromycin from CYP3A inhibition and possible P-gp inhibition)	Caution should be exercised when clarithromycin is combined with darunavir co-administered with low dose ritonavir. For patients with renal impairment the product information of clarithromycin should be consulted for the recommended dose.
ANTICOAGULANTS		
Apixaban Dabigatran etexilate Rivaroxaban	Not studied. Co-administration of darunavir with these anticoagulants may increase concentrations of the anticoagulant. (CYP3A and/or P-gp inhibition)	The use of darunavir co-administered with low dose ritonavir and these anticoagulants is not 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 darunavir co-administered with low dose ritonavir.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
ANTICONVULSANTS		
Phenobarbital Phenytoin	Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir (induction of CYP450 enzymes)	Darunavir co-administered with low dose ritonavir should not be used in combination with these medicines.
Carbamazepine	darunavir AUC ↔ C_{min} ↓ C_{max} ↔ carbamazepine AUC ↑ C_{min} ↑ C_{max} ↑	No dose adjustment for darunavir/ritonavir is recommended. If there is a need to combine darunavir /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 darunavir/ritonavir.
ANTIDEPRESSANTS		
Paroxetine	#darunavir AUC ↔ C_{min} ↔ C_{max} ↔ paroxetine AUC ↓ C_{min} ↓ C_{max} ↓	If antidepressants are co-administered with darunavir co-administered 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 darunavir with low dose ritonavir should be monitored for antidepressant response.
Sertraline	#darunavir AUC ↔ C_{min} ↓ C_{max} ↔ sertraline AUC ↓ C_{min} ↓ C_{max} ↓	

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
Amitriptyline Desipramine Imipramine Nortriptyline Trazodone	Concomitant use of darunavir co-administered with low dose ritonavir and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or CYP3A inhibition)	Clinical monitoring is recommended when co-administering darunavir with low dose ritonavir with these antidepressants and a dose adjustment of the antidepressant may be needed.
ANTIFUNGALS		
Voriconazole	Not studied. Ritonavir may decrease plasma concentrations of voriconazole. (induction of CYP450 enzymes)	Voriconazole should not be combined with darunavir co-administered with low dose ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Ketoconazole	#darunavir AUC ↑ C_{min} ↑ C_{max} ↑ ketoconazole AUC ↑ C_{min} ↑ C_{max} ↑ (CYP3A inhibition)	Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of ketoconazole should not exceed 200 mg.
Fluconazole Posaconazole	Not studied. Darunavir may increase antifungal plasma concentrations (P-gp inhibition) and posaconazole or fluconazole may increase darunavir concentrations. (CYP3A inhibition)	Caution is warranted and clinical monitoring is recommended.
Itraconazole	Not studied. Concomitant systemic use of itraconazole and darunavir co-administered with low dose ritonavir may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of itraconazole may be increased by darunavir co-administered with low dose ritonavir. (CYP3A inhibition)	Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of itraconazole should not exceed 200 mg.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
Clotrimazole	Not studied. Concomitant systemic use of clotrimazole and darunavir co-administered with low dose ritonavir may increase plasma concentrations of darunavir. darunavir AUC24h ↑ (based on population pharmacokinetic model)	Caution is warranted and clinical monitoring is recommended, when co-administration of clotrimazole is required.
ANTIGOUT MEDICINES		
Colchicine	Not studied. Concomitant use of colchicine and darunavir co-administered with low dose ritonavir may increase the exposure to colchicine.	A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with darunavir co-administered with low dose ritonavir is required. Patients with renal or hepatic impairment should not be given colchicine with darunavir co-administered with low dose ritonavir (see section 4.3).
ANTIMALARIALS		
Artemether/Lumefantrine	darunavir AUC ↔ C_{min} ↓ C_{max} ↔ Artemether AUC ↓ C_{min} ↔ C_{max} ↓ dihydroartemisinin AUC ↓ C_{min} ↔ C_{max} ↓ lumefantrine AUC ↑ C_{min} ↑ C_{max} ↑	The combination of darunavir and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Not studied. Rifapentine and rifampicin are strong CYP3A inducers and cause decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction).	The combination of rifampicin and darunavir with concomitant low dose ritonavir is contraindicated (see section 4.3). The combination of rifapentine and darunavir with concomitant low dose ritonavir is not recommended.
Rifabutin	darunavir AUC ↑ C_{min} ↑ C_{max} ↑ rifabutin AUC↑ C_{max} ↔ (Rifabutin is an inducer and substrate of CYP3A.)	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 darunavir 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. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients. Based upon the safety profile of darunavir/ritonavir, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for darunavir/ritonavir.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
ANTINEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine	Not studied. Darunavir is expected to increase these antineoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when co-administered with darunavir with low dose ritonavir resulting in the potential for increased adverse events usually associated with these agents. Caution should be exercised when combining one of these antineoplastic agents with darunavir with low dose ritonavir
Everolimus		Concominant use of everolimus and darunavir co-administered with low dose ritonavir is not recommended.
ANTIPLATELETS		
Ticagrelor	Not studied. Co-administration with darunavir boosted with low dose ritonavir may lead to a substantial increase in exposure to ticagrelor.	Concomitant administration of darunavir with low dose ritonavir with ticagrelor is contraindicated. Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended.
ANTIPSYCHOTICS/NEUROLEPTICS		
Quetiapine	Not studied. Due to CYP3A inhibition by darunavir, concentrations of the antipsychotics/neuroleptics are expected to increase.	Concomitant administration of darunavir with low dose ritonavir and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased concentrations of quetiapine may lead to coma.
Risperidone Thioridazine	Not studied. Darunavir is expected to increase these antipsychotic plasma concentrations. (CYP2D6 inhibition and/or P-gp)	A dose decrease may be needed for these drugs when co-administered with darunavir co-administered with low dose ritonavir.
Pimozide Sertindole		Concominant administration of darunavir with low dose ritonavir and pimozide or sertindole is contraindicated.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
β-BLOCKERS		
Carvedilol Metoprolol Timolol	Not Studied. Darunavir is expected to increase these β-blocker plasma concentrations. (CYP2D6 inhibition)	Clinical monitoring is recommended when co-administering darunavir with β-blockers. A lower dose of the β-blocker should be considered.
CALCIUM CHANNEL BLOCKERS		
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Not studied. Darunavir co-administered with low dose ritonavir can be expected to increase the plasma concentrations of calcium channel blockers. (CYP3A and/or CYP2D6 inhibition)	Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with darunavir with low dose ritonavir
CORTICOSTEROIDS		
Fluticasone Budesonide	darunavir AUC ↓ C_{min} ↓ C_{max} ↓ fluticasone propionate AUC ↑ C_{min} ↑ C_{max} ↑	Concomitant administration of darunavir/ritonavir and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid which is not a substrate for CYP3A (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period.
Dexamethasone (systemic)	Not studied. Dexamethasone may decrease plasma concentrations of darunavir. (CYP3A induction)	Systemic dexamethasone should be used with caution when combined with darunavir co-administered with low dose ritonavir.
Prednisone	Not studied. Darunavir may increase plasma concentrations of prednisone. (CYP3A inhibition)	Concomitant use of darunavir with low dose ritonavir and prednisone may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when co-administering darunavir with low dose ritonavir with

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
		corticosteroids.
ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Not studied. Concomitant use of bosentan and darunavir co-administered with low dose ritonavir may increase plasma concentrations of bosentan.	When administered concomitantly with darunavir and low dose ritonavir, the patient's tolerability of bosentan should be monitored.
HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS		
Boceprevir	darunavir AUC ↓ C_{min} ↓ C_{max} ↓ boceprevir AUC ↓ C_{min} ↓ C_{max} ↓	It is not recommended to co-administer darunavir with low dose ritonavir and boceprevir.
Simeprevir	darunavir AUC ↑ C_{min} ↑ C_{max} ↔ simeprevir AUC ↑ C_{min} ↑ C_{max} ↑	It is not recommended to co-administer darunavir with low dose ritonavir and simeprevir.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
Dasabuvir+ ombitasvir/paritaprevir/ritonavir	darunavir C_{max} ↓ AUC ↓ C_{min} ↓ dasabuvir C_{max}↔ AUC↔ C_{min} ↔ ombitasvir C_{max}↔ AUC ↔ C_{min}↔ paritaprevir C_{max} ↑ AUC ↑ C_{min} ↑	The recommended dose of darunavir is 800 mg once daily, without ritonavir, when administered at the same time as ombitasvir/paritaprevir/ ritonavir + dasabuvir (ritonavir dose in ombitasvir/paritaprevir/ ritonavir will provide darunavir pharmacokinetic enhancement). This regimen can be used in the absence of extensive PI resistance (i.e. lack of darunavir associated RAMs). Darunavir combined with ombitasvir/paritaprevir/ ritonavir + dasabuvir is not recommended in patients with extensive PI resistance.
Ombitasvir/paritaprevir/ritonavir	darunavir C_{max} ↔ AUC ↔ C_{min} ↔ ombitasvir C_{max}↔ AUC ↔ C_{min}↔ paritaprevir Cmax ↑ AUC ↑ C_{min} ↑	No dose adjustment needed for dasabuvir + ombitasvir/paritaprevir/ ritonavir. Treatment with darunavir +ombitasvir/paritaprevir/ritonavir without dasabuvir is not recommended due to a larger increase of paritaprevir plasma concentrations in the absence of dasabuvir.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
Ledipasvir	Darunavir C_{max} ↔ AUC↔ C_{min}↔ Ledipasvir C_{max}↑ AUC↑ C_{min} ↑	No dose adjustment is required.
Sofosbuvir	Darunavir C_{max} ↔ AU C ↔ C_{min} ↔ Sofosbuvir C_{max} ↑ AUC ↑ GS-331007 C_{max} ↔ AUC ↔	
Daclatasvir	Darunavir AUC: ↔ C_{max}: ↔ C_{min}: ↔ Daclatasvir AUC ↔ C_{max} ↔	No dose adjustment is required.
HERBAL PRODUCTS		
St John's wort *(Hypericum perforatum)*	Not studied. St John's wort is expected to decrease the plasma concentrations of darunavir at ritonavir (CYP450 induction)	Darunavir co-administered with low dose ritonavir must not be used concomitantly with products containing St John's wort (*Hypericum perforatum*) (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.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
HMG CO-A REDUCTASE INHIBITORS		
Lovastatin Simvastatin	Not studied. Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with darunavir/ritonavir. (CYP3A inhibition)	Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of darunavir, co-administered with low dose ritonavir, with lovastatin and simvastatin is therefore contraindicated (see section 4.3).
Atorvastatin	atorvastatin AUC ↑ C_{min} ↑ C_{max} ↑	When administration of atorvastatin and darunavir 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	pravastatin AUC ↑ C_{max} ↑	When administration of pravastatin and darunavir 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	rosuvastatin AUC ↑ C_{max} ↑	When administration of rosuvastatin and darunavir , 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.
H2-RECEPTOR ANTAGONISTS		
Ranitidine	#darunavir AUC ↔ C_{min} ↔ C_{max} ↔	Darunavir , co-administered with low dose ritonavir, can be co-administered with H2-receptor antagonists without dose adjustments.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus	Not studied. Exposure to these immunosuppressants will be increased when co-administered with darunavir/ritonavir. (CYP3A inhibition)	Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs. Concomitant use of everolimus and darunavir, co-administered with low dose ritonavir is not recommended.
INHALED BETA AGONISTS		
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 darunavir , 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.
NARCOTIC ANALGESICS / TREATMENT OF OPIOID DEPENDENCE		
Methadone	R(-) methadone AUC ↓ C_{min} ↓ C_{max} ↓	No adjustment of methadone dosage is required when initiating co-administration with darunavir/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.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
Buprenorphine/naloxone	buprenorphine AUC ↓ C_{min} ↔ C_{max} ↓ norbuprenorphine AUC ↑ C_{min} ↑ C_{max} ↑ naloxone AUC ↔ C_{max} ↔	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 darunavir/ritonavir but a careful clinical monitoring for signs of opiate toxicity is recommended.
OESTROGEN-BASED CONTRACEPTIVES		
Ethinylestradiol Norethindrone 35 µg/1 mg once daily	ethinylestradiol AUC ↓ C_{min} ↓ C_{max} ↓ norethindrone AUC ↓ C_{min} ↓ C_{max} ↔	Alternative or additional contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with darunavir and low dose ritonavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.
PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS		
For the treatment of erectile dysfunction Avanafil Sildenafil Tadalafil Vardenafil	↑ PDE-5 inhibitors	The combination of avanafil and darunavir with low dose ritonavir is contraindicated (see section 4.3). Concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with darunavir co-administered with low dose ritonavir should be done with caution. If concomitant use of darunavir, 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.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
For the treatment of pulmonary arterial hypertension Sildenafil 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 darunavir 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 darunavir 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 darunavir and low dose ritonavir is not recommended.
PROTON PUMP INHIBITORS		
Omeprazole 20 mg once daily	#darunavir AUC ↔ C_{min} ↔ C_{max} ↔	Darunavir, co-administered with low dose ritonavir, can be co-administered with proton pump inhibitors without dose adjustments.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
SEDATIVES/HYPNOTICS		
Buspirone Clorazepate Diazepam Estazolam Flurazepam Triazolam Zoldipem	Not studied. Sedative/hypnotics are extensively metabolised by CYP3A. Co-administration with darunavir/ritonavir may cause a large increase in the concentration of these medicines.	Clinical monitoring is recommended when co-administering darunavir with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. Darunavir co-administered with low dose ritonavir is contraindicated with triazolam.
Midazolam	Based on data for other CYP3A inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally with darunavir co-administered with low dose ritonavir. If parenteral midazolam is co-administered with darunavir co-administered with low dose ritonavir it may cause a large increase in the concentration of this benzodiazepine. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.	Darunavir co-administered with low dose ritonavir is contraindicated with orally administered midazolam (see section 4.3); whereas, caution should be used with co-administration of darunavir with low dose ritonavir and parenteral midazolam. If parenteral midazolam is co-administered with darunavir with a low dose ritonavir, it should be done in an intensive care unit (ICU) or similar setting, which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.

† The efficacy and safety of the use of darunavir with 100 mg ritonavir and any other HIV PI (e.g. (fos)amprenavir, nelfinavir and tipranavir) has not been established in HIV patients. According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended.

4.6 Fertility, pregnancy and lactation

4.7 *Pregnancy*

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

Darunavir co-administered with low dose ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk.

Breast-feeding

Studies in rats have demonstrated that darunavir is excreted in milk and at high levels (1,000 mg/kg/day) resulted in toxicity. It is not known whether darunavir is excreted in human milk. The most recent official treatment guidelines (e.g. those issued by WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

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).

4.8 Effects on ability to drive and use machines

Darunavir 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 darunavir 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).

4.9 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions with darunavir/ritonavir 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.

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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and not known (frequency cannot be estimated from the available data).

Adverse reactions in clinical trials and post-marketing

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

Endocrine disorders	
uncommon	hypothyroidism, increased blood thyroid, stimulating hormone
Metabolism and nutrition disorders	
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
Psychiatric disorders	
common	insomnia
uncommon	depression, disorientation, anxiety, sleep disorder, abnormal dreams, nightmare, decreased libido
rare	confusional state, altered mood, restlessness
Nervous system disorders	
common	headache, peripheral neuropathy, dizziness
uncommon	lethargy, paraesthesia, hypoaesthesia, dysgeusia, disturbance in attention, memory impairment, somnolence
rare	syncope, convulsion, ageusia, sleep phase rhythm disturbance
Eye disorders	
uncommon	conjunctival hyperaemia, dry eye
rare	visual disturbance
Ear and labyrinth disorders	
uncommon	Vertigo
Cardiac disorders	
uncommon	myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia
rare	acute myocardial infarction, sinus bradycardia, palpitations
Vascular disorders	
uncommon	hypertension, flushing
Respiratory, thoracic and mediastinal disorders	
uncommon	dyspnoea, cough, epistaxis, throat irritation
rare	rhinorrhoea
Gastrointestinal disorders	
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
Hepatobiliary disorders	
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
Skin and subcutaneous tissue disorders	
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 generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders	
uncommon	myalgia, osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphokinase
rare	musculoskeletal stiffness, arthritis, joint stiffness
Renal and urinary disorders	
uncommon	acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria
rare	decreased creatinine renal clearance
Reproductive system and breast disorders	
uncommon	erectile dysfunction, gynaecomastia
General disorders and administration site conditions	
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 darunavir + raltegravir compared to those containing darunavir without raltegravir or raltegravir without darunavir. 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) 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

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

Other special populations

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

Co-infected patients receiving darunavir co-administered with ritonavir are more likely to have baseline and treatment emergent hepatic transaminase elevations than those without chronic viral hepatitis (see section 4.4).

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 to the marketing authorisation holder, or, if available, via the national reporting system.

4.10 Overdose

Human experience of acute overdose with darunavir co-administered with low dose ritonavir is limited. Single doses up to 1,600 mg of darunavir tablets in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

There is no specific antidote for overdose with darunavir. Treatment of overdose with darunavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis.

Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 (KD of 4.5 x 10-12M). 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 EC50 values ranging from < 0.1 to 4.3 nM.
These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 μM to> 100 μM.

Resistance

Clinical trial data showed that virologic response to darunavir 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≤ 10 are susceptible; isolates with FC > 10 to 40 have decreased susceptibility; isolates with FC > 40 are resistant.

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.

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 observed in clinical trials there was no cross-resistance with other PIs .

Clinical efficacy

A randomised, controlled, open-label Phase III trial compared darunavir co-administered with ritonavir (600/100 mg twice daily) versus lopinavir/ritonavir (400/100 mg twice daily) in 595 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). Results showed that 60.4% of patients in the darunavir/ritonavir arm had 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)].

Another Phase III, randomised, open-label trial compared darunavur/ritonavir 800/100 mg once daily versus darunavir/ritonavir 600/100 mg twice daily in 590 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. Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs. Efficacy analysis based on 48 weeks of treatment showed virologic response, defined as the percentage of patients with plasma HIV-1 RNA level< 50 copies/ml, with darunavir/ritonavir 800/100 mg once daily treatment was non-inferior (at the pre-defined 12% non-inferiority margin) compared to darunavir/ritonavir 600/100 mg twice daily for both ITT and OP populations.

Two randomised, controlled trials, each enrolling 255 patients, compared darunavir 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. Analyses of data through 96 weeks of treatment in the two trials demonstrated sustained antiretroviral efficacy and immunologic benefit with 38.9% of patients in the darunavir/ritonavir arm having HIV RNA < 50 copies/ml at week 96 compared to 8.9% in the control arm [difference: 30.1%, 95% CI (20.1; 40.0)]. 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.

Paediatric patients

An open-label, Phase II trial evaluated the pharmacokinetics, safety, tolerability, and efficacy of darunavir 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 darunavir/ritonavir twice 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 $\log_{10}$ versus baseline. 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.

The pharmacokinetics, safety, tolerability and efficacy of darunavir/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. 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 darunavir/ritonavir in combination with other antiretroviral agents.

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 34 pregnant women (17 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 29 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 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 α1-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 inhibit 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.

No pharmacokinetic data are available for Darunavir (as ethanolate) 400mg Tablets. A bioequivalence study was conducted with Darunavir 600 mg Tablets, which is proportionally similar to Darunavir (as ethanolate) 400mg Tablets in composition. Following single dose administration of Darunavir 600 mg Tablets in healthy volunteers, the mean (± SD) darunavir C_{max} value was 8667 (± 2182) µg/ml, and the corresponding value for AUC was 101867 (± 40859) µg.h/ml. The mean (± SD) darunavir t_{max} value was 3.92 (± 1.02) 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.

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

Distribution

Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma α1-acid glycoprotein.

Following intravenous administration, the volume of distribution of darunavir alone was 88.1 ± 59.0 l (Mean ± SD) and increased to 131 ± 49.9 l (Mean ± 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 14C-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 darunavir/ritonavir resulted in darunavir exposure comparable to that in adults receiving darunavir/ritonavir 600/100 mg twice daily.

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 darunavir/ritonavir 600/100 mg twice daily.

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 darunavir/ritonavir 800/100 mg once daily results in darunavir exposure that was comparable to that achieved in adults receiving darunavir/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 ≥ 100 cells x 106/l.
* 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 darunavir/ritonavir 800/100 mg once daily. 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 Darunavir/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 ≥ 100 cells x 106/l.
* 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≥65). 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 darunavir 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, darunavir 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.

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			
Pharmacokinetics of total darunavir (mean ± SD)	**Second trimester of pregnancy (n=11)[a]**	**Third trimester of pregnancy (n=11)**	**Postpartum (6-12 weeks) (n=11)**
C_{max}, ng/ml	4,601 ± 1,125	5,111 ± 1,517	6,499 ± 2,411
AUC_{12h}, ng.h/ml	38,950 ± 10,010	43,700 ± 16,400	55,300 ± 27,020
Cmin, ng/ml[b]	1,980 ± 839.9	2,498 ± 1,193	2,711 ± 2,268

[a] n=10 for AUC12h

[b] excluding Cmin value below LLOQ, n=10 for reference

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			
Pharmacokinetics of total darunavir (mean ± SD)	**Second trimester of pregnancy (n=16)**	**Third Trimester of pregnancy (n=14)**	**Postpartum (6-12 weeks) (n=15)**
Cmax, ng/ml	4,988 ± 1,551	5,138 ± 1,243	7,445 ± 1,674
AUC_{12h}, ng.h/ml	61,303 ± 16,232	60,439 ± 14,052	94,529 ± 28,572
Cmin, ng/ml[a]	1,193 ± 509	1,098 ± 609	1,572 ± 1,108

[a] n=12 for postpartum, n=15 for second trimester and n=14 for third trimester

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%, 24% and 17% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir C_{max}, AUC_{12h} and C_{min} values were 19%, 17% 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_{12h} and C_{min} were 34%, 34% and 32% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir C_{max}, AUC_{12h} and C_{min} values were 31%, 35% 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. 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 at 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, darunavir with low dose ritonavir should not be used in paediatric patients below 3 years of age.

In a carcinogenicity study in mice and 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

Core tablet:

Silicified microcrystalline cellulose
Crospovidone
Colloidal silicon dioxide
Magnesium stearate

Film coat:

Polyvinyl alcohol part hydrolysed
Titanium dioxide
Macrogol/PEG
Talc
FD&C yellow #6/Sunset yellow FCF Aluminium Lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Opaque, white, 85cc high density polyethylene (HDPE) plastic bottle containing 60 tablets, fitted with a HDPE non child resistant closure, and foil induction seal.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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India

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

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June 2017

References

General reference sources for this SmPC include:

Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach 2016, available at: http://www.who.int/hiv/pub/arv/arv-2016/en/

European SmPC, Prezista, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000707/WC500041756.pdf