DARUNAVIR TABLETS 600 MG

MODULE – 1

1.5. Product Information

1.5.1 Prescribing information (Summary of products characteristics)

Hetero Labs Limited. India

1. Name of the medicinal product

INN Name : Darunavir amorphous

Propriority Name : Darunavir Tablets 600 mg

Strength : 600 mg

2. Qualitative and quantitative composition

Each film coated tablet contains 600 mg of Darunavir

For Excipients kindly refer to 6.1 list of excipients

3. Pharmaceutical form

Film coated tablet.

Description: Orange, oval shaped, biconvex, film coated tablets de-bossed with "J" on one side and "7" on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Darunavir, 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.

Darunavir 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 Darunavir 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 Darunavir.

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 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

Darunavir 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 Darunavir.

Darunavir is also available as an oral suspension for use in patients who are unable to swallow Darunavir tablets (please refer to the Summary of Product Characteristics for Darunavir 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. Darunavir 600 mg tablets can be used to construct the twice daily 600 mg regimen.

The use of 75 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 600 mg tablets.

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 ≥ 100 cells x 10^6/l (see the Summary of Product Characteristics for Darunavir 400 mg and 800 mg tablets).

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

ART-naïve adult patients

For dosage recommendations in ART-naïve patients see the Summary of Product Characteristics for Darunavir 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 Darunavir and ritonavir in paediatric patients is provided in the table below

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

[a] ritonavir oral solution: 80 mg/ml

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

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

A once daily dose regimen of Darunavir 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 ≥ 100 cells x 10^6/l.

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

The recommended dose of Darunavir with low dose ritonavir for paediatric patients is based on body weight and should not exceed the recommended adult dose (600/100 mg twice daily or 800/100 mg once daily)

Recommended dose for treatment-experienced paediatric patients (3 to 17 years of age) for Darunavir tablets and ritonavir[a]		
Body weight (kg)	**Dose (once daily with food)**	**Dose(twice daily with food)**
≥ 15 kg–< 30 kg	600 mg Darunavir /100 mg ritonavir once daily	375 mg Darunavir /50 mg ritonavir twice daily
≥ 30 kg–< 40 kg	675 mg Darunavir /100 mg ritonavir once daily	450 mg Darunavir /60 mg ritonavir twice daily
≥ 40 kg	800 mg Darunavir /100 mg ritonavir once daily	600 mg Darunavir /100 mg ritonavir twice daily

[a] with 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 Darunavir /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.

Advice on missed doses

In case a dose of Darunavir and/or ritonavir was missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of Darunavir and ritonavir with food as soon as possible. If this was 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, 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 in patients with renal impairment (see sections 4.4 and 5.2).

Paediatric patients

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

Darunavir exposures in treatment-naïve adolescents 12 to 17 years weighing at least 40 kg receiving Darunavir 800 mg once daily have been determined and were found to be within the therapeutic range as has been established in adults receiving Darunavir 800 mg once daily. As a consequence, since Darunavir once daily has also been registered for use in treatment-experienced adults 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 10^6/l, the same indication of Darunavir once daily applies to treatment-experienced children 3 to 17 years weighing at least 15 kg.

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

Pregnancy and postpartum

No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. Darunavir 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 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 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 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)
- elbasvir/grazoprevir (hepatitis C virus direct-acting antiviral)
- cisapride (gastrointestinal motility agent)
- lurasidone, 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

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.

Darunavir should only be used in combination with low dose ritonavir as a pharmacokinetic enhancer (see section 5.2).

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

Darunavir binds predominantly to α_1-acid glycoprotein. This protein binding is concentration-dependent indicative for saturation of binding. Therefore, protein displacement of medicinal products highly bound to α_1-acid glycoprotein cannot be ruled out (see section 4.5).

ART-experienced patients – once daily dosing

Darunavir 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 ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10^6/l (see section 4.2). Combinations with optimised background regimen (OBRs) other than ≥ 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

Darunavir 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

Darunavir 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 Darunavir in patients aged 65 and over, caution should be exercised in the administration of Darunavir 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 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. Darunavir /ritonavir 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 Darunavir + raltegravir compared to patients receiving Darunavir without raltegravir or raltegravir without Darunavir (see section 4.8).

Darunavir contains a sulphonamide moiety. Darunavir 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 Darunavir. During the clinical development program (N=3,063), hepatitis was 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.

Patients with coexisting conditions

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, Darunavir 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 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 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

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 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 the Summary of Product Characteristics for Darunavir 75 mg, 150 mg or 300 mg tablets (see section 4.5).

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

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).

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 and ritonavir and 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 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 and 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 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, systemic azoles like ketoconazole and clotrimazole). These interactions are described in the interaction table below.

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 Geometric mean change (%)	Recommendations concerning co-administration
HIV ANTIRETROVIRALS		
Integrase strand transfer inhibitors		
Dolutegravir	dolutegravir AUC ↓ 32% dolutegravir C24h 38% dolutegravir Cmax ↓ 11% darunavir ↔* * Using cross-study comparisons to historical pharmacokinetic data	Darunavir co-administered with low dose ritonavir and dolutegravir can be used without dose adjustment.
Elvitegravir	elvitegravir AUC ↔ elvitegravir Cmin ↔ elvitegravir Cmax ↔ darunavir AUC ↔ darunavir Cmin 17%	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

	darunavir Cmax ↔	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 400 mg once daily	didanosine AUC ↓ 9% didanosine Cmin ND didanosine Cmax ↓ 16% darunavir AUC ↔ darunavir Cmin ↔ darunavir Cmax ↔	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.
Tenofovir disoproxil fumarate	tenofovir AUC ↑ 22% tenofovir Cmin ↑ 37%	Monitoring of renal function may be indicated when Darunavir co-

300 mg once daily	tenofovir Cmax ↑ 24% #darunavir AUC ↑ 21% #darunavir Cmin ↑ 24% #darunavir Cmax ↑ 16% (↑ tenofovir from effect on MDR-1 transport in the renal tubules)	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 600 mg once daily	efavirenz AUC ↑ 21% efavirenz Cmin ↑ 17% efavirenz Cmax ↑ 15% #darunavir AUC ↓ 13% #darunavir Cmin ↓ 31% #darunavir Cmax ↓ 15% (↑ 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 Cmin. 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).
Etravirine 100 mg twice daily	etravirine AUC ↓ 37% etravirine Cmin ↓ 49% etravirine Cmax ↓ 32% darunavir AUC ↑ 15% darunavir Cmin ↔ darunavir Cmax ↔	Darunavir co-administered with low dose ritonavir and etravirine 200 mg twice daily can be used without dose adjustments.
Nevirapine 200 mg twice daily	nevirapine AUC ↑ 27% nevirapine Cmin ↑ 47% nevirapine Cmax ↑ 18% #darunavir: concentrations were consistent with historical data (↑ nevirapine from CYP3A inhibition)	Darunavir co-administered with low dose ritonavir and nevirapine can be used without dose adjustments.
Rilpivirine 150 mg once daily	rilpivirine AUC ↑ 130% rilpivirine Cmin ↑ 178% rilpivirine Cmax ↑ 79% darunavir AUC ↔ darunavir Cmin ↓ 11% darunavir Cmax ↔	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 300 mg once daily	atazanavir AUC ↔ atazanavir Cmin ↑ 52% atazanavir Cmax ↓ 11% #darunavir AUC ↔ #darunavir Cmin ↔ #darunavir Cmax ↔	Darunavir co-administered with low dose ritonavir and atazanavir can be used without dose adjustments.

	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. 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.	
Indinavir 800 mg twice daily	indinavir AUC ↑ 23% indinavir Cmin ↑ 125% indinavir Cmax ↔ #darunavir AUC ↑ 24% #darunavir Cmin ↑ 44% #darunavir Cmax ↑ 11% Indinavir: comparison of indinavir/ritonavir 800/100 mg twice daily vs. indinavir/darunavir/ritonavir 800/400/100 mg twice daily. 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 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.

Saquinavir 1,000 mg twice daily	#darunavir AUC ↓ 26% #darunavir Cmin ↓ 42% #darunavir Cmax ↓ 17% saquinavir AUC ↓ 6% saquinavir Cmin ↓ 18% saquinavir Cmax ↓ 6% Saquinavir: comparison of saquinavir/ritonavir 1,000/100 mg twice daily vs. saquinavir/darunavir/ritonavir 1,000/400/100 mg twice daily 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 Darunavir co-administered with low dose ritonavir with saquinavir.
HIV Protease inhibitors (PIs) - with co-administration of low dose ritonavir†		
Lopinavir/ritonavir 400/100 mg twice daily Lopinavir/ritonavir 533/133.3 mg twice daily	lopinavir AUC ↑ 9% lopinavir Cmin ↑ 23% lopinavir Cmax ↓ 2% darunavir AUC ↓ 38%‡ darunavir Cmin ↓ 51%‡ darunavir Cmax ↓ 21%‡ lopinavir AUC ↔ lopinavir Cmin ↑ 13% lopinavir Cmax ↑ 11% darunavir AUC ↓ 41% darunavir Cmin ↓ 55% darunavir Cmax ↓ 21% ‡ based upon non dose normalised	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).

	values	
CCR5 ANTAGONIST		
Maraviroc 150 mg twice daily	maraviroc AUC ↑ 305% maraviroc Cmin ND maraviroc Cmax ↑ 129% darunavir, ritonavir concentrations were consistent with historical data	The maraviroc dose should be 150 mg twice daily when co-administered with Darunavir with low dose ritonavir.
α1-ADRENORECEPTOR ANTAGONIST		
Alfuzosin	Based on theoretical considerations Darunavir is expected to increase alfuzosin plasma concentrations. (CYP3A inhibition)	Co-administration of Darunavir 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 Darunavir co-administered with low dose ritonavir.	The concomitant use with Darunavir 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 Flecainide	Not studied. Darunavir is expected to increase these antiarrhythmic plasma	Caution is warranted and therapeutic concentration monitoring, if
Digoxin 0.4 mg single dose	digoxin AUC ↑ 61% digoxin Cmin ND digoxin Cmax ↑ 29% (↑ 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 500 mg twice daily	clarithromycin AUC ↑ 57% clarithromycin Cmin ↑ 174% clarithromycin Cmax ↑ 26% #darunavir AUC ↓ 13% #darunavir Cmin ↑ 1% #darunavir Cmax ↓ 17% 14-OH-clarithromycin concentrations were not detectable when combined with **D**arunavir /ritonavir. (↑ 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.
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.
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 200 mg twice daily	carbamazepine AUC ↑ 45% carbamazepine Cmin ↑ 54% carbamazepine Cmax ↑ 43% darunavir AUC ↔ darunavir Cmin ↓ 15% darunavir Cmax ↔	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 20 mg once daily Sertraline 50 mg once daily Amitriptyline	paroxetine AUC ↓ 39% paroxetine Cmin ↓ 37% paroxetine Cmax ↓ 36% #darunavir AUC ↔ #darunavir Cmin ↔ #darunavir Cmax ↔ sertraline AUC ↓ 49% sertraline Cmin ↓ 49% sertraline Cmax ↓ 44% #darunavir AUC ↔	If antidepressants are co-administered with Darunavir 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

Desipramine Imipramine Nortriptyline Trazodone	#darunavir Cmin ↓ 6% #darunavir Cmax ↔ Concomitant use of Darunavir co-administered wirth low dose ritonavir and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or CYP3A inhibition).	monitored for antidepressant response. 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 by ritonavir)	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 200 mg twice daily	ketoconazole AUC ↑ 212% ketoconazole Cmin ↑ 868% ketoconazole Cmax ↑ 111% #darunavir AUC ↑ 42% #darunavir Cmin ↑ 73% #darunavir Cmax ↑ 21% (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.
Posaconazole	Not studied. Darunavir may increase antifungal plasma concentrations (P-gp inhibition) and posaconazole 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.	Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of itraconazole should not exceed 200 mg.
Clotrimazole	Not studied. Concomitant systemic use of clotrimazole and darunavir co-administered with low dose ritonavir may increase plasma concentrations of darunavir. darunavir AUC24h ↑ 33% (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 4.4).
ANTIMALARIALS		

Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	artemether AUC ↓ 16% artemether Cmin ↔ artemether Cmax ↓ 18% dihydroartemisinin AUC ↓ 18% dihydroartemisinin Cmin ↔ dihydroartemisinin Cmax ↓ 18% lumefantrine AUC ↑ 175% lumefantrine Cmin ↑ 126% lumefantrine Cmax ↑ 65% darunavir AUC ↔ darunavir Cmin ↓ 13% darunavir Cmax ↔	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.
ANTIMYCOBACTERIALS		
Rifampicin 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 Darunavir with concomitant low dose ritonavir is not recommended. The combination of rifampicin and Darunavir with concomitant low dose ritonavir is contraindicated (see section 4.3).
Rifabutin 150 mg once every other day	rifabutin AUC** ↑ 55% rifabutin Cmin** ↑ ND rifabutin Cmax** ↔	A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg once every

	darunavir AUC ↑ 53% darunavir Cmin ↑ 68% darunavir Cmax ↑ 39% ** sum of active moieties of rifabutin (parent drug + 25-O-desacetyl metabolite) 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 Darunavir /ritonavir (600/100 mg twice daily) with an about 10-fold increase in the daily exposure to the active metabolite 25-O-desacetylrifabutin. Furthermore, AUC of the sum of active moieties of rifabutin (parent drug + 25-O-desacetyl metabolite) was increased 1.6-fold, while Cmax remained comparable. Data on comparison with a 150 mg once daily reference dose is lacking. (Rifabutin is an inducer and substrate of CYP3A.) An increase of systemic exposure to darunavir was observed when Darunavir co-administered with 100 mg ritonavir was co-administered with rifabutin (150 mg once every other day).	other day) and increased monitoring for rifabutin related adverse events is warranted in patients receiving the combination. 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. Based on pharmacokinetic modeling, this dosage reduction of 75% is also applicable if patients receive rifabutin at doses other than 300 mg/day.
ANTINEOPLASTICS		

Dasatinib Nilotinib Vinblastine Vincristine Everolimus	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. 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 (see section 4.3). Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended.
ANTIPSYCHOTICS/NEUROLEPTICS		
Quetiapine	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 (see

		section 4.3).
Risperidone Thioridazine Lurasidone Pimozide Sertindole	Not studied. Darunavir is expected to increase these antipsychotic plasma concentrations. (CYP3A, 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. Concominant administration of Darunavir with low dose ritonavir and lurasidone, pimozide or sertindole is contraindicated (see section 4.3).
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		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide,	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	Concomitant use of Darunavir 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

fluticasone, mometasone, prednisone, triamcinolone)	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. Other corticosteroids: interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with Darunavir with low dose ritonavir, resulting in reduced serum cortisol concentrations.	systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. 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. 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. (CYP3A induction)	Systemic dexamethasone should be used with caution when combined with Darunavir co-administered with low dose ritonavir.
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		
NS3-4A protease inhibitors		
Elbasvir/grazoprevir	Darunavir with low dose ritonavir may increase the exposure to grazoprevir. (CYP3A and OATP1B inhibition)	Concomitant use of Darunavir with low dose ritonavir and elbasvir/grazoprevir is contraindicated (see section 4.3).
Telaprevir 750 mg every 8 hours	telaprevir AUC ↓ 35% telaprevir Cmin ↓ 32% telaprevir Cmax ↓ 36% darunavir AUC12 ↓ 40% darunavir Cmin ↓ 42% darunavir Cmax ↓ 40%	It is not recommended to co-administer Darunavir with low dose ritonavir and telaprevir
Boceprevir 800 mg three times daily	boceprevir AUC ↓ 32% boceprevir Cmin ↓ 35% boceprevir Cmax ↓ 25% darunavir AUC ↓ 44% darunavir Cmin ↓ 59% darunavir Cmax ↓ 36%	It is not recommended to co-administer Darunavir with low dose ritonavir and boceprevir.
Simeprevir	simeprevir AUC ↑ 159% simeprevir Cmin ↑ 358% simeprevir Cmax ↑ 79% darunavir AUC ↑ 18% darunavir Cmin ↑ 31% darunavir Cmax ↔ The dose of simeprevir in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir, compared to 150 mg	It is not recommended to co-administer Darunavir with low dose ritonavir and simeprevir.

	in the simeprevir alone treatment group.	
HERBAL PRODUCTS		
St John's wort (Hypericum perforatum)	Not studied. St John's wort is expected to decrease the plasma concentrations of darunavir and 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.
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 co-administered with low dose 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 10 mg once daily	atorvastatin AUC ↑ 3-4 fold atorvastatin Cmin ↑ ≈5.5-10 fold atorvastatin Cmax ↑ ≈2 fold	When administration of atorvastatin and Darunavir co-administered with low dose ritonavir is desired, it is

	#darunavir	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 40 mg single dose	pravastatin AUC ↑ 81%¶ pravastatin Cmin ND pravastatin Cmax ↑ 63% ¶ an up to five-fold increase was seen in a limited subset of subjects	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 10 mg once daily	rosuvastatin AUC ↑ 48%‖ rosuvastatin Cmax ↑ 144%‖ ‖ based on published data	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 150 mg twice daily	#darunavir AUC ↔ #darunavir Cmin ↔ #darunavir Cmax ↔	Darunavir co-administered with low dose ritonavir can be co-administered with H2-receptor antagonists without dose adjustments.
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus	Not studied. Exposure to these immunosuppressants will be increased	Therapeutic drug monitoring of the immunosuppressive agent must be
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 individual dose ranging from 55 mg to 150 mg once daily	R(-) methadone AUC ↓ 16% R(-) methadone Cmin ↓ 15% R(-) methadone Cmax ↓ 24%	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.
Buprenorphine/naloxone 8/2 mg–16/4 mg once daily	buprenorphine AUC ↓ 11% buprenorphine Cmin ↔ buprenorphine Cmax ↓ 8% norbuprenorphine AUC ↑ 46% norbuprenorphine Cmin ↑ 71% norbuprenorphine Cmax ↑ 36% naloxone AUC ↔ naloxone Cmin ND	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

	naloxone Cmax ↔	is recommended.
OESTROGEN-BASED CONTRACEPTIVES		
Ethinylestradiol Norethindrone 35 µg/1 mg once daily	ethinylestradiol AUC ↓ 44% ethinylestradiol Cmin ↓ 62% ethinylestradiol Cmax ↓ 32% norethindrone AUC ↓ 14% norethindrone Cmin ↓ 30% norethindrone Cmax ↔	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	In an interaction study #, a comparable systemic exposure to sildenafil was	The combination of avanafil and Darunavir with low dose ritonavir is
For the treatment of pulmonary arterial hypertension Sildenafil	Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and darunavir co-administered with low dose	A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with Darunavir and low dose ritonavir
PROTON PUMP INHIBITORS		
Omeprazole 20 mg once daily	#darunavir AUC ↔ #darunavir Cmin ↔ #darunavir Cmax ↔	Darunavir co-administered with low dose ritonavir can be co-administered with proton pump inhibitors without dose adjustments.
SEDATIVES/HYPNOTICS		

Buspirone Clorazepate Diazepam Estazolam Flurazepam Triazolam Zoldipem Midazolam	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. 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.	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. 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

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account.

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

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 Darunavir.

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

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).

4.8 Undesirable effects

Summary of the safety profile

During the clinical development program (N=2,613 treatment-experienced subjects who initiated therapy with Darunavir/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 Darunavir /ritonavir 800/100 mg once daily in treatment-naïve subjects was similar to that seen with Darunavir /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 Darunavir /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 (≥ 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, gastrooesophageal 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 generalised 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. 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) 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 Darunavir 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 Darunavir 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 Darunavir 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 Darunavir 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:

4.9 Overdose

Human experience of acute overdose with Darunavir 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 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 (K_D of 4.5 x 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 μM to > 100 μM.

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 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 (see Clinical results).

Viruses isolated from patients on Darunavir/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 mutations and loss of susceptibility to PIs in virologic failures at endpoint in the *ARTEMIS*, *ODIN* and *TITAN* trials.

	ARTEMIS	ODIN		TITAN
	DARUNAVIR/ ritonavir 800/100 mg once daily N=343	DARUNAVIR/ ritonavir 800/100 mg once daily N=294	DARUNAVIR/ ritonavir 600/100 mg twice daily N=296	DARUNAVIR/ ritonavir 600/100 mg twice daily N=298
Total number of virologic failures[a], n (%)	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 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[b] at endpoint, n/N				
Primary (major) PI 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 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

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

[b] 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 DARUNAVIR 400 mg and 800 mg tablets or 100 mg/ml oral suspension.

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

The evidence of efficacy of Darunavir 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 Darunavir 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	DARUNAVIR/ritonavir 600/100 mg twice daily + OBR N=298	Lopinavir/ritonavir 400/100 mg twice daily + OBR N=297	Treatment difference (95% CI of difference)

HIV-1 RNA < 50 copies/ml[a]	70.8% (211)	60.3% (179)	10.5% (2.9; 18.1)[b]
median CD4+ cell count change from baseline (x 10^6/l)[c]	88	81	

[a] Imputations according to the TLOVR algorithm
[b] Based on a normal approximation of the difference in % response
[c] NC=F

At 48 weeks non-inferiority in virologic response to the Darunavir/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 Darunavir/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 Darunavir/ritonavir 800/100 mg once daily versus Darunavir/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	DARUNAVIR/ritonavir 800/100 mg once daily + OBR N=294	DARUNAVIR/ritonavir 600/100 mg twice daily + OBR N=296	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[a]	72.1% (212)	70.9% (210)	1.2% (-6.1; 8.5)[b]
With Baseline HIV-1 RNA (copies/ml)	77.6% (198/255)	73.2% (194/265)	4.4% (-3.0; 11.9)

< 100,000 ≥ 100,000	35.9% (14/39)	51.6% (16/31)	-15.7% (-39.2; 7.7)
With Baseline CD4+ cell count (x 10^6/l) ≥ 100 < 100	75.1% (184/245) 57.1% (28/49)	72.5% (187/258) 60.5% (23/38)	2.6% (-5.1; 10.3) -3.4% (-24.5; 17.8)
With HIV-1 clade Type B Type AE Type C Other[c]	 70.4% (126/179) 90.5% (38/42) 72.7% (32/44) 55.2% (16/29)	 64.3% (128/199) 91.2% (31/34) 78.8% (26/33) 83.3% (25/30)	 6.1% (-3.4; 15.6) -0.7% (-14.0; 12.6) -6.1% (-2.6; 13.7) -28.2% (-51.0; -5.3)
mean CD4+ cell count change from baseline (x 10^6/l)[e]	108	112	-5[d] (-25; 16)

[a] Imputations according to the TLOVR algorithm

[b] Based on a normal approximation of the difference in % response

[c] Clades A1, D, F1, G, K, CRF02_AG, CRF12_BF, and CRF06_CPX

[d] Difference in means

[e] 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 Darunavir/ritonavir 800/100 mg once daily treatment was demonstrated to be 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.

Darunavir/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 10^6/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 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.

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

[a] Imputations according to the TLOVR algorithm

[b] Last Observation Carried Forward imputation

[c] 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 Darunavir co-administered with ritonavir (600/100 mg twice daily) by baseline genotype[a], and baseline darunavir FC and by use of enfuvirtide (ENF): As treated analysis of the POWER and DUET trials.

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

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

[b] fold change in EC_{50}

[c] "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

[d] "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 Darunavir 400 mg and 800 mg tablets or Darunavir 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 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 (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 $\log_{10}$ 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	DARUNAVIR/ritonavir N=80
HIV-1 RNA < 50 copies/ml[a]	47.5% (38)
CD4+ cell count mean change from baseline[b]	147

[a] Imputations according to the TLOVR algorithm.

[b] 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 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, ***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 Darunavir/ritonavir in combination with other antiretroviral agents (see section 4.2 for dosage recommendations per body weight).

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

[a] Imputations according to the TLOVR algorithm.

[b] 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 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, 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 α_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, 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 α_1-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 ^{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 Darunavir/ritonavir resulted in darunavir exposure comparable to that in adults receiving Darunavir/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 Darunavir/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 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 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 Darunavir/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 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 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 ≥ 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 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
C_{min}, ng/ml[b]	1,980 ± 839.9	2,498 ± 1,193	2,711 ± 2,268

[a] n=10 for AUC_{12h}

[b] excluding C_{min} 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)**
C_{max}, ng/ml	4,988 ± 1,551	5,138 ± 1,243	7,445 ± 1,674
AUC_{24h}, ng.h/ml	61,303 ± 16,232	60,439 ± 14,052	94,529 ± 28,572
C_{min}, 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_{24h} 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_{24h} 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. 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, Darunavir 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

Film coated tablet:

Tablet contents: Silicified microcrystalline cellulose, Colloidal silicon dioxide, Crospovidone, Magnesium stearate, Opadry II Orange (85F530007)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C and protect from moisture.

6.5 Nature and contents of container

HDPE Container Pack: 60's count : High density polyethylene containers 150 cc – 38 mm neck

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing Authorisation Holder and Manufacturing Site Addresses

Marketing authorization Holder:

Name: **Hetero Labs Limited**

Business Address: 7-2-A2, Hetero Corporate, Industrial Estates, Sanath Nagar, Hyderabad-500 018, Telangana. India

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E-Mail : contact@heterodrugs.com

Manufacturing site:

(Company) Name : Hetero Labs Limited (Unit-III)

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Telephone : +91 40-23096171/172/173/174

Telefax : + 91 40-23095105

E-Mail : contact@heterodrugs.com

8. Marketing authorization number

9. Date of first registration/renewal of the registration

10. Date of revision of the text