เอกสารกำกับยาภาษาอังกฤษ

DARUTAB Tablets

1. Name of the medicinal product

DARUTAB (150 mg)

DARUTAB (400 mg)

DARUTAB (600 mg)

2. Qualitative and quantitative composition

DARUTAB (150 mg)

Each tablet contains 150 mg of darunavir

DARUTAB (400 mg)

Each tablet contains 400 mg of darunavir

DARUTAB (600 mg)

Each tablet contains 600 mg of darunavir

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

DARUTAB (150 mg)
Film coated tablet.
White, biconvex, oval, film coated tablets one site bisected and debossed with “D” on the left side and “A” on the right side, the other side debossed with “150”

DARUTAB (400 mg)

Film coated tablet.
White, biconvex, oval, film coated tablets one site bisected and debossed with “D” on the left side and “A” on the right side, the other side debossed with “400”

DARUTAB (600 mg)
Film coated tablet.
White, biconvex, oval, film coated tablets one site bisected and debossed with “D” on the left side and “A” on the right side, the other side debossed with “600”

4. Clinical particulars

4.1 Therapeutic indications

DARUTAB, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection (see section 4.2).
DARUTAB 150 mg, 400 mg, and 600 mg tablets may be used to provide suitable dose regimens (see section 4.2):

• For the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced adult patients, including those that have been highly pre-treated.

• For the treatment of HIV-1 infection in paediatric patients from the age of 3 years and at least 15 kg body weight.

In deciding to initiate treatment with DARUTAB 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 DARUTAB (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a health care provider experienced in the management of HIV infection. After therapy with DARUTAB 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

DARUTAB 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 DARUTAB.

ART-experienced adult patients

The recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. DARUTAB 150 mg, 400 mg, and 600 mg tablets can be used to construct the twice daily 600 mg regimen.

The use of 150 mg tablets to achieve the recommended dose is appropriate when there is a possibility of difficulty in swallowing the 400 mg or 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. DARUTAB 400 mg tablets can be used to construct the once daily 800 mg regimen.

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

ART-naïve adult patients

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

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

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

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

DARUTAB twice daily taken with ritonavir taken with food is usually recommended.
A once daily dose regimen of DARUTAB 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 weight-based dose of DARUTAB and ritonavir in paediatric patients is provided in the table below. The recommended dose of DARUTAB with low dose ritonavir 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) with DARUTAB 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] 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 DARUTAB/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 DARUTAB and/or ritonavir is missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of DARUTAB and ritonavir with food as soon as possible. If this is noticed later than 6 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

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

Special populations

Elderly

Limited information is available in this population, and therefore, DARUTAB 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, DARUTAB 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, DARUTAB must not be used in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3, 4.4 and 5.2).

Renal impairment

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

Paediatric population

DARUTAB/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). DARUTAB/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 DARUTAB/ritonavir during pregnancy and postpartum. DARUTAB 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 DARUTAB 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 DARUTAB 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 DARUTAB with low dose ritonavir, with active substances that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These active substances include e.g.:

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

4.4 Special warnings and precautions for use

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

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

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

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

Darunavir binds predominantly to 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

DARUTAB 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

DARUTAB 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

DARUTAB 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 DARUTAB in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy (see sections 4.2 and 5.2).

Severe skin reactions

During the darunavir/ritonavir clinical development program (N=3,063), severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens-Johnson Syndrome has been rarely (< 0.1%) reported, and during post-marketing experience toxic epidermal necrolysis and acute generalised exanthematous pustulosis have been reported. DARUTAB 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/ritonavir + raltegravir compared to patients receiving darunavir/ritonavir without raltegravir or raltegravir without darunavir (see section 4.8).

Darunavir contains a sulphonamide moiety. DARUTAB 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 darunavir/ritonavir 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 DARUTAB/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 DARUTAB is therefore contraindicated in patients with severe hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, DARUTAB should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal impairment

No special precautions or dose adjustments for DARUTAB/ritonavir are required in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis. Therefore, no special precautions or dose adjustments are required in these patients (see sections 4.2 and 5.2).

Haemophiliac patients

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

Weight and metabolic parameters

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

Osteonecrosis

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

Immune reconstitution inflammatory syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia caused by Pneumocystis jirovecii (formerly known as Pneumocystis carinii). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. In addition, reactivation of herpes simplex and herpes zoster has been observed in clinical studies with 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 boosted darunavir once daily may result in sub-optimal darunavir C_{min}. If efavirenz is to be used in combination with DARUTAB, the DARUTAB/ritonavir 600/100 mg twice daily regimen should be used (see section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Medicinal products that may be affected by darunavir boosted with ritonavir

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

DARUTAB 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, DARUTAB must only be used in combination with low dose ritonavir as a pharmacokinetic enhancer (see sections 4.4 and 5.2).

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

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

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

Medicinal products that affect darunavir/ritonavir exposure

Darunavir and ritonavir are metabolised by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir (e.g. rifampicin, St John's wort, lopinavir). Co-administration of darunavir and ritonavir and other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (e.g. indinavir, azole antifungals likeclotrimazole). 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 ↓ 22% dolutegravir C_{24h} ↓ 38% dolutegravir C_{max} ↓ 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.
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 C_{min} ND didanosine C_{max} ↓ 16% darunavir AUC ↔ darunavir C_{min} ↔ darunavir C_{max} ↔	Darunavir co-administered with low dose ritonavir and didanosine can be used without dose adjustments. Didanosine is to be administered on an empty stomach, thus it should be administered 1 hour before or 2 hours after darunavir/ritonavir given with food.
Tenofovir disoproxil 245 mg once daily‡	tenofovir AUC ↑ 22% tenofovir C_{min} ↑ 37% tenofovir C_{max} ↑ 24% #darunavir AUC ↑ 21% #darunavir C_{min} ↑ 24% #darunavir C_{max} ↑ 16% (↑ tenofovir from effect on MDR-1 transport in the renal tubules)	Monitoring of renal function may be indicated when darunavir co-administered with low dose ritonavir is given in combination with tenofovir disoproxil, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.
Emtricitabine/tenofovir alafenamide	Tenofovir alafenamide ↔ Tenofovir ↑	The recommended dose of emtricitabine/tenofovir alafenamide is 200/10 mg once daily when used with darunavir with low dose ritonavir.
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 C_{min} ↑ 17% efavirenz C_{max} ↑ 15% #darunavir AUC ↓ 13% #darunavir C_{min} ↓ 31% #darunavir C_{max} ↓ 15% (↑ efavirenz from CYP3A inhibition)	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 from CYP3A induction)	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 C_{min} ↓ 49% etravirine C_{max} ↓ 32% darunavir AUC ↑ 15% darunavir C_{min} ↔ darunavir C_{max} ↔	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 C_{min} ↑ 47% nevirapine C_{max} ↑ 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 C_{min} ↑ 178% rilpivirine C_{max} ↑ 79% darunavir AUC ↔ darunavir C_{min} ↓ 11% darunavir C_{max} ↔	Darunavir co-administered with low dose ritonavir and rilpivirine can be used without dose adjustments.
HIV Protease inhibitors (PIs) - without additional co-administration of low dose ritonavir[†]		
Atazanavir 300 mg once daily	atazanavir AUC ↔ atazanavir C_{min} ↑ 52% atazanavir C_{max} ↓ 11% [#]darunavir AUC ↔ [#]darunavir C_{min} ↔ [#]darunavir C_{max} ↔ 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 co-administered with low dose ritonavir and atazanavir can be used without dose adjustments.

	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 C_{min} ↑ 125% indinavir C_{max} ↔ [#]darunavir AUC ↑ 24% [#]darunavir C_{min} ↑ 44% [#]darunavir C_{max} ↑ 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 C_{min} ↓ 42% [#]darunavir C_{max} ↓ 17% saquinavir AUC ↓ 6% saquinavir C_{min} ↓ 18% saquinavir C_{max} ↓ 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 C_{min} ↑ 23% lopinavir C_{max} ↓ 2% darunavir AUC ↓ 38%‡ darunavir C_{min} ↓ 51%‡ darunavir C_{max} ↓ 21%‡ lopinavir AUC ↔ lopinavir C_{min} ↑ 13% lopinavir C_{max} ↑ 11% darunavir AUC ↓ 41% darunavir C_{min} ↓ 55% darunavir C_{max} ↓ 21% ‡ based upon non dose normalised values	Due to a decrease in the exposure (AUC) of darunavir by 40%, appropriate doses of the combination have not been established. Hence, concomitant use of darunavir co-administered with low dose ritonavir and the combination product lopinavir/ritonavir is contraindicated (see section 4.3).
CCR5 ANTAGONIST		
Maraviroc 150 mg twice daily	maraviroc AUC ↑ 305% maraviroc C_{min} ND maraviroc C_{max} ↑ 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.
α_1-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 Lidocaine (systemic) Mexiletine Propafenone	Not studied. Darunavir is expected to increase these antiarrhythmic plasma concentrations. (CYP3A and/or CYP2D6 inhibition)	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with darunavir with low dose ritonavir.

Amiodarone Bepridil Dronedarone Quinidine Ranolazine		Darunavir co-administered with low dose ritonavir and amiodarone, bepridil, dronedarone, quinidine, or ranolazine is contraindicated (see section 4.3).
Digoxin 0.4 mg single dose	digoxin AUC ↑ 61% digoxin C_{min} ND digoxin C_{max} ↑ 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 C_{min} ↑ 174% clarithromycin C_{max} ↑ 26% [#]darunavir AUC ↓ 13% [#]darunavir C_{min} ↑ 1% [#]darunavir C_{max} ↓ 17% 14-OH-clarithromycin concentrations were not detectable when combined with darunavir/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. For patients with renal impairment the Summary of Product Characteristics for clarithromycin should be consulted for the recommended dose.
ANTICOAGULANTS		
Apixaban Dabigatran etexilate Rivaroxaban	Not studied. Co-administration of darunavir with these anticoagulants may increase concentrations of the anticoagulant. (CYP3A and/or P-gp inhibition)	The use of darunavir co-administered with low dose ritonavir and these anticoagulants is not recommended.
Warfarin	Not studied. Warfarin concentrations may be affected when co-administered with darunavir with low dose ritonavir.	It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with darunavir co-administered with low dose ritonavir.

ANTICONVULSANTS		
Phenobarbital Phenytoin	Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir and its pharmacoenhancer. (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 C_{min} ↑ 54% carbamazepine C_{max} ↑ 43% darunavir AUC ↔ darunavir C_{min} ↓ 15% darunavir C_{max} ↔	No dose adjustment for darunavir/ritonavir is recommended. If there is a need to combine darunavir/ritonavir and carbamazepine, patients should be monitored for potential carbamazepine-related adverse events. Carbamazepine concentrations should be monitored and its dose should be titrated for adequate response. Based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of darunavir/ritonavir.
Clonazepam	Not studied. Co-administration of boosted darunavir with clonazepam may increase concentrations of clonazepam. (CYP3A inhibition)	Clinical monitoring is recommended when co-administering darunavir with low dose ritonavir and clonazepam.
ANTIDEPRESSANTS		
Paroxetine 20 mg once daily Sertraline 50 mg once daily	paroxetine AUC ↓ 39% paroxetine C_{min} ↓ 37% paroxetine C_{max} ↓ 36% [#]darunavir AUC ↔ [#]darunavir C_{min} ↔ [#]darunavir C_{max} ↔ sertraline AUC ↓ 49% sertraline C_{min} ↓ 49% sertraline C_{max} ↓ 44% [#]darunavir AUC ↔ [#]darunavir C_{min} ↓ 6% [#]darunavir C_{max} ↔ Concomitant use of darunavir co-administered with low dose ritonavir	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 monitored for antidepressant response. Clinical monitoring is recommended when co-administering darunavir with low dose ritonavir with these antidepressants and a dose adjustment

Amitriptyline Desipramine Imipramine Nortriptyline Trazodone	and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or CYP3A inhibition)	of the antidepressant may be needed.
ANTIFUNGALS		
Voriconazole	Not studied. Ritonavir may decrease plasma concentrations of voriconazole. (induction of CYP450 enzymes)	Voriconazole should not be combined with darunavir co-administered with low dose ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Fluconazole Isavuconazole Itraconazole Posaconazole	Not studied. Darunavir may increase antifungal plasma concentrations and posaconazole, isavuconazole, itraconazole, or fluconazole may increase darunavir concentrations. (CYP3A and/or P-gp inhibition)	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 and/or clotrimazole. darunavir AUC24h ↑ 33% (based on population pharmacokinetic model)	
ANTIGOUT MEDICINES		
Colchicine	Not studied. Concomitant use of colchicine and darunavir co-administered with low dose ritonavir may increase the exposure to colchicine. (CYP3A and/ or P-gp inhibition)	A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with darunavir co-administered with low dose ritonavir is required. For patients with renal or hepatic impairment colchicine with darunavir co-administered with low dose ritonavir is contraindicated (see sections 4.3 and 4.4).

ANTIMALARIALS		
Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	artemether AUC ↓ 16% artemether C_{min} ↔ artemether C_{max} ↓ 18% dihydroartemisinin AUC ↓ 18% dihydroartemisinin Cmin ↔ dihydroartemisinin Cmax ↓ 18% lumefantrine AUC ↑ 175% lumefantrine C_{min} ↑ 126% lumefantrine C_{max} ↑ 65% darunavir AUC ↔ darunavir C_{min} ↓ 13% darunavir C_{max} ↔	The combination of darunavir and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.
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 C_{min}** ↑ ND rifabutin C_{max}** ↔ darunavir AUC ↑ 53% darunavir C_{min} ↑ 68% darunavir C_{max} ↑ 39% ** sum of active moieties of rifabutin (parent drug + 25-O-desacetyl metabolite) The interaction trial showed a comparable daily systemic exposure	A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg once every other day) and increased monitoring for rifabutin related adverse events is warranted in patients receiving the combination with darunavir co-administered with ritonavir. In case of safety issues, a further increase of the dosing interval for rifabutin and/or monitoring of rifabutin levels should be considered. Consideration should be given to

	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 C_{max} 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).	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. Concomitant 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	Concomitant administration of darunavir with low dose ritonavir with

	ritonavir may lead to a substantial increase in exposure to ticagrelor	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	Not studied. Darunavir is expected to increase these antipsychotic plasma concentrations. (CYP3A inhibition)	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).
Perphenazine Risperidone Thioridazine Lurasidone Pimozide Sertindole	Not studied. Darunavir is expected to increase these antipsychotic plasma concentrations. (CYP3A, CYP2D6 and/or P-gp inhibition)	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	Fluticasone: in a clinical study where ritonavir 100 mg capsules twice daily were co-administered with 50 µg	Concomitant use of darunavir with low dose ritonavir and corticosteroids that are metabolised by CYP3A (e.g.

betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone)	intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, fluticasone propionate plasma concentrations increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% CI 82-89%). Greater effects may be expected when fluticasone is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone. The effects of high fluticasone systemic exposure on ritonavir plasma levels are unknown. 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.	fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. 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. Bosentan is expected to decrease plasma concentrations of darunavir and/or its pharmacoenhancer. (CYP3A induction)	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).
Boceprevir 800 mg three times daily	boceprevir AUC ↓ 32% boceprevir C_{min} ↓ 35% boceprevir C_{max} ↓ 25% darunavir AUC ↓ 44% darunavir C_{min} ↓ 59% darunavir C_{max} ↓ 36%	It is not recommended to co-administer darunavir with low dose ritonavir and boceprevir.
Simeprevir	simeprevir AUC ↑ 159% simeprevir C_{min} ↑ 358% simeprevir C_{max} ↑ 79% darunavir AUC ↑ 18% darunavir C_{min} ↑ 31% darunavir C_{max} ↔ The dose of simeprevir in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir, compared to 150 mg in the simeprevir alone treatment group.	It is not recommended to co-administer darunavir with low dose ritonavir and simeprevir.
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 [#]darunavir/ritonavir	When administration of atorvastatin and darunavir co-administered with low dose ritonavir is desired, it is recommended to start with an atorvastatin dose of 10 mg once daily. A gradual dose increase of atorvastatin may be tailored to the clinical response.
Pravastatin 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 C_{max} ↑ 144%[‖] [‖] based on published data with darunavir/ritonavir	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.
OTHER LIPID MODIFYING AGENTS		
Lomitapide	Based on theoretical considerations boosted darunavir is expected to increase the exposure of lomitapide when co-administered. (CYP3A inhibition)	Co-administration is contraindicated (see section 4.3)
H_2-RECEPTOR ANTAGONISTS		
Ranitidine 150 mg twice daily	[#]darunavir AUC ↔ [#]darunavir C_{min} ↔	Darunavir co-administered with low dose ritonavir can be co-administered

	[#]darunavir C_{max} ↔	with H2-receptor antagonists without dose adjustments.
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus	Not studied. Exposure to these immunosuppressants will be increased when co-administered with darunavir co-administered with low dose ritonavir. (CYP3A inhibition)	Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs. Concomitant use of everolimus and darunavir co-administered with low dose ritonavir is not recommended.
INHALED BETA AGONISTS		
Salmeterol	Not studied. Concomitant use of salmeterol and darunavir co-administered with low dose ritonavir may increase plasma concentrations of salmeterol.	Concomitant use of salmeterol and darunavir co-administered with low dose ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS / TREATMENT OF OPIOID DEPENDENCE		
Methadone individual dose ranging from 55 mg to 150 mg once daily	R(-) methadone AUC ↓ 16% R(-) methadone C_{min} ↓ 15% R(-) methadone C_{max} ↓ 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 C_{min} ↔ buprenorphine C_{max} ↓ 8% norbuprenorphine AUC ↑ 46% norbuprenorphine C_{min} ↑ 71% norbuprenorphine C_{max} ↑ 36% naloxone AUC ↔ naloxone C_{min} ND naloxone C_{max} ↔	The clinical relevance of the increase in norbuprenorphine pharmacokinetic parameters has not been established. Dose adjustment for buprenorphine may not be necessary when co-administered with darunavir/ritonavir but a careful clinical monitoring for signs of opiate toxicity is recommended.

Fentanyl Oxycodone Tramadol	Based on theoretical considerations boosted darunavir may increase plasma concentrations of these analgesics. (CYP2D6 and/or CYP3A inhibition)	Clinical monitoring is recommended when co-administering darunavir with low dose ritonavir with these analgesics.
OESTROGEN-BASED CONTRACEPTIVES		
Drospirenone Ethinylestradiol (3 mg/0.02 mg once daily) Ethinylestradiol Norethindrone 35 µg/1 mg once daily	Not studied with darunavir/ritonavir. ethinylestradiol AUC ↓ 44%[β] ethinylestradiol C_{min} ↓ 62%[β] ethinylestradiol C_{max} ↓ 32%[β] norethindrone AUC ↓ 14%[β] norethindrone C_{min} ↓ 30%[β] norethindrone C_{max} ↔[β] [β] with darunavir/ritonavir	When darunavir is coadministered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalaemia. Alternative or additional contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with darunavir and low dose ritonavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.
PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS		
For the treatment of erectile dysfunction Avanafil Sildenafil Tadalafil Vardenafil	In an interaction study [#], a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with darunavir and low dose ritonavir.	The combination of avanafil and darunavir with low dose ritonavir is contraindicated (see section 4.3). Concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with darunavir co-administered with low dose ritonavir should be done with caution. If concomitant use of darunavir co-administered with low dose ritonavir with sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended.

For the treatment of pulmonary arterial hypertension Sildenafil Tadalafil	Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and darunavir co-administered with low dose ritonavir may increase plasma concentrations of sildenafil or tadalafil. (CYP3A inhibition)	A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with darunavir and low dose ritonavir has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope). Therefore, co-administration of DARUNAVIR with low dose ritonavir and sildenafil when used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3). Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with DARUNAVIR and low dose ritonavir is not recommended.
PROTON PUMP INHIBITORS		
Omeprazole 20 mg once daily	[#]darunavir AUC ↔ [#]darunavir C_{min} ↔ [#]darunavir C_{max} ↔	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 Midazolam (parenteral) Zoldipem	Not studied. Sedative/hypnotics are extensively metabolised by CYP3A. Co-administration with darunavir/ritonavir may cause a large increase in the concentration of these medicines. 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	Clinical monitoring is recommended when co-administering darunavir with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. If parenteral midazolam is co-administered with darunavir with 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

Midazolam (oral) Triazolam	3-4 fold increase in midazolam plasma levels.	be considered, especially if more than a single dose of midazolam is administered. Darunavir with low dose ritonavir with triazolam or oral midazolam is contraindicated (see section 4.3)
[#] studies have been performed at lower than recommended doses of darunavir or with a different dosing regimen (see section 4.2 Posology). [†] 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. [‡] Study was conducted with tenofovir disoproxil fumarate 300 mg once daily.		

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

Metabolic parameters

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

Musculoskeletal abnormalities

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

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

Immune reconstitution inflammatory syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) 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).

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. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitors, ATC code: J05AE10.

Mechanism of action

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (KD of 4.5 x 10-12M). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of darunavir, co-administered with ritonavir, have been evaluated in healthy adult volunteers and in HIV-1 infected patients. Exposure to darunavir was higher in HIV-1 infected patients than in healthy subjects. The increased exposure to darunavir in HIV-1 infected patients compared to healthy subjects may be explained by the higher concentrations of α1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG and, therefore, higher plasma concentrations.

Darunavir is primarily metabolised by CYP3A. Ritonavir 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 14C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir with ritonavir dose was due to the parent active substance. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 10-fold less than the activity of darunavir against wild type HIV.

Elimination

After a 400/100 mg ^{14}C-darunavir with ritonavir dose, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir could be retrieved in faeces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in faeces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir.

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

Special populations

Paediatric population

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 74 treatment-experienced paediatric patients, aged 6 to 17 years and weighing at least 20 kg, showed that the administered weight-based doses of darunavir/ritonavir resulted in darunavir exposure comparable to that in adults receiving darunavir/ritonavir 600/100 mg twice daily (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 106/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 postpartum			

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.

6. Pharmaceutical particulars

6.1 List of excipients

DARUTAB (150 mg)

Tablet core
Microcrystalline cellulose
Crospovidone
Sodium starch glycolate
Hydroxypropyl methylcellulose
Colloidal silicon dioxide
Magnesium stearate
Tablet film-coat
Polyvinyl alcohol
Polyethylene glycol
Titanium dioxide
Talcum

DARUTAB (400 mg)

Tablet core
Microcrystalline cellulose
Crospovidone
Sodium starch glycolate
Hydroxypropyl methylcellulose
Colloidal silicon dioxide
Magnesium stearate
Tablet film-coat
Polyvinyl alcohol
Polyethylene glycol
Titanium dioxide
Talcum

DARUTAB (600 mg)

Tablet core
Microcrystalline cellulose
Crospovidone
Sodium starch glycolate
Hydroxypropyl methylcellulose
Colloidal silicon dioxide
Magnesium stearate
Tablet film-coat
Polyvinyl alcohol

Polyethylene glycol
Titanium dioxide
Talcum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

DARUTAB (150 mg), DARUTAB (400 mg), DARUTAB (600 mg)
2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

DARUTAB (150 mg)
Opaque, white, high density polyethylene (HDPE) plastic bottle containing 120 tablets.
Pack size of one bottle.
DARUTAB (400 mg)
Opaque, white, high density polyethylene (HDPE) plastic bottle containing 60 tablets.
Pack size of one bottle.
DARUTAB (600 mg)
Opaque, white, high density polyethylene (HDPE) plastic bottle containing 60 tablets.
Pack size of one bottle.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

The Government Pharmaceutical Organization, 75/1 Rama VI Road, Ratchathewi, Bangkok, Thailand

8. Marketing authorisation number(s)

DARUTAB (150 mg) 1A 15065/61

DARUTAB (400 mg) 1A 15066/61

DARUTAB (600 mg) 1A 15067/61

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 31/10/2018
Date of latest renewal: 21/12/2018

10. Date of revision of the text

21 December 2018