

WHO-PQ recommended clinical and preclinical information for the health care provider

This information reflects the recommendations of current WHO guidelines and the scope of WHO's prequalification programme.

1. TYPE OF THE MEDICINAL PRODUCT

Darunavir 600 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For product-specific information, see WHOPAR part 4.

3. PHARMACEUTICAL FORM

Film-coated tablets

For product-specific information, see WHOPAR part 4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Darunavir 600 mg film-coated tablet is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infection.

The choice of treatment regimen is based on the patient's weight, treatment history and likelihood of viral resistance to Darunavir (see sections 4.2, 4.4 and 5.1).

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

Darunavir 600 mg film-coated tablet may be used as part of a regimen for post-exposure prophylaxis to HIV. For use of antiretroviral agents for post-exposure prophylaxis the most recent official guidelines, e.g. those by WHO should be consulted.

4.2 Posology and method of administration

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

Posology

Darunavir 600 mg film-coated tablet must always be given with low-dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicines. The product information of ritonavir must therefore be consulted before starting therapy with Darunavir 600 mg film-coated tablet.

Adults and adolescents weighing at least 35 kg

The recommended dose of darunavir 600 mg film-coated tablet is:

1 tablet of darunavir 600 mg film-coated tablet co-administered with 100 mg ritonavir twice daily.

Paediatric patients from the age of 3 years weighing 14 to 34 kg

In patients without expected or confirmed darunavir resistance associated mutations, the recommended dose of darunavir 600 mg film-coated tablet is:

1 tablet of darunavir 600 mg film-coated tablet co-administered with 100 mg ritonavir once daily.

When HIV drug resistance testing is not feasible, darunavir 600 mg film-coated tablet may not be suitable and other formulations should be used.

Missed doses and vomiting after a dose

Adult patients on a twice-daily regimen

If a dose of darunavir 600 mg film-coated tablet is missed within 6 hours of the time it is usually taken, the patient should take the dose of darunavir 600 mg film-coated tablets with food as soon as possible. If more than 6 hours have passed after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

Paediatric patients on a once-daily regimen

If a dose of darunavir 600 mg film-coated tablet is missed within 12 hours of the time it is usually taken, the patient should take the dose of darunavir 600 mg film-coated tablets with food as soon as possible. If more than 12 hours have passed after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

If a patient vomits within 4 hours of taking darunavir 600 mg film-coated tablets, the patient should take another dose with food as soon as possible. If the patient vomits more than 4 hours after taking the medicine, the patient does not need to take another dose and take the next one when it is due.

Special populations

Elderly

Limited information is available on the use of darunavir 600 mg film-coated tablet in the elderly. It should be used with caution in this age group.

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 600 mg film-coated tablet should be used with caution in these patients.

No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could increase darunavir exposure and worsen side effects. Therefore, darunavir 600 mg film-coated tablet must not be used in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3, 4.4 and 5.2).

Renal impairment

No dose adjustment is required for darunavir 600 mg film-coated tablet in patients with renal impairment.

Paediatric population

Darunavir should not be used in children below 3 years of age or weighing less than 14 kg.

Method of administration

Patients should take darunavir within 30 minutes after a meal. The type of food does not affect the exposure to darunavir.

4.3 Contraindications

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

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

Concomitant treatment with medicines listed below because they can decrease plasma concentrations of darunavir and ritonavir which could lead to loss of therapeutic effect and development of resistance (see sections 4.4 and 4.5). The following should not be used with darunavir 600 mg film-coated tablets:

- lopinavir/ritonavir.
- the strong CYP3A inducers rifampicin, rifapentine and herbal preparations containing St John's wort (*Hypericum perforatum*).

Darunavir boosted with ritonavir inhibits the elimination of active substances that are highly dependent on CYP3A for clearance. Therefore, concomitant treatment is contraindicated with medicines for which

elevated plasma concentrations are associated with serious or life-threatening side effects (see also section 4.5). These active substances include:

- alfuzosin
- amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine
- astemizole, terfenadine
- avanafil (for erectile dysfunction), sildenafil (when used for the treatment of pulmonary arterial hypertension)
- colchicine when used in patients with renal or hepatic impairment
- dapoxetine
- domperidone
- elbasvir/grazoprevir, glecaprevir/pibrentasvir
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergometrine)
- halofantrine
- lomitapide, lovastatin and simvastatin
- lurasidone, pimozide, quetiapine, sertindole
- naloxegol
- neratinib, venetoclax
- phenobarbital, phenytoin
- ticagrelor
- triazolam, midazolam administered orally

4.4 Special warnings and precautions for use

Virological response should be assessed regularly. Resistance testing is required if virological response diminishes.

Darunavir 600 mg film-coated tablet must always be given with low-dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The product information of ritonavir must therefore be consulted before starting therapy with darunavir 600 mg film-coated tablets.

Antiretroviral therapy-experienced patients – once daily dosing

Darunavir in combination with ritonavir once daily should not be used in patients with one or more darunavir resistance associated mutations or HIV-1 RNA $\geq 100\ 000$ copies/mL or CD4+ cell count $< 100 \times 10^6$ /L cells. Data are limited in patients with HIV-1 clades other than B (see section 5.1).

Elderly

As information is limited on the use of darunavir/ritonavir in patients aged 65 years and over, darunavir 600 mg film-coated tablets should be used with care 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 and hypersensitivity

Severe skin reactions, which may be accompanied with fever and elevated transaminases, have been reported. DRESS (drug rash with eosinophilia and systemic symptoms) and Stevens-Johnson syndrome has been reported rarely ($< 0.1\%$), and during post-marketing experience toxic epidermal necrolysis and acute generalised exanthematous pustulosis have been reported. Symptoms can include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and eosinophilia (see also section 4.8). Darunavir 600 mg film-coated tablet must be discontinued immediately if signs or symptoms of severe skin reactions develop.

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

Darunavir contains a sulfonamide moiety. Darunavir 600 mg film-coated tablet should be used with caution in patients with sulfonamide allergy.

Hepatotoxicity

Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported in 0.5% of patients receiving combination antiretroviral therapy with darunavir /ritonavir. Patients with 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 medicines.

Appropriate laboratory testing should be conducted before starting 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 symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients using darunavir/ritonavir, interruption or discontinuation of treatment should be considered promptly.

Hepatic impairment

The safety and efficacy of darunavir have not been established in patients with severe liver disorders and darunavir 600 mg film-coated tablet is therefore contraindicated in patients with severe hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, this medicine should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal impairment

No special precautions or dose adjustments for darunavir 600 mg film-coated tablets 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).

Patients with haemophilia

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

Weight, blood lipids and glucose

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

Osteonecrosis

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

Opportunistic infections

Health care providers should tell patients with impaired immunity that opportunistic infections or other complications of HIV infection may still develop while receiving antiretroviral medicines. This risk reduces as the immune system recovers.

Immune reactivation syndrome

Immune reactivation syndrome has been reported in patients treated with combination antiretroviral therapy. During early stages of treatment, patients whose immune system responds to antiretroviral therapy may develop an inflammatory response to slow-developing or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus retinitis, *Pneumocystis jirovecii* pneumonia, or tuberculosis). These reactions may require further evaluation and treatment.

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

Use with efavirenz

Efavirenz in combination with darunavir 600 mg film-coated tablet once daily may result in sub-optimal trough concentration of darunavir. If efavirenz is to be used for HIV-1 treatment, darunavir/ritonavir 600 mg/100 mg twice daily is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Darunavir and ritonavir inhibit CYP3A, CYP2D6 and P-gp. Co-administration of darunavir/ritonavir with medicines primarily metabolised by CYP3A or CYP2D6 or transported by P-gp may increase systemic exposure to such medicines, which could increase or prolong their therapeutic effect and adverse reactions.

Co-administration of darunavir/ritonavir with drugs that have active metabolite(s) formed by CYP3A4 may reduce plasma concentrations of these active metabolite(s), potentially leading to reduced therapeutic effect (see the Interaction table below).

Darunavir binds predominantly to α_1 -acid glycoprotein. This protein binding is concentration-dependent, indicative for saturation of binding. Therefore, there is a potential for displacement of medicines that are highly bound to α_1 -acid glycoprotein.

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

Darunavir/ ritonavir must not be combined with medicines that are highly dependent on CYP3A for clearance and for which increased systemic exposure is associated with serious or life-threatening events (narrow therapeutic index) (see section 4.3).

A clinical study using a cocktail of medicines metabolised by cytochromes CYP2C9, CYP2C19 and CYP2D6 found 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/ritonavir with medicines which are primarily metabolised by CYP2D6 (such as flecainide, propafenone and metoprolol) may result in increased plasma concentrations of these medicines, which could increase or prolong their therapeutic effect and adverse reactions. Co-administration of darunavir/ritonavir and medicines primarily metabolised by CYP2C9 (such as warfarin) and CYP2C19 (such as methadone) may decrease systemic exposure to such medicines, which could decrease or shorten their therapeutic effect.

Co-administration of darunavir/ritonavir and medicines primarily metabolised by CYP2C8 (such as paclitaxel, rosiglitazone and repaglinide) may decrease systemic exposure to such medicines, 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 increase plasma concentrations of these compounds (e.g. dabigatran etexilate, digoxin, statins and bosentan; see the table below).

Medicines that affect darunavir/ritonavir exposure

Darunavir and ritonavir are metabolised by CYP3A. Medicines that induce CYP3A activity are expected to increase the clearance of darunavir and ritonavir, resulting in lower plasma concentrations of these compounds, leading to loss of therapeutic effect and possible development of resistance (see sections 4.3). CYP3A inducers that are contraindicated include rifampicin, rifapentine, St John's wort and lopinavir.

Co-administration of darunavir/ritonavir with other medicines that inhibit CYP3A may decrease the clearance of darunavir and ritonavir, which may increase plasma concentrations of darunavir and ritonavir. Strong CYP3A inhibitors should be co-administered only if clinically vital and precautions taken to ensure effective levels of darunavir; these interactions are described in the table below (e.g. systemic azoles like ketoconazole and clotrimazole).

Interaction table

Interactions between darunavir/ritonavir and antiretroviral and non-antiretroviral medicinal products are listed in the table below. The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (\leftrightarrow), below (\downarrow) or above (\uparrow) the 80–125% range.

Several interaction studies (indicated by # in the table below) used doses of darunavir that are lower than recommended or a different dosing regimen (see section 4.2). The effects on co-administered medicines may thus be underestimated, and clinical monitoring of safety may be indicated.

The below list of examples of drug-drug interactions is not comprehensive and therefore the product information for each drug that is co-administered with darunavir 600 mg film-coated tablets should be consulted for information on the route of metabolism, interaction pathways, potential risks, and specific actions to take with regard to co-administration.

Drugs	Interaction	Recommendations on co-administration
HIV ANTIRETROVIRALS		
<i>Integrase strand transfer inhibitors</i>		
Dolutegravir	darunavir \leftrightarrow dolutegravir AUC \downarrow C _{max} \downarrow	Darunavir/ritonavir co-administered with dolutegravir can be used without dose adjustment.
Raltegravir	Some clinical studies suggest raltegravir may modestly decrease darunavir plasma concentrations.	The effect of raltegravir on darunavir plasma concentrations does not appear clinically relevant. Darunavir/ritonavir and raltegravir can be used without dose adjustments.
<i>Nucleo(s)ide reverse transcriptase inhibitors (NRTIs)</i>		
Didanosine	darunavir AUC \leftrightarrow C _{min} \leftrightarrow C _{max} \leftrightarrow didanosine AUC \downarrow C _{max} \downarrow	Darunavir/ritonavir and didanosine can be used without dose adjustments. Didanosine is to be taken on an empty stomach, thus it should be taken 1 hour before or 2 hours after darunavir/ritonavir given with food.

Drugs	Interaction	Recommendations on co-administration
Tenofovir disoproxil	#darunavir AUC ↑ C _{min} ↑ C _{max} ↑ tenofovir AUC ↑ C _{min} ↑ C _{max} ↑ (↑tenofovir from effect on MDR-1 transport in the renal tubules)	Monitoring of renal function may be indicated when darunavir/ritonavir is given in combination with tenofovir, 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 mg/10 mg once daily when used with darunavir/ritonavir.
Abacavir Emtricitabine Lamivudine Stavudine Zidovudine	Not studied. Based on the elimination pathways of zidovudine, emtricitabine, stavudine and lamivudine, that are primarily renally excreted, and of abacavir for which metabolism is not mediated by CYP450, no interactions are expected for these medicines and darunavir/ritonavir.	Darunavir/ritonavir can be used with these NRTIs without dose adjustment.
<i>Non-nucleoside (or -nucleotide) reverse transcriptase inhibitors (NNRTIs)</i>		
Efavirenz	#darunavir AUC ↓ C _{min} ↓ C _{max} ↓ efavirenz AUC ↑ C _{min} ↑ C _{max} ↑ (↑ efavirenz from CYP3A inhibition) (↓ darunavir from CYP3A induction)	Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when darunavir/ritonavir is given in combination with efavirenz. Efavirenz in combination with darunavir/ritonavir 800 mg/100 mg once daily may result in sub-optimal darunavir C _{min} . If efavirenz is to be used, then darunavir/ritonavir 600 mg/100 mg twice-daily regimen should be used.
Etravirine	darunavir AUC ↑ C _{min} ↔ C _{max} ↔ etravirine AUC ↓ C _{min} ↓ C _{max} ↓	Darunavir/ritonavir and etravirine 200 mg twice daily can be used without dose adjustments.

Drugs	Interaction	Recommendations on co-administration
Nevirapine	#darunavir: concentrations were consistent with historical data nevirapine AUC ↑ C _{min} ↑ C _{max} ↑ (↑ nevirapine from CYP3A inhibition)	Darunavir/ritonavir and nevirapine can be used without dose adjustments.
Rilpivirine	darunavir AUC ↔ C _{min} ↓ C _{max} ↔ rilpivirine AUC ↑ C _{min} ↑ C _{max} ↑	Darunavir/ritonavir and rilpivirine can be used without dose adjustments.
<i>HIV Protease inhibitors (PIs) - without additional low-dose ritonavir†</i>		
Atazanavir	#darunavir AUC ↔ C _{min} ↔ C _{max} ↔ atazanavir AUC ↔ C _{min} ↑ C _{max} ↓	Darunavir/ritonavir and atazanavir can be used without dose adjustments.
<i>HIV Protease inhibitor (PI) – with co-administration of low-dose ritonavir†</i>		
Lopinavir/ritonavir	darunavir AUC ↓ C _{min} ↓ C _{max} ↓ lopinavir AUC ↑ C _{min} ↑ C _{max} ↓	Due to a decrease in the exposure of darunavir by 40%, appropriate doses of the combination have not been established. Hence, concomitant use of darunavir/ritonavir and the combination product lopinavir/ritonavir is contraindicated (see section 4.3).
<i>CCR5 Antagonist</i>		
Maraviroc	darunavir, ritonavir concentrations were consistent with historical data maraviroc AUC ↑ C _{max} ↑	Maraviroc dose should be 150 mg twice daily when co-administered with darunavir/ritonavir.

Drugs	Interaction	Recommendations on co-administration
α1-ADRENORECEPTOR ANTAGONIST		
Alfuzosin	Darunavir/ritonavir is expected to increase alfuzosin plasma concentrations. (CYP3A inhibition)	Co-administration of darunavir/ritonavir and alfuzosin is contraindicated (see section 4.3).
ANAESTHETICS AND PERI-OPERATIVE MEDICINES		
Alfentanil	Not studied. The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by darunavir/ritonavir.	The concomitant use with darunavir/ritonavir may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.
Ketamine	Co-administration may increase ketamine exposure.	Dose adjustment may be needed. Monitor clinical effect.
ANTHELMINTICS		
Albendazole		No pharmacokinetic interaction is expected with a short duration treatment but the clinical effect of albendazole may be reduced when used for a long duration treatment.
ANTIANGINA/ANTIARRHYTHMICS		
Disopyramide Flecainide Lidocaine (systemic) Mexiletine Propafenone Amiodarone Bepridil Dronedarone Ivabradine Quinidine Ranolazine	Not studied. Darunavir/ritonavir is expected to increase plasma concentrations of these medicines. (CYP3A and CYP2D6 inhibition)	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these medicines when co-administered with darunavir/ritonavir. Darunavir/ritonavir co-administration with amiodarone, bepridil, dronedarone, ivabradine, quinidine, or ranolazine is contraindicated (see section 4.3).
Digoxin	digoxin AUC ↑ C _{max} ↑ (↑ digoxin from probable inhibition of P-gp)	Because digoxin has a narrow therapeutic index, it is recommended that the lowest possible dose of digoxin should initially be prescribed for patients taking darunavir/ritonavir. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject.
ANTIBIOTICS		
Bedaquiline	Co-administration may increase comedication exposure.	Use with caution and with ECG monitoring. Co-administration for more than 14 consecutive days should be avoided.

Drugs	Interaction	Recommendations on co-administration
Clarithromycin	#darunavir AUC ↓ C _{min} ↑ C _{max} ↓ clarithromycin AUC ↑ C _{min} ↑ C _{max} ↑ (↑ clarithromycin from CYP3A inhibition and possible P-gp inhibition)	Caution should be exercised when clarithromycin is combined with darunavir/ritonavir. For patients with renal impairment the product information for clarithromycin should be consulted for the recommended dose.
Delamanid	Co-administration may increase delamanid exposure.	Caution is recommended due to the risk of QT prolongation. ECG monitoring is recommended.
Moxifloxacin	Co-administration may decrease comedication exposure.	Monitor clinical effect and increase dose if needed.
Rifamycins		
Rifampicin Rifapentine	Not studied. Rifapentine and rifampicin are strong CYP3A inducers and decrease 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 rifampicin or rifapentine and darunavir/ritonavir is contraindicated (see section 4.3).
Rifabutin	darunavir AUC ↑ C _{min} ↑ C _{max} ↑ rifabutin AUC↑ C _{max} ↔ (Rifabutin is an inducer and substrate of CYP3A.)	A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (to 150 mg once every other day) and increased monitoring for rifabutin-related adverse events is warranted in patients receiving darunavir/ritonavir. In case of side effects, a further increase of the dosing interval for rifabutin and monitoring of rifabutin levels should be considered. Based on 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.

Drugs	Interaction	Recommendations on co-administration
ANTICOAGULANTS/ PLATELET AGGREGATION INHIBITORS		
Apixaban Rivaroxaban	Not studied. Co-administration of darunavir/ritonavir with these anticoagulants may increase concentrations of the anticoagulant. (CYP3A and P-gp inhibition)	Concomitant administration of darunavir/ritonavir with a direct oral anticoagulant metabolised by CYP3A4 and transported by P-gp is not recommended as this may lead to an increased bleeding risk.
Dabigatran etexilate Edoxaban	Dabigatran etexilate: AUC ↑ C _{max} ↑	If either dabigatran etexilate or edoxaban is co-administered with darunavir/ritonavir, clinical monitoring or dose reduction of the anticoagulant should be considered. These anticoagulants are transported by P-gp but not metabolised by CYP3A4.
Ticagrelor	Co-administration with darunavir/ritonavir may increase exposure to ticagrelor. (CYP3As and/or P-gp inhibition)	Concomitant administration of darunavir/ritonavir with ticagrelor is contraindicated (see section 4.3).
Clopidogrel	Not studied. Co-administration of clopidogrel with darunavir/ritonavir is expected to decrease plasma concentration of clopidogrel active metabolite, which may reduce the antiplatelet activity of clopidogrel.	Concomitant administration of darunavir/ritonavir with clopidogrel is not recommended. Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended.
Warfarin	Not studied. Warfarin concentrations may be affected when co-administered with darunavir/ritonavir.	It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with darunavir/ritonavir.
ANTIPILEPTICS		
Phenobarbital Phenytoin	Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir/ritonavir (induction of CYP450 enzymes)	Darunavir/ritonavir should not be used in combination with these medicines (see section 4.3).
Carbamazepine	darunavir AUC ↔ C _{min} ↓ C _{max} ↔ carbamazepine AUC ↑ C _{min} ↑ C _{max} ↑	No dose adjustment for darunavir/ritonavir is recommended. If darunavir/ritonavir and carbamazepine need to be co-administered, patients should be monitored for carbamazepine-related adverse events. Carbamazepine concentrations should be monitored if possible and its dose titrated for adequate response. The carbamazepine dose may need to be reduced by 25–50% in the presence of darunavir/ritonavir.
Clonazepam	Not studied. Co-administration of darunavir/ritonavir, with clonazepam may increase concentrations of clonazepam. (CYP3A inhibition)	Clinical monitoring is recommended when co-administering darunavir/ritonavir and clonazepam.

Drugs	Interaction	Recommendations on co-administration
Lamotrigine	Co-administration may decrease comedication exposure.	Monitor clinical effect and increase dose if needed.
Oxcarbazepine	Co-administration may decrease exposure of the darunavir/ritonavir, although to a moderate extent.	A dose adjustment may be needed. Monitor clinical effect. An alternative anticonvulsant should be considered.
Valproate	Co-administration may decrease comedication exposure.	Monitor clinical effect of valproate and increase dose if needed.
ANTI-DIABETICS		
Glibenclamide	Co-administration may increase comedication exposure.	Dose adjustment of glibenclamide may be needed. Monitor clinical effect.
Gliclazide	Co-administration may decrease comedication exposure.	Monitor clinical effect of gliclazide and increase dose if needed.
ANTIDEPRESSANTS		
Paroxetine	#darunavir AUC ↔ C _{min} ↔ C _{max} ↔ paroxetine AUC ↓ C _{min} ↓ C _{max} ↓	If antidepressants are co-administered with darunavir/ritonavir, dose titration of the antidepressant based on an assessment of antidepressant response is recommended. Also, patients on a stable dose of antidepressants who start treatment with darunavir/ritonavir should be monitored for antidepressant response.
Sertraline	#darunavir AUC ↔ C _{min} ↓ C _{max} ↔ sertraline AUC ↓ C _{min} ↓ C _{max} ↓	
Amitriptyline Desipramine Imipramine Nortriptyline Trazodone	Concomitant use of darunavir/ritonavir and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and CYP3A inhibition)	Clinical monitoring is recommended when co-administering darunavir/ritonavir with these antidepressants and dose adjustment of the antidepressant may be needed.
ANTIEMETICS		
Domperidone	Not studied. Domperidone is mainly metabolised by CYP3A4.	Co-administration of domperidone with darunavir/ritonavir is contraindicated because risk of domperidone's cardiac adverse events may be increased.

Drugs	Interaction	Recommendations on co-administration
ANTIFUNGALS		
Clotrimazole	Not studied. Concomitant systemic use of clotrimazole and darunavir/ritonavir may increase plasma concentrations of darunavir and clotrimazole. darunavir AUC _{24h} ↑ (based on population pharmacokinetic model)	Caution is warranted and clinical monitoring is recommended, when co-administration of clotrimazole is required.
Fluconazole Isavuconazole Itraconazole Posaconazole	Not studied. Darunavir may increase antifungal plasma concentrations; fluconazole, isavuconazole, itraconazole, or posaconazole may increase darunavir concentrations. (CYP3A inhibition and 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.
Ketoconazole	darunavir AUC ↑ C _{min} ↑ C _{max} ↑ ketoconazole AUC ↑ C _{min} ↑ C _{max} ↑ (CYP3A inhibition)	Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of ketoconazole should not exceed 200 mg.
Voriconazole	Not studied. Ritonavir may decrease plasma concentrations of voriconazole. (induction of CYP450 enzymes)	Voriconazole should not be combined with darunavir/ritonavir unless an assessment of the benefits and risks justifies the use of voriconazole.
ANTIHISTAMINES		
Astemizole Terfenadine	Not studied. Darunavir/ritonavir may increase concentrations of astemizole and terfenadine (CYP3A inhibition).	The co-administration is contraindicated (see section 4.3).
ANTIGOUT MEDICINE		
Colchicine	Not studied. Concomitant use of colchicine and darunavir/ritonavir may increase the exposure to colchicine. (CYP3A and P-gp inhibition)	Reducing colchicine dosage or interrupting colchicine treatment is recommended in patients with normal renal and hepatic function if treatment with darunavir/ritonavir is required. Patients with renal or hepatic impairment must not be given colchicine with darunavir/ritonavir (see section 4.3).

Drugs	Interaction	Recommendations on co-administration
ANTIMALARIALS		
Artemether/lumefantrine	darunavir AUC ↔ C _{min} ↓ C _{max} ↔ artemether and dihydroartemisinin AUC ↓ C _{min} ↔ C _{max} ↓ lumefantrine AUC ↑ C _{min} ↑ C _{max} ↑	The combination of darunavir/ritonavir and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.
Artemisinin	Co-administration may increase comedication exposure. and a dose adjustment may be needed. Monitor clinical effect.	Dose adjustment may be needed. Monitor for adverse effects of artemisinin.
Halofantrine	Not studied. Halofantrine is extensively metabolised by CYP3A4. Inhibition of halofantrine metabolism by ritonavir is expected to increase halofantrine exposure could potentially prolong the QT interval.	Concomitant administration of darunavir/ritonavir and halofantrine is contraindicated. Halofantrine has a narrow therapeutic index with an increased risk of QT-prolongation at higher exposures.
Mefloquine	Co-administration may increase mefloquine exposure.	Caution and close monitoring is recommended.
Proguanil Atovaquone/proguanil	Co-administration of atovaquone/proguanil with darunavir/ritonavir may decrease atovaquone/proguanil exposure.	Co-administration of atovaquone/proguanil should be avoided whenever possible. If concomitant use is necessary, consider possibility of taking atovaquone/proguanil with a high fat meal to increase its bioavailability and consider increasing the dosage if required.
Quinine	Co-administration may increase quinine exposure.	If quinine is co-administration is necessary, caution is recommended as quinine has a risk of QT prolongation. ECG monitoring is recommended.

Drugs	Interaction	Recommendations on co-administration
ANTINEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine Vinorelbine Everolimus Irinotecan	Not studied. darunavir/ritonavir is expected to increase plasma concentrations of these antineoplastic medicines. (CYP3A inhibition)	Concentrations of these medicines may increase when co-administered with darunavir/ritonavir, potentially resulting in increased adverse events usually associated with these agents. Caution should be exercised when combining these antineoplastic medicines with darunavir/ritonavir. Concomitant use of everolimus or irinotecan and darunavir/ritonavir is not recommended.
Cisplatin	Co-administration may increase cisplatin exposure, thus increasing the risk of nephrotoxicity.	Close monitoring of renal function is recommended.
Cyclophosphamide Dacarbazine	Co-administration may increase the efficacy and the toxicity of the comedication.	Careful monitoring of efficacy and toxicity is recommended.
Docetaxel Imatinib	Co-administration may increase comedication exposure.	Monitor for chemotherapy-induced toxicity.
Ifosfamide	Co-administration may reduce conversion of ifosfamide to the active metabolite and thereby reduce efficacy.	Use with caution.
Neratinib	Not studied. Darunavir/ ritonavir is expected to increase plasma concentrations of neratinib. (CYP3A and P-gp inhibition)	Co-administration of darunavir/ritonavir and neratinib is contraindicated (see section 4.3)
Paclitaxel	Co-administration may increase paclitaxel exposure. Life-threatening toxicity reported when paclitaxel co-administered with protease inhibitors	Avoid co-administration with paclitaxel if possible. If co-administration unavoidable, paclitaxel dose should be reduced and the patient monitored closely for paclitaxel toxicity.
Tamoxifen	Co-administration may reduce conversion to the active metabolite and thereby reduce efficacy of the comedication.	Monitor response to tamoxifen treatment.
Venetoclax	Not studied. Darunavir/ ritonavir is expected to increase plasma concentrations of venetoclax. (CYP3A inhibition)	Co-administration of darunavir/ritonavir and venetoclax is contraindicated (see section 4.3)
ANTIPSYCHOTICS		
Quetiapine	Not studied. Due to CYP3A inhibition by darunavir/ ritonavir, concentrations of the antipsychotics are expected to increase. (CYP3A inhibition)	Concomitant administration of darunavir/ritonavir and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased concentrations of quetiapine may lead to coma (see section 4.3).

Drugs	Interaction	Recommendations on co-administration
<p>Clozapine Perphenazine Risperidone Thioridazine</p> <p>Lurasidone Pimozide Sertindole</p>	<p>Not studied. Darunavir/ ritonavir is expected to increase plasma concentrations of these antipsychotics. (CYP3A, CYP2D6 and P-gp inhibition)</p>	<p>The dose of these antipsychotics may need to be decreased when co-administered with darunavir/ritonavir.</p> <p>Concomitant administration of darunavir/ritonavir and lurasidone, pimozide or sertindole is contraindicated (see section 4.3).</p>
BETA-BLOCKERS		
<p>Carvedilol Metoprolol Timolol</p>	<p>Not studied. Darunavir/ ritonavir is expected to increase plasma concentrations of these beta-blockers. (CYP2D6 inhibition)</p>	<p>Clinical monitoring is recommended when co-administering darunavir/ritonavir with beta-blockers. A lower dose of the beta-blocker should be considered.</p>
CALCIUM CHANNEL BLOCKERS		
<p>Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil</p>	<p>Not studied. Darunavir/ ritonavir is expected to increase the plasma concentrations of calcium channel blockers. (CYP3A and CYP2D6 inhibition)</p>	<p>Monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with darunavir/ritonavir.</p>
CORTICOSTEROIDS		
<p>Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone)</p>	<p>darunavir AUC ↓ C_{min} ↓ C_{max} ↓ fluticasone propionate AUC ↑ C_{min} ↑ C_{max} ↑ Other corticosteroids: interaction not studied. Plasma concentrations of these medicines may increase when co-administered with darunavir/ritonavir, resulting in reduced serum cortisol concentrations</p>	<p>Concomitant use of darunavir/ritonavir and corticosteroids that are metabolised by CYP3A may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.</p> <p>Concomitant administration of darunavir/ritonavir and budesonide or fluticasone is contraindicated (see section 4.3).</p> <p>Co-administration with other 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.</p> <p>Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone should be considered, particularly for long-term use.</p>
<p>Dexamethasone (systemic)</p>	<p>Not studied. Dexamethasone may decrease plasma concentrations of darunavir. (CYP3A induction)</p>	<p>Systemic dexamethasone should be used with caution when combined with darunavir/ritonavir.</p>

Drugs	Interaction	Recommendations on co-administration
ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Not studied. Concomitant use of bosentan and darunavir/ritonavir may increase plasma concentrations of bosentan. Bosentan is expected to decrease plasma concentrations of darunavir and/or ritonavir. (CYP3A induction).	When administered concomitantly with darunavir/ritonavir, the patient should be monitored for bosentan side effects.
ERGOT DERIVATIVES		
Dihydroergotamine, ergometrine, ergotamine, methylergometrine	Not studied. Co-administration of darunavir/ritonavir may increase concentrations of ergot derivatives. (CYP3A inhibition).	Co-administration of darunavir/ritonavir and ergot derivatives is contraindicated (see section 4.3).
HEPATITIS C VIRUS DIRECT-ACTING ANTIVIRALS		
Elbasvir/grazoprevir	Darunavir/ritonavir may increase the exposure to grazoprevir. (CYP3A and OATP1B inhibition)	Concomitant use of darunavir/ritonavir and elbasvir/grazoprevir is contraindicated (see section 4.3).
Glecaprevir/pibrentasvir	Darunavir/ritonavir may increase the exposure to glecaprevir and pibrentasvir. (P-gp, BCRP and OATP1B1/3 inhibition)	Concomitant use of darunavir/ritonavir with glecaprevir/pibrentasvir is contraindicated (see section 4.3).
HERBAL PRODUCTS		
St John's wort (<i>Hypericum perforatum</i>)	Not studied. St John's wort is expected to decrease the plasma concentrations of darunavir or ritonavir. (CYP450 induction)	Darunavir/ritonavir must not be used concomitantly with products containing St John's wort (see section 4.3). St John's wort should be stopped in a patient already taking it and virus levels checked if possible. The enzyme-inducing effect of St John's wort may persist for at least 2 weeks after stopping it. As the inducing effect reduces, darunavir (and ritonavir) exposure may increase.
HMG CO-A REDUCTASE INHIBITORS		
Lovastatin Simvastatin	Not studied. Lovastatin and simvastatin are expected to markedly have increased plasma concentrations when co-administered with darunavir/ritonavir. (CYP3A inhibition)	Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of darunavir/ritonavir with lovastatin and simvastatin is therefore contraindicated (see section 4.3).
Atorvastatin	Atorvastatin AUC ↑ C _{min} ↑ C _{max} ↑	When administration of atorvastatin and darunavir/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.

Drugs	Interaction	Recommendations on co-administration
Pravastatin	Pravastatin AUC ↑ C _{max} ↑	When administration of pravastatin and darunavir/ritonavir is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effect while monitoring for safety.
Rosuvastatin	Rosuvastatin AUC ↑ C _{max} ↑	When administration of rosuvastatin and darunavir/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 AGENT		
Lomitapide	Darunavir/ritonavir is expected to increase the exposure of lomitapide when co-administered. (CYP3A inhibition)	Co-administration is contraindicated (see section 4.3).
GASTROINTESTINAL AGENTS		
Loperamide	Cardiac events including QT interval prolongation have been reported with high doses of loperamide.	Caution is advised when loperamide is used at high doses for reducing stoma output, particularly as patients may be at increased risk of cardiac events due to electrolytes disturbances.
Omeprazole	#darunavir AUC ↔ C _{min} ↔ C _{max} ↔	Darunavir/ritonavir can be co-administered with proton pump inhibitors without dose adjustments.
Ranitidine	#darunavir AUC ↔ C _{min} ↔ C _{max} ↔	Darunavir/ritonavir can be co-administered with ranitidine without dose adjustments.
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus	Not studied. Exposure to these immunosuppressants will be increased when co-administered with darunavir/ritonavir. (CYP3A inhibition)	Therapeutic drug monitoring of the immunosuppressants must be done when co-administered. Concomitant use of everolimus and darunavir/ritonavir is not recommended.
INHALED BETA AGONIST		
Salmeterol	Not studied. Concomitant use of salmeterol and darunavir/ritonavir may increase plasma concentrations of salmeterol.	Concomitant use of salmeterol and darunavir/ritonavir is not recommended. The combination may increase the risk of cardiovascular adverse events of salmeterol, including QT prolongation, palpitations and sinus tachycardia.

Drugs	Interaction	Recommendations on co-administration
OPIOID ANALGESICS / TREATMENT OF OPIOID DEPENDENCE		
Methadone	methadone AUC ↓ C _{min} ↓ C _{max} ↓	No adjustment of methadone dosage is required when initiating co-administration with darunavir/ritonavir. However, increased methadone dose may be necessary when concomitantly administered for prolonged period 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	buprenorphine AUC ↓ C _{min} ↔ C _{max} ↓ norbuprenorphine AUC ↑ C _{min} ↑ C _{max} ↑ naloxone AUC ↔ C _{max} ↔	The clinical relevance of the increase in norbuprenorphine pharmacokinetic parameters has not been established. Dose adjustment for buprenorphine may not be necessary when co-administered with darunavir/ritonavir but careful clinical monitoring for opioid toxicity is recommended.
Morphine	Co-administration may increase exposure to the active metabolite and potentiate the effects of the opioid in the CNS.	Monitor for sign of opioid toxicity.
Fentanyl Oxycodone Tramadol	Darunavir/ritonavir may increase plasma concentrations of these analgesics. (CYP2D6 and/or CYP3A inhibition)	Clinical monitoring is recommended when co-administering darunavir/ritonavir with these analgesics.

Drugs	Interaction	Recommendations on co-administration
COMBINED HORMONAL CONTRACEPTIVES/HORMONAL REPLACEMENT THERAPY		
<p>Drospirenone/ethinylestradiol (3 mg/20 µg once daily)</p> <p>Ethinylestradiol/norethindrone 35 µg/1 mg once daily</p>	<p>Drospirenone AUC ↑ C_{max} ↑</p> <p>ethinylestradiol AUC ↓ C_{max} ↓</p> <p>ethinylestradiol AUC ↓ C_{min} ↓ C_{max} ↓</p> <p>norethindrone AUC ↓ C_{min} ↓ C_{max} ↔</p>	<p>When darunavir is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalaemia.</p> <p>Alternative or additional contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with darunavir/ritonavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.</p>
<p>Dydrogesterone Norethisterone</p>	<p>Co-administration may increase comedication exposure.</p>	<p>The clinical significance of this increase in terms of overall risk of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women receiving hormone replacement therapy is unknown. Postmenopausal women should be re-evaluated periodically to determine if treatment is still necessary.</p>
<p>Etonogestrel (vaginal ring)</p>	<p>Co-administration may increase etonogestrel exposure and decrease ethinylestradiol exposure.</p>	<p>Since no dosage adjustment of ethinylestradiol is possible with the combined vaginal ring, alternative forms of contraception or barrier contraception in addition to the vaginal ring should be used.</p>
<p>Medroxyprogesterone (oral)</p>	<p>Co-administration may increase comedication exposure.</p>	<p>The clinical significance of this increase in terms of overall risk of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women receiving substitution hormones is unknown. Postmenopausal women should be re-evaluated periodically to determine if treatment is still necessary.</p>
OPIOID ANTAGONIST		
<p>Naloxegol</p>	<p>Not studied.</p>	<p>Co-administration of darunavir/ritonavir and naloxegol is contraindicated.</p>

Drugs	Interaction	Recommendations on co-administration
PARKINSONISM AGENTS		
Levodopa/carbidopa	Enhanced levodopa effects including severe dyskinesia have been reported with some protease inhibitors.	Monitor for levodopa/carbidopa efficacy.
PHOSPHODIESTERASE, TYPE 5 INHIBITORS		
<p>For the treatment of erectile dysfunction</p> <p>Avanafil Sildenafil Tadalafil Vardenafil</p>	↑ PDE-5 inhibitors	<p>The combination of avanafil and darunavir/ritonavir is contraindicated (see section 4.3). Caution is required for concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with darunavir/ritonavir. If concomitant use of darunavir/ritonavir with sildenafil, tadalafil or vardenafil is required, 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 can be used.</p>
<p>For the treatment of pulmonary arterial hypertension</p> <p>Sildenafil Tadalafil</p>	<p>Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and darunavir/ritonavir may increase plasma concentrations of sildenafil or tadalafil. (CYP3A inhibition)</p>	<p>A safe and effective dose of sildenafil for treating pulmonary arterial hypertension co-administered with darunavir/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/ritonavir and sildenafil for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3).</p> <p>Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with darunavir/ritonavir is not recommended.</p>

Drugs	Interaction	Recommendations on co-administration
SEDATIVES/HYPNOTICS		
Buspirone Clorazepate Diazepam Estazolam Flurazepam Zoldipem Midazolam (parenteral)	Not studied. Sedatives/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/ritonavir it may cause a large increase in midazolam concentration. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3- to 4-fold increase in midazolam plasma levels.	Clinical monitoring is recommended when co-administering darunavir/ritonavir with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. If parenteral midazolam is co-administered with darunavir/ritonavir, it should be in an intensive care unit or similar setting, which ensures close clinical monitoring and appropriate medical management in case of respiratory depression or prolonged sedation. Dose adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
Midazolam (oral) Triazolam		Darunavir/ritonavir with triazolam or oral midazolam is contraindicated (see section 4.3).
TREATMENT FOR PREMATURE EJACULATION		
Dapoxetine	Not studied.	Co-administration of darunavir/ritonavir with dapoxetine is contraindicated.
UROLOGICAL DRUGS		
Fesoterodine Solifenacin	Not studied.	Use with caution. Monitor for fesoterodine or solifenacin adverse reactions; dose reduction of fesoterodine or solifenacin may be necessary.
<p># Studies used lower than recommended doses of darunavir or with a different dosing regimen</p> <p>† The efficacy and safety of the use of darunavir with 100 mg ritonavir and any other protease inhibitors (e.g. fosamprenavir and tipranavir) have not been established in HIV patients. Treatment with two protease inhibitors is generally not recommended.</p>		

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There are no adequate and well controlled studies on pregnancy outcome with darunavir in pregnant women. Studies in animals do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal 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 passes into breast milk. The most recent official treatment guidelines (e.g. those issued by WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Studies in lactating rats found that darunavir appears in milk.

Fertility

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

4.7 Effects on ability to drive and use machines

Darunavir 600 mg film-coated tablet has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients 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

The most frequent adverse reactions with darunavir/ritonavir 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.

List of adverse reactions

Adverse reactions are listed by system organ class (SOC) and frequency. Within each frequency category, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1000$) and not known (frequency cannot be estimated from the available data).

Infections and infestations

uncommon herpes simplex

Blood and lymphatic system disorders

uncommon thrombocytopenia, neutropenia, anaemia, leucopenia

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 appetite, increased weight, hyperglycaemia, insulin resistance, decreased high density lipoprotein, polydipsia, increased blood lactate dehydrogenase

Psychiatric disorders

common insomnia

uncommon depression, disorientation, anxiety, sleep disturbance, 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 QT interval, tachycardia
- rare acute myocardial infarction, sinus bradycardia, palpitations

Vascular disorders

- uncommon hypertension, flushing

Respiratory, thoracic and mediastinal disorders

- uncommon dyspnoea, cough, epistaxis, throat irritation
- rare rhinorrhoea

Gastrointestinal disorders

- very common diarrhoea
- common vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence
- uncommon pancreatitis, gastritis, gastroesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia
- rare stomatitis, haematemesis, cheilitis, dry lip, coated tongue

Hepatobiliary disorders

- common increased alanine aminotransferase
- uncommon hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-glutamyltransferase

Skin and subcutaneous tissue disorders

- common rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus
- uncommon angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation
- rare drug reaction with eosinophilia and systemic symptoms (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 kinase
- 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, crystal nephropathy

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 4 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 programme of raltegravir in treatment-experienced patients, rash, irrespective of causality, was more common with regimens containing darunavir + raltegravir compared to those containing darunavir without raltegravir or raltegravir without darunavir. The rashes in clinical studies were mild to moderate and did not result in discontinuation of therapy (see section 4.4).

Metabolic parameters

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

Musculoskeletal abnormalities

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

Osteonecrosis has been reported, particularly in patients with risk factors, advanced HIV disease or on long-term combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Immune reconstitution inflammatory syndrome

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

Bleeding in haemophilic patients

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

Paediatric population

Overall, the safety profile in paediatric patients is similar to that in adults.

Patients co-infected with hepatitis B or hepatitis C virus

Patients with hepatitis B or C receiving darunavir/ritonavir are 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

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Symptoms

Experience of acute overdose with darunavir/ritonavir is limited. Single doses up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptoms.

Management

There is no specific antidote for overdose with darunavir/ritonavir. Treatment of overdose with darunavir/ritonavir consists of general supportive measures including monitoring vital signs and the patient's clinical status.

Since ritonavir is extensively metabolised by the liver and both ritonavir and darunavir are highly protein bound, dialysis is unlikely to be beneficial in removing the active substances.

5. PHARMACOLOGICAL PROPERTIES

Information on pharmacological properties is shown in the product information as approved by the reference authority, stated in WHOPAR part 1. Additional data for those uses approved by WHO may be found in the references given at the end of this document.

6. PHARMACEUTICAL PARTICULARS

Information on the pharmaceutical particulars is shown in the product information as approved by the reference authority, stated in WHOPAR part 1.

7. SUPPLIER

Information on the supplier is shown in the product information as approved by the reference authority, stated in WHOPAR part 1

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

The WHO reference number is shown in WHOPAR part 1

9. DATE OF PREQUALIFICATION

The date of prequalification can be found in WHOPAR part 1.

10. DATE OF REVISION OF THE TEXT

May 2026

References

General reference sources for this SmPC include:

World Health Organization (2021) Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, available at <https://www.who.int/publications/i/item/9789240031593>, accessed 09 May 2026

Prezista: summary of product characteristics. European Medicines Agency; 26 July 2024 (https://www.ema.europa.eu/en/documents/product-information/prezista-epar-product-information_en.pdf, accessed 09 May 2026)

HIV drug interactions: interactions checker [online database]. Liverpool Drug Interactions Group, University of Liverpool; 2023 (<https://hiv-druginteractions.org/checker>, accessed 09 May 2026).