WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA719 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 433.64mg darunavir ethanolate equivalent to 400mg darunavir and 50mg ritonavir.

3. PHARMACEUTICAL FORM

Film-coated tablet.

[HA719 trade name] is yellow, capsule-shaped, film coated tablets. They are biconvex (rounded on top and bottom) with a bevelled edge. The tablets have 'H' debossed (stamped into) on one side and 'D8' debossed (stamped into) on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA719 trade name] 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.

[HA719 trade name] 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

Patients weighing at least 40 kg

In PI-naïve patients and in PI-experienced patients without darunavir resistance associated mutations and who have plasma HIV-1 RNA < 100 000 copies/mL and CD4+ cell count ≥ 100×10^6 cells/L (see section 4.1), the recommended dose of [HA719 trade name] is:

2 tablets taken once daily with food at around the same time each day.

[HA719 trade name] is not suitable for treating all other ART-experienced patients or if HIV-1 genotype testing is not available.

Missed doses

If a dose of [HA719 trade name] is missed within 12 hours of the time it is usually taken, patients should be instructed to take the dose of [HA719 trade name] 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.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

If a patient vomits within 4 hours of taking [HA719 trade name], 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.

Special populations

Elderly

Limited information is available in this population, and therefore, [HA719 trade name] 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, [HA719 trade name] 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 side effects. Therefore, [HA719 trade name] 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 [HA719 trade name] in patients with renal impairment (see sections 4.4 and 5.2).

Paediatric population

[HA719 trade name] is not suitable for children weighing less than 40 kg. Other formulations of darunavir/ritonavir may be required.

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

Pregnancy and postpartum

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

Method of administration

Patients should be instructed to take darunavir/ritonavir within 30 minutes after a meal. The type of food does not affect the exposure to darunavir (see section 5.2).

4.3 Contraindications

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

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

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 [HA719 trade name]:

- lopinavir/ritonavir.
- the strong CYP3A inducers rifampicin 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 with medicines for which elevated plasma concentrations are associated with serious or life-threatening side effects is contraindicated (see also section 4.5). These active substances include:

- alfuzosin
- amiodarone, bepridil, dronedarone, encainide, flecainide, ivabradine, propafenone, quinidine, ranolazine

- astemizole, terfenadine
- avanafil, sildenafil when used for the treatment of pulmonary arterial hypertension, vardenafil
- cisapride
- clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam
- clozapine, lurasidone, pimozide, quetiapine, sertindole
- colchicine when used in patients with renal or hepatic impairment
- dabigatran, ticagrelor
- dapoxetine
- domperidone
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir
- fusidic acid
- halofantrine, lumefantrine
- lomitapide, lovastatin and simvastatin
- naloxegol
- neratinib, venetoclax
- pethidine, piroxicam, propoxyphene

4.4 Special warnings and precautions for use

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

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 ≥ 100 000 copies/mL or CD4+ cell count < 100 × 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, [HA719 trade name] 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). [HA719 trade name] 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. [HA719 trade name] 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 [HA719 trade name] 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 [HA719 trade name] 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 [HA719 trade name] 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 (↔), below (↓) or above (↑) 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 [HA719 trade name] 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		
Integrase strand transfer inhibitors		
Dolutegravir	darunavir ↔ dolutegravir AUC ↓ C_{max} ↓	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.
Nucleo(s/t)ide reverse transcriptase inhibitors (NRTIs)		
Didanosine	darunavir AUC ↔ C_{min} ↔ C_{max} ↔ didanosine AUC ↓ C_{max} ↓	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.
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.

Drugs	Interaction	Recommendations on co-administration
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.
Non-nucleoside (or -nucleotide) reverse transcriptase inhibitors (NNRTIs)		
Efavirenz	#darunavir AUC ↓ C_{min} ↓ C_{max} ↓ efavirenz AUC ↑ C_{min} ↑ C_{max} ↑ (↑ efavirenz from CYP3A inhibition) (↓ darunavir from CYP3A induction)	Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when darunavir/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.
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.

Drugs	Interaction	Recommendations on co-administration
Rilpivirine	darunavir AUC ↔ C_{min} ↓ C_{max} ↔ rilpivirine AUC ↑ C_{min} ↑ C_{max} ↑	Darunavir/ritonavir and rilpivirine can be used without dose adjustments.
HIV Protease inhibitors (PIs) - without additional low-dose ritonavir†		
Atazanavir	#darunavir AUC ↔ C_{min} ↔ C_{max} ↔ atazanavir AUC ↔ C_{min} ↑ C_{max} ↓	Darunavir/ritonavir and atazanavir can be used without dose adjustments.
HIV Protease inhibitor (PI) – with co-administration of low-dose ritonavir†		
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).
CCR5 Antagonist		
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.
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.

Drugs	Interaction	Recommendations on co-administration
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.
ANTIEPILEPTICS		
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 daruavir/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
Clozapine Perphenazine Risperidone Thioridazine Lurasidone Pimozide Sertindole	Not studied. Darunavir/ ritonavir is expected to increase plasma concentrations of these antipsychotics. (CYP3A, CYP2D6 and P-gp inhibition)	The dose of these antipsychotics may need to be decreased when co-administered with darunavir/ritonavir. Concomitant administration of darunavir/ritonavir and lurasidone, pimozide or sertindole is contraindicated (see section 4.3).
BETA-BLOCKERS		
Carvedilol Metoprolol Timolol	Not studied. Darunavir/ ritonavir is expected to increase plasma concentrations of these beta-blockers. (CYP2D6 inhibition)	Clinical monitoring is recommended when co-administering darunavir/ritonavir with beta-blockers. A lower dose of the beta-blocker should be considered.
CALCIUM CHANNEL BLOCKERS		
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Not studied. Darunavir/ ritonavir is expected to increase the plasma concentrations of calcium channel blockers. (CYP3A and CYP2D6 inhibition)	Monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with darunavir/ritonavir.
CORTICOSTEROIDS		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone)	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	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. Concomitant administration of darunavir/ritonavir and budesonide or fluticasone is contraindicated (see section 4.3). 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. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone 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/ritonavir.

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 (*Hypericum perforatum*)	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		
Drospirenone/ethinylestradiol (3 mg/20 µg once daily) Ethinylestradiol/norethindrone 35 µg/1 mg once daily	Drospirenone AUC ↑ C_{max} ↑ ethinylestradiol AUC ↓ C_{max} ↓ ethinylestradiol AUC ↓ C_{min} ↓ C_{max} ↓ norethindrone AUC ↓ C_{min} ↓ C_{max} ↔	When darunavir is co-administered 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/ritonavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.
Dydrogesterone Norethisterone	Co-administration may increase comedication exposure.	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 in unknown. Postmenopausal women should be re-evaluated periodically to determine if treatment is still necessary.
Etonogestrel (vaginal ring)	Co-administration may increase etonogestrel exposure and decrease ethinylestradiol exposure.	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.
Medroxyprogesterone (oral)	Co-administration may increase comedication exposure.	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 in unknown. Postmenopausal women should be re-evaluated periodically to determine if treatment is still necessary.
OPIOID ANTAGONIST		
Naloxegol	Not studied.	Co-administration of darunavir/ritonavir and naloxegol is contraindicated.

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		
For the treatment of erectile dysfunction Avanafil Sildenafil Tadalafil Vardenafil	↑ PDE-5 inhibitors	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.
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/ritonavir may increase plasma concentrations of sildenafil or tadalafil. (CYP3A inhibition)	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). Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with darunavir/ritonavir is not recommended.

Drugs	Interaction	Recommendations on co-administration
SEDATIVES/HYPNOTICS		
Buspirone Clorazepate Diazepam Estazolam Flurazepam Zoldipem Midazolam (parenteral) Midazolam (oral) Triazolam	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. 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.

[#] Studies used lower than recommended doses of darunavir or with a different dosing regimen

† 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.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Darunavir

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.

Ritonavir

A large number of pregnant women (corresponding to 6100 live births) were exposed to ritonavir during pregnancy; of these, 2800 live births were exposed during the first trimester. These data largely refer to exposure of ritonavir used as a booster for protease inhibitors in combination therapy. There was no increase in the rate of birth defects compared to rates in population-based birth defect surveillance systems. Animal data have shown reproductive toxicity (see section 5.3).

Ritonavir interacts with oral contraceptives. Therefore, an alternative, effective and safe method of contraception should be used during treatment.

Breast-feeding

The most recent official treatment guidelines (e.g. those issued from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Darunavir

It is not known if darunavir passes into breast milk. Studies in lactating rats found that darunavir appears in milk.

Ritonavir

Ritonavir has been detected in milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production.

Fertility

No human data on the effect of darunavir or ritonavir on fertility are available. Animal studies do not indicate harmful effects of darunavir or ritonavir on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

[HA719 trade name] 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 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 haemophiliac 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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC code: J05AR26.

Mechanism of action

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

Pharmacokinetic enhancement by ritonavir is based on its potent inhibition of CYP3A- mediated metabolism. The degree of enhancement is related to the metabolic pathway of the co-administered protease inhibitor and the impact of the co-administered protease inhibitor on the metabolism of ritonavir. Maximal inhibition of metabolism of darunavir is generally achieved with ritonavir doses of 100 mg daily to 200 mg twice daily.

Antiviral activity in vitro

Darunavir is active against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/ml). Darunavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM.

These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 to > 100 μM.

Resistance

In clinical trials, virologic response to darunavir/ritonavir was decreased when 3 or more darunavir resistance-associated mutations (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) were present at baseline or when these mutations developed during treatment.

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

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

Cross-resistance

Darunavir FC was less than 10 for 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir, showing that viruses resistant to most PIs remain susceptible to darunavir.

Samples from patients with virologic failure observed in clinical trials, showed a very low rate of cross-resistance with other PIs in treatment-experienced patients and none in treatment-naïve patients.

Clinical efficacy

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

Non-inferiority in virologic response to the darunavir/ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/mL (lopinavir/ritonavir 78.3% vs. darunavir/ritonavir 83.7%), was demonstrated (at the pre-defined 12% non-inferiority margin) in the 48-week analysis. These results were confirmed by data at 96 weeks of treatment and were sustained up to 192 weeks of treatment.

Another phase III, randomised, open-label trial compared darunavir/ritonavir 800 mg/100 mg once daily with darunavir/ritonavir 600 mg/100 mg twice daily in 590 ART-experienced HIV-1 infected patients with no darunavir RAMs and a screening HIV-1 RNA > 1000 copies/mL. Both arms used an optimised background regimen of at least 2 NRTIs. After 48 weeks of treatment, virologic response (percentage of patients with plasma HIV-1 RNA level < 50 copies/mL) with darunavir/ritonavir 800 mg/100 mg once daily was non-inferior (at 12% non-inferiority margin) to darunavir/ritonavir 600 mg/100 mg twice daily.

Baseline genotype or phenotype and virologic outcome

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

Paediatric patients

An open-label, Phase II trial evaluated the pharmacokinetics, safety, tolerability, and efficacy of darunavir with low-dose ritonavir in 12 ART-naïve HIV-1 infected patients aged 12 to less than 18 years and weighing at least 40 kg. These patients received darunavir/ritonavir 800 mg/100 mg once daily in combination with other antiretrovirals. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at

least 1.0 log_{10} versus baseline. All patients (100%) had a virologic response at week 48. In addition, in 10 (83.3%) patients, viral load was reduced to HIV-1 RNA < 50 copies/mL according to the TLOVR non-virologic failure censored algorithm at week 48.

An open-label, Phase II trial evaluated the pharmacokinetics, safety, tolerability, and efficacy of darunavir with low-dose ritonavir in 80 ART-experienced HIV-1 infected patients aged 6 to 17 years and weighing at least 20 kg. These patients received darunavir/ritonavir twice daily in combination with other antiretrovirals. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 log_{10} versus baseline. According to the TLOVR non-virologic failure censored algorithm, 24 (30%) patients experienced virological failure, of which 17 (21.3%) patients were rebounders and 7 (8.8%) patients were non-responders.

Pregnancy and postpartum

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

5.2 Pharmacokinetic properties

The absorption characteristics of [HA719 trade name] have been determined after administration of two darunavir/ritonavir 400mg/50mg tablets in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**	
	Darunavir	**Ritonavir**
Maximum concentration (C_{max})	8872 (± 2250) ng/mL	681 (± 225) ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	94972 (± 34187) ng.h/mL	5523 (± 2387) ng.h/mL
Time to attain maximum concentration (T_{max})#	4.33 (1.67-4.67) h	4.35 (1.33-6.00) h

*arithmetic mean; #median (range)

Pharmacokinetics of Darunavir and Ritonavir

	Darunavir	**Ritonavir**
General	Exposure to darunavir co-administered with ritonavir was higher in HIV-1 infected patients than in healthy subjects, possibly because of 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.	

Absorption		
Oral bioavailability	Rapidly absorbed. Single 600 mg dose: approximately 37% In the presence of ritonavir 100 mg twice daily: approximately 82% Overall PK enhancement effect by ritonavir: approximate 14-fold increase in the systemic exposure of darunavir (single dose of 600 mg darunavir + ritonavir 100 mg twice daily).	
Food effect	Relative bioavailability of darunavir in the presence of low-dose ritonavir administered without food is lower compared to administration with food.	Food slightly decreases the bioavailability of ritonavir. A single oral dose of ritonavir 100 mg with a moderate-fat meal (857 kcal, 31% calories from fat) or a high-fat meal (907 kcal, 52% calories from fat) was associated with a mean decrease of 20–23% in ritonavir AUC and C_{max}.
Distribution		
Volume of distribution (mean ± SD)	After IV administration: 88.1 ± 59.0 L; increased to 131 ± 49.9 L in the presence of ritonavir 100 mg twice-daily.	After single 600-mg dose: approximately 20-40 L
Plasma protein binding *in vitro*	Approximately 95% (primarily to plasma α1-acid glycoprotein)	Approximately 98–99%, constant over the concentration range of 1–100 µg/mL. Ritonavir binds to both α1-acid glycoprotein and human serum albumin with comparable affinities.
Tissue distribution		Studies in rats showed highest concentrations of ritonavir in the liver, adrenals, pancreas, kidneys and thyroid. Tissue to plasma ratios of approximately 1 in rat lymph nodes suggest that ritonavir distributes into lymphatic tissues. Ritonavir penetrates minimally into the brain.
Metabolism		
	Primarily oxidative metabolism according to *in vitro* experiments with human liver microsomes. A ^{14}C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400 mg/100 mg darunavir/ritonavir dose was due to the parent active substance. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed at least 10-fold less activity than the activity of darunavir against wild type HIV.	Primarily oxidative metabolism according to animal studies and *in vitro* studies with human liver microsomes. Four ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite. Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (and other products metabolised by CYP3A4) and other protease inhibitors may influence the pharmacokinetics of ritonavir (see section 4.5).

Active metabolite(s)	None	M-2 has antiviral activity similar to that of parent compound but its AUC was about 3% of the parent compound's AUC.
Elimination		
Elimination half life	Approximately 15 hours when combined with ritonavir	
Mean systemic clearance (Cl/F)	Darunavir (150 mg): 32.8 L/hour Darunavir + low dose ritonavir: 5.9 L/hour	
% of dose excreted in urine	Following darunavir/ritonavir 400 mg/100 mg: approximately 13.9%, 7.7% as unchanged drug	Renal clearance of ritonavir is negligible
% of dose excreted in faeces	Following darunavir/ritonavir 400 mg/100 mg: approximately 79.5%, 41.2% as unchanged drug	86%, part of which is expected to be unabsorbed ritonavir
Drug interactions (in vitro)		
Transporters	P-glycoprotein and anion-transporting polypeptides OATP1A2 and OATP1B1	P-glycoprotein and anion-transporting polypeptides
Metabolising Enzymes	Hepatic CYP system, almost exclusively by isozyme CYP3A4	Hepatic CYP system, primarily by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform

Pharmacokinetics in 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 weight-based doses of darunavir/ritonavir resulted in darunavir exposure comparable to that in adults receiving darunavir/ritonavir 600 mg/100 mg twice daily.

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 12 ART-naïve paediatric patients, aged 12 to < 18 years and weighing at least 40 kg, showed that darunavir/ritonavir 800/100 mg once daily results in darunavir exposure that was comparable to that in adults receiving darunavir/ritonavir 800 mg/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 and who have plasma HIV-1 RNA < 100 000 copies/mL and CD4+ cell count ≥ 100×10^6 cells/L.

In addition, pharmacokinetic modeling and simulation of darunavir exposures in paediatric patients aged 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 who are either ART-naïve or treatment-experienced without darunavir resistance associated mutations and who have plasma HIV-1 RNA < 100 000 copies/mL and CD4+ cell count ≥ 100×10^6 cells/L.

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 (12 patients aged ≥ 65 years).

Ritonavir plasma exposures in patients 50–70 years of age when dosed with ritonavir 100 mg in combination with lopinavir or at higher doses in the absence of other protease inhibitors is similar to that in younger adults.

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.

No clinically significant differences in AUC or C_{max} of ritonavir were noted between males and females.

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).

Ritonavir pharmacokinetic parameters have not been studied in patients with renal impairment. However, since the renal clearance of ritonavir is negligible, no changes in the total body clearance are expected in patients with renal impairment.

Hepatic impairment

Darunavir is primarily metabolised and eliminated by the liver. A multiple-dose study with darunavir/ritonavir 600 mg/100 mg twice daily found 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 raised by approximately 55% (Child-Pugh Class A) and 100% (Child-Pugh Class B). 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).

After multiple dosing of ritonavir to healthy volunteers (500 mg twice daily) and subjects with mild to moderate hepatic impairment (Child Pugh Class A and B, 400 mg twice daily) exposure to ritonavir after dose normalisation was not significantly different between the two groups.

Pregnancy and postpartum

The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 600 mg/100 mg twice daily and darunavir/ritonavir 800 mg/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 after darunavir/ritonavir 600 mg/100 mg twice daily as part of an antiretroviral regimen, during the second and trimesters of pregnancy and postpartum

Pharmacokinetics of total darunavir	**Second trimester (n = 12)[a]**	**Third trimester (n = 12)**	**Postpartum (6-12 weeks) (n = 12)**
C_{max} (mean ± SD)	4668 ± 1097 ng/mL	5328 ± 1631 ng/mL	6659 ± 2364 ng/mL
AUC_{12h} (mean ± SD)	39 370 ± 9597 ng·h/mL	45 880 ± 17 360 ng·h/mL	56 890 ± 26 340 ng·h/mL

C_{min} (mean ± SD)	1922 ± 825 ng/mL	2661 ± 1269 ng/mL	2851 ± 2216 ng/mL

[a] n = 11 for AUC_{12h}

Pharmacokinetic results of after darunavir/ritonavir at 800 mg/100 mg once daily as part of an antiretroviral regimen, during the second and thirds trimester of pregnancy and postpartum

Pharmacokinetics of total darunavir	Second trimester (n = 17)	Third trimester (n = 15)	Postpartum (6-12 weeks) (n = 16)
C_{max} (mean ± SD)	4964 ± 1505 ng/mL	5132 ± 1198 ng/mL	7310 ± 1704 ng/mL
AUC_{24h} (mean ± SD)	62 289 ± 16 234 ng·h/mL	61 112 ± 13 790 ng·h/mL	92 116 ± 29 241 ng·h/mL
C_{min} (mean ± SD)	1248 ± 542 ng/mL	1075 ± 594 ng/mL	1473 ± 1141 ng/mL

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

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

5.3 Preclinical safety data

Darunavir

Animal toxicology studies have been conducted at exposures up to clinical exposure levels with darunavir alone, in mice, rats and dogs and in combination with ritonavir in rats and dogs.

In repeated-dose toxicology studies in mice, rats and dogs, there were only limited effects of treatment with darunavir. In rodents the target organs identified were the hematopoietic system, the blood coagulation system, liver and thyroid. A variable but limited decrease in red blood cell (RBC) parameters was observed, together with increases in activated partial thromboplastin time.

Changes were observed in liver (hepatocyte hypertrophy, vacuolation, increased liver enzymes) and thyroid (follicular hypertrophy). In the rat, the combination of darunavir with ritonavir lead to a small increase in effect on RBC parameters, liver and thyroid and increased incidence of islet fibrosis in the pancreas (in male rats only) compared to treatment with darunavir alone. In the dog, no major toxicity findings or target organs were identified up to exposures equivalent to clinical exposure at the recommended dose.

In a study in rats, the number of corpora lutea and implantations were decreased in the presence of maternal toxicity. Otherwise, there were no effects on mating or fertility with darunavir treatment up to 1 000 mg/kg/day and exposure levels below (AUC-0.5 fold) of that in humans at the clinically recommended dose. Up to same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. The exposure levels were lower than those with the recommended dose in humans. In a pre- and postnatal development assessment in rats, darunavir with and without ritonavir caused a transient reduction in body weight gain of the offspring pre-weaning and there was a slight delay in the opening of eyes and ears. Darunavir in combination with ritonavir caused a reduction in the number of pups that exhibited the startle response on day 15 of lactation and reduced pup survival during lactation. These effects may be secondary to pup exposure to the active substance via the milk and/or maternal toxicity. No post-weaning functions were affected with darunavir alone or in combination with ritonavir. In juvenile rats receiving darunavir up to days 23–26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher

than in adult rats after comparable doses in mg/kg between days 5 and 11 of age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals. No treatment-related mortalities were noted in juvenile rats dosed at 1000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats.

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumors in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

After 2 years' administration of darunavir at exposures at or below the human exposure, kidney changes were observed in mice (nephrosis) and rats (chronic progressive nephropathy). Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

Ritonavir

Repeated dose toxicity studies in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium (RPE) and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. All thyroid changes were reversible upon discontinuation of ritonavir. Renal changes including tubular degeneration, chronic inflammation and proteinurea were noted in rats and are felt to be attributable to species-specific spontaneous disease.

Developmental toxicity observed in rats (embryolethality, decreased fetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased fetal weights) occurred at a maternally toxic dosage.

Ritonavir was not found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Long-term carcinogenicity studies of ritonavir in mice and rats revealed tumourigenic potential specific for these species, but are regarded as of no relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:
Silicified microcrystalline cellulose
Crospovidone
Colloidal silicon dioxide
Magnesium stearate
Copovidone
Sorbitan monolaurate
Dibasic calcium phosphate anhydrous
Sodium stearyl fumarate

Film coat:
Hypromellose
Titanium dioxide
Macrogol/PEG
Hydroxypropyl cellulose
Iron oxide yellow
Talc
Colloidal anhydrous silica
Polysorbate

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per *tablet*.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from moisture.

6.5 Nature and contents of container

HDPE container

[HA719 trade name] is provided in a white opaque heavy-weight HDPE container containing 30 and 120 tablets. It also contains a desiccant canister. The bottle is closed with a polypropylene child-resistant cap with pulp liner.

[HA719 trade name] is provided in a white opaque heavy-weight HDPE container containing 60 tablets. It also contains a desiccant canister and purified cotton. The bottle is closed with a polypropylene child-resistant cap with pulp liner.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA719

9. DATE OF PREQUALIFICATION

01 July 2021

10. DATE OF REVISION OF THE TEXT

January 2026

References

General reference sources for this SmPC include:

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HIV drug interactions: interactions checker [online database]. Liverpool Drug Interactions Group, University of Liverpool; 2023 (https://hiv-druginteractions.org/checker, accessed 16 July 2025).

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products