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/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT
[HA725 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 800 mg darunavir.

Excipients with known effect:
Each tablet contains 52.5 mg sodium chloride equivalent to 20.66 mg (0.90 mmol) sodium. See section 4-4.
Each tablet contains 25 mg polacrilin potassium equivalent to about 5.7mg (0.14 mmol) potassium.

For the full list of excipients, see section 6-1.

3. PHARMACEUTICAL FORM
Tablets.
Brown coloured, oval shaped, biconvex film-coated tablets, debossed with 'D' on one side and '800' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
[HA725 trade name] is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing at least 35 kg who:
- have not previously been treated with a protease inhibitor (‘protease inhibitor-naïve patients’, see section 4.2) or
- have previously been treated with a protease inhibitor (‘protease inhibitor-experienced’) but do not harbour darunavir resistance associated mutations (see below) and who have plasma HIV-1 RNA < 100 000 copies/mL and CD4+ cell count ≥ 100×10^6 cells/L (see sections 4.4 and 5.1).

[HA725 trade name] is used for protease inhibitor-experienced patients when HIV-1 genotype testing is available. Darunavir resistance associated mutations include: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V.
See section 4.4 for advice on darunavir treatment in protease inhibitor-experienced patients when genotype testing is not available.
Consideration should be given to official guidelines for treatment of HIV-1 infection (e.g. those by WHO).
[HA725 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
[HA725 trade name] must always be given orally with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The product information of ritonavir must therefore be consulted prior to initiation of therapy with [HA725 trade name].
Patients weighing at least 35 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 [HA725 trade name] is:

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

1 tablet of [HA725 trade name] coadministered with 100 mg ritonavir, taken once daily with food at around the same time each day.

[HA725 trade name] is not suitable for treating all other ART-experienced patients or when HIV-1 genotype testing is not available.

Missed doses

If a dose of [HA725 trade name] is missed within 12 hours of the time it is usually taken, patients should be instructed to take the dose of [HA725 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.

If a patient vomits within 4 hours of taking [HA725 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, [HA725 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, [HA725 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, [HA725 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 [HA725 trade name] in patients with renal impairment (see sections 4.4 and 5.2).

Paediatric population

[HA725 trade name] is not suitable for children weighing less than 35 kg. Other formulations of darunavir may be required.

Darunavir should not be used in children below 3 years of age or weighing less than 14 kg (see section 5.3)

Pregnancy and postpartum

No dose adjustment is required for darunavir during pregnancy and postpartum. [HA725 trade name] should be used during pregnancy only if the potential benefit justifies the potential risk (see sections 4.6 and 5.2).

Method of administration

Patients should be instructed to take darunavir 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 [HA725 trade name]:

- 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
- apixaban, rivaroxaban, clopidogrel, ticagrelor
- astemizole, terfenadine
- avanafil (for erectile dysfunction), sildenafil (when used for the treatment of pulmonary arterial hypertension)
- budesonide, fluticasone
- cisapride
- colchicine when used in patients with renal or hepatic impairment
- dapoxetine
- domperidone
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- elbasvir/grazoprevir, glecaprevir/pibrentasvir
- halofantrine
- lomitapide, lovastatin and simvastatin
- lurasidone, pimozide, quetiapine, sertindole
- naloxegol
- phenobarbital, phenytoin
- triazolam, midazolam administered orally

4.4 Special warnings and precautions for use

Protease inhibitor-experienced patients

When genotypic testing is not feasible in protease inhibitor-experienced patients, darunavir/ritonavir 600 mg/100 mg twice daily is recommended. [HA725 trade name] is not suitable and other formulations should be used.

Transmission

While effective viral suppression with antiretroviral therapy substantially reduces the risk of sexual transmission, a residual risk may remain. Precautions to prevent transmission should be taken in accordance with relevant guidelines.

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

[HA725 trade name] must always be given orally with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products (see section 5.2). The product information of ritonavir must therefore be consulted before starting therapy with [HA725 trade name].

Antiretroviral therapy-experienced patients – once daily dosing

Darunavir in combination with ritonavir once daily for ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA $\geq$ 100 000 copies/mL or CD4+ cell count < 100×10^6/L cells (see section 4.2). Only combinations providing an optimised background regimen with two or more nucleotide (or nucleoside) reverse transcriptase inhibitors (NRTIs) have been studied in this population. 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, [HA725 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
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). [HA725 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. [HA725 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 [HA725 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 [HA725 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
Patients receiving darunavir or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by health care providers experienced in the treatment of these associated HIV diseases.

Immune reconstitution inflammatory syndrome
When starting combination antiretroviral therapy (CART) in patients with severe immune deficiency, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravate symptoms. Typically, such reactions occur within the first weeks or months of starting CART. Relevant examples are cytomegalovirus retinitis, generalised or focal mycobacterial infections and pneumonia caused by *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treated when necessary. Also, reactivation of herpes simplex and herpes zoster has occurred in clinical studies with darunavir/ ritonavir.
Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported in the setting of immune reactivation; however, the time to onset is more variable and these events can occur many months after starting treatment (see section 4.8).

Use with efavirenz
Efavirenz in combination with [HA725 trade name] once daily may result in sub-optimal trough concentration of darunavir. If efavirenz is to be used, darunavir/ritonavir 600 mg/100 mg twice daily is recommended in HIV protease inhibitor-experienced patients.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say, is essentially 'sodium-free'.
It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction
Interaction studies have only been performed in adults.

Darunavir and ritonavir are inhibitors of CYP3A, CYP2D6 and P-gp. Co-administration of darunavir/ritonavir with 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.

Coadministration of darunavir/ritonavir with drugs that have active metabolite(s) formed by CYP3A4 may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their 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 protein 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 with low-dose 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 that are metabolised by cytochromes CYP2C9, CYP2C19 and CYP2D6 demonstrated an increase in CYP2C9 and CYP2C19 activity and inhibition of CYP2D6 activity in the presence of darunavir/ritonavir, which may be attributed to the presence of low-dose ritonavir. Co-administration of darunavir/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.

Although the effect on CYP2C8 has only been studied *in vitro*, 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 transporter P-glycoproteins, 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. indinavir, systemic azoles like ketoconazole and clotrimazole).

Interaction table
Interactions between darunavir/ritonavir and antiretroviral and non-antiretroviral medicinal products are listed in the table below. 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 Posology). 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 [HA725 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 ↓ Cmax ↓	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 ↔ Cmin ↔ Cmax ↔ didanosine AUC ↓ Cmax ↓	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 ↑ Cmin ↑ Cmax ↑ tenofovir AUC ↑ Cmin ↑ Cmax ↑ (↑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.
Non-nucleo(s/t)ide reverse transcriptase inhibitors (NNRTIs)		
Efavirenz	#Darunavir AUC ↓ Cmin ↓ Cmax ↓ efavirenz AUC ↑ Cmin ↑ Cmax ↑ (↑ 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 Cmin. If efavirenz is to be used, then darunavir/ritonavir 600 mg/100 mg twice-daily regimen should be used (see section 4.4).

Drugs	Interaction	Recommendations on co-administration
Etravirine	Darunavir AUC ↑ Cmin ↔ Cmax ↔ etravirine AUC ↓ Cmin ↓ Cmax ↓	Darunavir/ritonavir and etravirine 200 mg twice daily can be used without dose adjustments.
Nevirapine	#Darunavir: concentrations were consistent with historical data nevirapine AUC ↑ Cmin ↑ Cmax ↑ (↑ nevirapine from CYP3A inhibition)	Darunavir/ritonavir and nevirapine can be used without dose adjustments.
Rilpivirine	Darunavir AUC ↔ Cmin ↓ Cmax ↔ rilpivirine AUC ↑ Cmin ↑ Cmax ↑	Darunavir/ritonavir and rilpivirine can be used without dose adjustments.
HIV Protease inhibitors (PIs) - without additional low-dose ritonavir†		
Atazanavir	#Darunavir AUC ↔ Cmin ↔ Cmax ↔ atazanavir AUC ↔ Cmin ↑ Cmax ↓	Darunavir/ritonavir and atazanavir can be used without dose adjustments.
Indinavir	#Darunavir AUC ↑ Cmin ↑ Cmax ↑ indinavir AUC ↑ Cmin ↑ Cmax ↔	When used in combination with darunavir/ritonavir, the dose of indinavir may to be reduced from 800 mg twice daily to 600 mg twice daily to manage side effects.
Saquinavir	#Darunavir AUC ↓ Cmin ↓ Cmax ↓ saquinavir AUC ↓ Cmin ↓ Cmax ↓	It is not recommended to combine darunavir/ritonavir with saquinavir.
HIV Protease inhibitor (PI) – with co-administration of low dose ritonavir†		

Drugs	Interaction	Recommendations on co-administration
Lopinavir/ritonavir 400 mg/100 mg twice daily	Darunavir AUC ↓ Cmin ↓ Cmax ↓ lopinavir AUC ↑ Cmin ↑ Cmax ↓	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 ↑ Cmax ↑	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		
Alfentanil Ketamine	Not studied. The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by PREZISTA co-administered with low dose ritonavir. Coadministration may increase ketamine exposure.	The concomitant use with PREZISTA and low dose ritonavir may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression. 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 ↑ Cmax ↑ (↑ 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.

Drugs	Interaction	Recommendations on co-administration
ANTIBIOTICS		
Bedaquilline	Coadministration may increase comedication exposure.	Use with caution and with ECG monitoring. Coadministration for more than 14 consecutive days should be avoided.
Clarithromycin	#Darunavir AUC ↓ Cmin ↑ Cmax ↓ clarithromycin AUC ↑ Cmin ↑ Cmax ↑ (↑ 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 of clarithromycin should be consulted for the recommended dose.
Delamanid	Coadministration may increase delamanid exposure.	Caution is recommended due to the risk of QT prolongation. ECG monitoring is recommended.
Moxifloxacin	Coadministration 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 ↑ Cmin ↑ Cmax ↑ rifabutin AUC↑ Cmax ↔ (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.
ANTICOAGULANTS/ PLATELET AGGREGATION INHIBITORS		
Apixaban Rivaroxaban Edoxaban	Not studied. Co-administration of darunavir/ritonavir with these anticoagulants may increase concentrations of the anticoagulant, and increase bleeding risk. (CYP3A and P-gp inhibition)	Concomitant administration of darunavir/ritonavir with apixaban or rivaroxaban is contraindicated (see section 4.3). Co-administration of edoxaban with darunavir/ritonavir is not recommended.

Drugs	Interaction	Recommendations on co-administration
Ticagrelor Dabigatran Clopidogrel	Not studied. Co-administration with darunavir/ritonavir may substantially increase exposure to ticagrelor. No interaction expected when administered simultaneously, but dabigatran exposure may decrease if administered separately. 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 ticagrelor is contraindicated (see section 4.3). Use with caution in patients with mild or moderate renal impairment as the dabigatran dose might need to be reduced. Dabigatran is not recommended in patients with severe renal impairment. Concomitant administration of darunavir/ritonavir with clopidogrel is contraindicated (see section 4.3). Use of 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.
ANTICONVULSANTS		
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 ↔ Cmin ↓ Cmax ↔ carbamazepine AUC ↑ Cmin ↑ Cmax ↑	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.
Lamotrigine	Coadministration may decrease comedication exposure.	Monitor clinical effect and increase dose if needed.
Oxcarbazepine	Coadministration may decrease exposure of the daruavir/ritonavir, although to a moderate extent.	A dose adjustment may be needed. Monitor clinical effect. Alternative anticonvulsants should be considered.
Valproate	Coadministration may decrease comedication exposure.	Monitor clinical effect and increase dose if needed.
ANTI-DIABETICS		
Glibenclamide	Coadministration may increase comedication exposure.	Dose adjustment may be needed. Monitor clinical effect.
Gliclazide	Coadministration may decrease comedication exposure.	Monitor clinical effect and increase dose if needed.
ANTIDEPRESSANTS		

Drugs	Interaction	Recommendations on co-administration
Paroxetine	#Darunavir AUC ↔ Cmin ↔ Cmax ↔ paroxetine AUC ↓ Cmin ↓ Cmax ↓	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 ↔ Cmin ↓ Cmax ↔ sertraline AUC ↓ Cmin ↓ Cmax ↓	
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 domperidon's cardiac adverse events may be increased.
ANTIFUNGALS		
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.
Ketoconazole	#Darunavir AUC ↑ Cmin ↑ Cmax ↑ ketoconazole AUC ↑ Cmin ↑ Cmax ↑ (CYP3A inhibition)	Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of ketoconazole should not exceed 200 mg.
Fluconazole 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.
Clotrimazole	Not studied. Concomitant systemic use of clotrimazole and darunavir/ritonavir may increase plasma concentrations of darunavir and clotrimazole. darunavir AUC24h ↑ (based on population pharmacokinetic model)	Caution is warranted and clinical monitoring is recommended, when co-administration of clotrimazole is required.

Drugs	Interaction	Recommendations on co-administration
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).
ANTIMALARIALS		
Artemether/lumefantrine	Darunavir AUC ↔ Cmin ↓ Cmax ↔ artemether and dihydroartemisinin AUC ↓ Cmin ↔ Cmax ↓ lumefantrine AUC ↑ Cmin ↑ Cmax ↑	The combination of boosted darunavir and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.
Artemisinin	Coadministration may increase comedication exposure. and a dose adjustment may be needed. Monitor clinical effect.	Dose adjustment may be needed. Monitor clinical effect.
Halofantrine	Not studied. Halofantrine is extensively metabolized by CYP3A4. Inhibition of halofantrine metabolism by ritonavir is expected to increase halofantrine exposure could potentially prolong the QT interval.	Concomitant administration of boosted darunavir and halofantrine is contraindicated. Halofantrine has a narrow therapeutic index with an increased risk of QT-prolongation at higher exposures.
Mefloquine	Coadministration may increase comedication exposure.	Caution and close monitoring is recommended.
Proguanil	Coadministration may decrease proguanil exposure.	Coadministration of atovaquone/proguanil should be avoided whenever possible. If judged clinically necessary, consider taking atovaquone/ proguanil with a high fat meal to increase its bioavailability and increase the dosage if required.
Quinine	Coadministration may increase quinine exposure.	In addition, caution is recommended as quinine has a risk of QT prolongation. ECG monitoring is recommended.
ANTINEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine Vinorelbine Everolimus Irinotecan	Not studied. Boosted darunavir is expected to increase plasma concentrations of these antineoplastic medicines. (CYP3A inhibition)	Concentrations of these medicines may increase when co-administered with boosted darunavir, potentially resulting in increased adverse events usually associated with these agents. Caution should be exercised when combining these antineoplastic medicines with boosted darunavir. Concominant use of everolimus or irinotecan and boosted darunavir.

Drugs	Interaction	Recommendations on co-administration
Cisplatin	Coadministration may increase cisplatin exposure, thus increasing the risk of nephrotoxicity.	Close monitoring of renal function is recommended.
Cyclophosphamide Dacarbazine	Coadministration may increase the efficacy and the toxicity of the comedication.	Careful monitoring of efficacy and toxicity is recommended.
Docetaxel Imatinib	Coadministration may increase comedication exposure.	Monitor for chemotherapy-induced toxicity.
Ifosfamide	Coadministration may reduce conversion of ifosfamide to the active metabolite and thereby reduce efficacy.	Use with caution.
Paclitaxel	Coadministration may increase paclitaxel exposure.	Monitor paclitaxel induced toxicity.
Tamoxifen	Coadministration may reduce conversion to the active metabolite and thereby reduce efficacy of the comedication.	Monitor response to chemotherapy.
ANTIPSYCHOTICS		
Quetiapine	Not studied. Due to CYP3A inhibition by boosted darunavir, concentrations of the antipsychotics are expected to increase. (CYP3A inhibition)	Concomitant administration of boosted darunavir and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased concentrations of quetiapine may lead to coma (see section 4.3).
Perphenazine Risperidone Thioridazine Lurasidone Pimozide Sertindole	Not studied. Boosted darunavir 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 boosted darunavir. Concomitant administration of boosted darunavir and lurasidone, pimozide or sertindole is contraindicated (see section 4.3).
BETA-BLOCKERS		
Carvedilol Metoprolol Timolol	Not studied. Boosted darunavir is expected to increase plasma concentrations of these beta-blockers. (CYP2D6 inhibition)	Clinical monitoring is recommended when co-administering boosted darunavir with beta-blockers. A lower dose of the beta-blocker should be considered.
CALCIUM CHANNEL BLOCKERS		
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Not studied. Boosted darunavir are 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 boosted darunavir.
CORTICOSTEROIDS		

Drugs	Interaction	Recommendations on co-administration
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone) dexamethasone (systemic))	Darunavir AUC ↓ Cmin↓ Cmax ↓ fluticasone propionate AUC ↑ Cmin↑ Cmax ↑ Other corticosteroids: interaction not studied. Plasma concentrations of these medicines may increase when co-administered with boosted darunavir, resulting in reduced serum cortisol concentrations	Concomitant use of boosted darunavir and corticosteroids (all routes of administration) 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 boosted darunavir 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 boosted darunavir.
ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Not studied. Concomitant use of bosentan and boosted darunavir may increase plasma concentrations of bosentan. Bosentan is expected to decrease plasma concentrations of darunavir and/or its pharmacoenhancer. (CYP3A induction).	When administered concomitantly with darunavir/ritonavir, the patient should be monitored for bosentan side effects.
HEPATITIS C VIRUS DIRECT-ACTING ANTIVIRALS		
Elbasvir/grazoprevir	Boosted darunavir may increase the exposure to grazoprevir. (CYP3A and OATP1B inhibition)	Concomitant use of boosted darunavir and elbasvir/grazoprevir is contraindicated (see section 4.3).
Glecaprevir/pibrentasvir	Boosted darunavir may increase the exposure to glecaprevir and pibrentasvir. (P-gp, BCRP and OATP1B1/3 inhibition)	Concomitant use of boosted darunavir 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 its pharmacoenhancers. (CYP450 induction).	Boosted darunavir must not be used concomitantly with products containing St John's wort (see section 4.3). If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Darunavir (and ritonavir) exposure may increase on stopping St John's wort. The inducing effect may persist for at least 2 weeks after stopping St John's wort.
HMG CO-A REDUCTASE INHIBITORS		

Drugs	Interaction	Recommendations on co-administration
Lovastatin Simvastatin	Not studied. Lovastatin and simvastatin is expected to markedly increase plasma concentrations when co-administered with boosted darunavir. (CYP3A inhibition)	Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of boosted darunavir with lovastatin and simvastatin is therefore contraindicated (see section 4.3).
Atorvastatin	Atorvastatin AUC ↑ Cmin ↑ Cmax ↑	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. The total daily dose of atorvastatin should not exceed 40 mg.
Pravastatin	Pravastatin AUC ↑ Cmax ↑	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 ↑ Cmax ↑	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	Boosted darunavir is expected to increase the exposure of lomitapide when co-administered. (CYP3A inhibition)	Co-administration is contraindicated (see section 4.3).
GASTROINTESTINAL AGENTS		
Loperamide	Coadministration may increase loperamide exposure, but this is unlikely to result in opioid CNS effects. 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 ↔ Cmin ↔ Cmax ↔	Boosted darunavir can be co-administered with proton pump inhibitors without dose adjustments.
Ranitidine	#Darunavir AUC ↔ Cmin ↔ Cmax ↔	Boosted darunavir 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 boosted darunavir. (CYP3A inhibition)	Therapeutic drug monitoring of the immunosuppressants must be done when co-administration occurs. Concomitant use of everolimus and boosted darunavir is not recommended.
INHALED BETA AGONIST		

Drugs	Interaction	Recommendations on co-administration
Salmeterol	Not studied. Concomitant use of salmeterol and boosted darunavir may increase plasma concentrations of salmeterol.	Concomitant use of salmeterol and boosted darunavir is not recommended. The combination may increase the risk of cardiovascular adverse events of salmeterol, including QT prolongation, palpitations and sinus tachycardia.
OPIOID ANALGESICS / TREATMENT OF OPIOID DEPENDENCE		
Methadone	R(-) methadone AUC ↓ Cmin ↓ Cmax ↓	No adjustment of methadone dosage is required when initiating co-administration with boosted darunavir. 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 ↓ Cmin ↔ Cmax ↓ norbuprenorphine AUC ↑ Cmin ↑ Cmax ↑ naloxone AUC ↔ Cmax ↔	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 boosted darunavir but careful clinical monitoring for opioid toxicity is recommended.
Morphine	Coadministration may increase exposure to the active metabolite and potentiate the effects of the opiate in the CNS.	Monitor for sign of opiate toxicity.
Fentanyl Oxycodone Tramadol	Boosted darunavir may increase plasma concentrations of these analgesics. (CYP2D6 and/or CYP3A inhibition)	Clinical monitoring is recommended when co-administering boosted darunavir with these analgesics.
COMBINED HORMONAL CONTRACEPTIVES/HORMONAL REPLACEMENT THERAPY		
Drospirenone Ethinylestradiol (3 mg/20 µg once daily) Ethinylestradiol Norethindrone 35 µg/1 mg once daily	Drospirenone AUC ↑ Cmax ↑ ethinylestradiol AUC ↓ Cmax ↓ ethinylestradiol AUC ↓ Cmin ↓ Cmax ↓ norethindrone AUC ↓ Cmin ↓ Cmax ↔	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 boosted darunavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.
Etonogestrel (vaginal ring)	Coadministration 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.

Drugs	Interaction	Recommendations on co-administration
Medroxyprogesterone (oral)	Coadministration 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.
Dydrogesterone (HRT) Norethisterone (HRT)	Coadministration 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 boosted darunavir and naloxegol is contraindicated.
PARKINSONISM AGENTS		
Carbidopa Levodopa	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 boosted darunavir is contraindicated (see section 4.3). Caution is required for concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with boosted darunavir. If concomitant use of boosted darunavir with sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended.
For the treatment of pulmonary arterial hypertension Sildenafil Tadalafil	Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and boosted darunavir 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 boosted darunavir 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 boosted darunavir and sildenafil used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3). Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with boosted darunavir is not recommended.
SEDATIVES/HYPNOTICS		

Drugs	Interaction	Recommendations on co-administration
Buspirone Clorazepate Diazepam Estazolam Flurazepam Zoldipem Midazolam (parenteral) Midazolam (oral) Triazolam	Not studied. Sedatives/hypnotics are extensively metabolised by CYP3A.Co-administration with boosted darunavir may cause a large increase in the concentration of these medicines. If parenteral midazolam is co-administered with boosted darunavir 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 boosted darunavir with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. If parenteral midazolam is co-administered with boosted darunavir, 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. Boosted darunavir with triazolam or oral midazolam is contraindicated (see section 4.3).
TREATMENT FOR PREMATURE EJACULATION		
Dapoxetine	Not studied.	Co-administration of boosted darunavir 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 (see section 4.2 Posology).
† The efficacy and safety of the use of darunavir with 100 mg ritonavir and any other protease inhibitors (e.g. (fos)amprenavir and tipranavir) have not been established in HIV patients. According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended

4.6 Fertility, pregnancy and breastfeeding

Pregnancy
There are no adequate and well controlled studies on pregnancy outcome with darunavir in pregnantwomen. Studies in animals do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).
Darunavir co-administered with low dose ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk.

Treatment with darunavir/cobicistat during pregnancy results in low darunavir exposure (see section 5.2), which may be associated with an increased risk of treatment failure and an increased risk of HIV transmission to the child. Therapy with [HA725 trade name]/cobicistat should not be initiated during pregnancy, and women who become pregnant during therapy with [HA725 trade name]/cobicistat should be switched to an alternative regimen (see sections 4.2 and 4.4).

Breast-feeding
It is not known whether darunavir is excreted in human milk Studies in rats have demonstrated that darunavir is excreted in milk and at high levels (1,000 mg/kg/day) resulted in toxicity.. The most recent official treatment guidelines (e.g. those issued by WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.
Fertility
No human data on the effect of darunavir on fertility are available. There was no effect on mating or fertility with darunavir treatment in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

[HA725 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
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	DRESS, Stevens-Johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma
not known	toxic epidermal necrolysis, acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	
uncommon	myalgia, osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphokinase
rare	musculoskeletal stiffness, arthritis, joint stiffness
Renal and urinary disorders	
uncommon	acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria
rare	decreased creatinine renal clearance
Reproductive system and breast disorders	
uncommon	erectile dysfunction, gynaecomastia
General disorders and administration site conditions	
common	asthenia, fatigue
uncommon	pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain
rare	chills, abnormal feeling, xerosis

Description of selected adverse reactions

Rash

In clinical trials, rash was mostly mild to moderate, often occurring within the first 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 phosphokinase, 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
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

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 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.

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 darunavur/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

Absorption of [HA725 trade name]
The absorption characteristics of [HA725 trade name] have been determined after administration of one darunavir 800 mg tablet in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Mean value* (±standard deviation)**
	Daclatasvir
Maximum concentration (C_{max})	11.4 ± 2.2 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	139 ± 49 µg·h/mL
Time to attain maximum concentration (T_{max})	3.63 ± 1.09 h

*arithmetic mean

Pharmacokinetics of darunavir

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) (see section 4.4).	
Food effect	Relative bioavailability of darunavir in the presence of low-dose ritonavir administered without food is lower compared to administration with food.	
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.	
Plasma protein binding *in vitro*	Approximately 95% (primarily to plasma α1-acid glycoprotein)	
Tissue distribution		
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.	
Active metabolite(s)	None	

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
% of dose excreted in faeces	Following darunavir/ritonavir 400 mg/100 mg: approximately 79.5%, 41.2% as unchanged drug
Drug interactions (in vitro)	
Transporters	P-glycoprotein and anion-transporting polypeptides OATP1A2 and OATP1B1
Metabolising Enzymes	Hepatic CYP system, almost exclusively by isozyme CYP3A4

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 $\geq 100 \times 10^6$ 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 $\geq 100 \times 10^6$ 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).

Gender

Population pharmacokinetic analysis showed a slightly higher darunavir exposure (16.8%) in HIV infected females compared to males. This difference is not clinically relevant.

Renal impairment

Results from a mass balance study with ^{14}C-darunavir with ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine unchanged.

Although darunavir has not been studied in patients with renal impairment, population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected patients with moderate renal impairment (CrCl between 30-60 ml/min, n=20) (see sections 4.2 and 4.4).

Hepatic impairment

Darunavir is primarily metabolised and eliminated by the liver. 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).

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

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

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

Changes were observed in liver (hepatocyte hypertrophy, vacuolation, increased liver enzymes) and thyroid (follicular hypertrophy). In the rat, the combination of darunavir with ritonavir lead to a small increase in effect on RBC parameters, liver and thyroid and increased incidence of islet fibrosis in the pancreas (in male

rats only) compared to treatment with darunavir alone. In the dog, no major toxicity findings or target organs were identified up to exposures equivalent to clinical exposure at the recommended dose.
In a study conducted in rats, the number of corpora lutea and implantations were decreased in the presence of maternal toxicity. Otherwise, there were no effects on mating or fertility with darunavir treatment up to 1,000 mg/kg/day and exposure levels below (AUC-0.5 fold) of that in human at the clinically recommended dose. Up to same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. The exposure levels were lower than those with the recommended clinical dose in humans. In a pre- and postnatal development assessment in rats, darunavir with and without ritonavir, caused a transient reduction in body weight gain of the offspring pre-weaning and there was a slight delay in the opening of eyes and ears. Darunavir in combination with ritonavir caused a reduction in the number of pups that exhibited the startle response on day 15 of lactation and a reduced pup survival during lactation. These effects may be secondary to pup exposure to the active substance via the milk and/or maternal toxicity. No post weaning functions were affected with darunavir alone or in combination with ritonavir. In juvenile rats receiving darunavir up to days 23-26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher than in adult rats after comparable doses in mg/kg between days 5 and 11 of age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals. No treatment related mortalities were noted in juvenile rats dosed at 1,000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats.

Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, darunavir with low dose ritonavir should not be used in paediatric patients below 3 years of age.
Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1,000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumours in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:
Silicified microcrystalline cellulose
Crospovidone
Hydroxypropyl cellulose
Sodium chloride
Silica colloidal anhydrous
Magnesium stearate
Polacrilin potassium

Film coat:
Polyvinyl alcohol -part hydrolyzed
Titanium dioxide
Macrogol/PEG-
Talc
Iron oxide red

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 30°C. Protect from light and moisture. Avoid excursions above 30°C.

6.5 Nature and contents of container
White, opaque HDPE container, closed with a white, opaque polypropylene child-resistant closure with wad having induction sealing liner.
Pack size: 30 tablets

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER
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10. DATE OF REVISION OF THE TEXT
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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

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

All weblinks were last accessed on 22 March 2022

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines