ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal Product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Darunavir Krka d.d. 400 mg film-coated tablets
Darunavir Krka d.d. 800 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Darunavir Krka d.d. 400 mg film-coated tablets:

Each film-coated tablet contains 400 mg darunavir.

Darunavir Krka d.d. 800 mg film-coated tablets:

Each film-coated tablet contains 800 mg darunavir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Darunavir Krka d.d. 400 mg film-coated tablets:

Yellowish brown, oval, biconvex film-coated tablets, engraved with a mark S1 on one side. Tablet dimension: 17 x 8.5 mm.

Darunavir Krka d.d. 800 mg film-coated tablets:

Brownish red, oval, biconvex film-coated tablets, engraved with a mark S3 on one side. Tablet dimension: 20 x 10 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Darunavir Krka d.d., co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.

Darunavir Krka d.d., co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection in adults and adolescents (aged 12 years and older, weighing at least 40 kg) (see section 4.2).

Darunavir Krka d.d. 400 mg and 800 mg tablets may be used to provide suitable dose regimens for the treatment of HIV-1 infection in adult and paediatric patients from the age of 3 years and at least 40 kg body weight who are:

- antiretroviral therapy (ART)-naïve (see section 4.2).
- ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/L. In deciding to initiate treatment with darunavir in such ART-experienced patients, genotypic testing should guide the use of darunavir (see sections 4.2, 4.3, 4.4 and 5.1).

4.2 Posology and method of administration

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Therapy should be initiated by a healthcare provider experienced in the management of HIV infection. After therapy with darunavir has been initiated, patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their healthcare provider.

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer. Darunavir may therefore have different contraindications and recommendations for concomitant medications depending on whether the compound is boosted with ritonavir or cobicistat (see sections 4.3, 4.4 and 4.5).

Posology

Darunavir must always be given orally with cobicistat or low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of cobicistat or ritonavir as appropriate, must therefore be consulted prior to initiation of therapy with darunavir. Cobicistat is not indicated for use in twice daily regimens or for use in the paediatric population less than 12 years of age weighing less than 40 kg.

This product is only available as film coated tablets and is thus not suitable for patients who are unable to swallow intact tablets, for example young children. For use in these patients, more suitable formulations containing darunavir should be checked for their availability.

ART-naïve adult patients

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

ART-experienced adult patients

The recommended dose regimens are as follows:

- In ART-experienced patients with no darunavir resistance associated mutations (DRV-RAMs)* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/L (see section 4.1) a regimen of 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food may be used. Darunavir Krka d.d. 400 mg and 800 mg tablets can be used to construct the once daily 800 mg regimen.
- In all other ART-experienced patients or if HIV-1 genotype testing is not available, the recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. See the Summary of Product Characteristics for Darunavir Krka d.d. 600 mg tablets.

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

ART-naïve paediatric patients (3 to 17 years of age and weighing at least 40 kg)

The recommended dose regimen is 800 mg once daily with ritonavir 100 mg once daily taken with food or 800 mg once daily with cobicistat 150 mg once daily taken with food (in adolescent patients 12 years of age or older). Darunavir Krka d.d. 400 mg and 800 mg tablets can be used to construct the once daily 800 mg regimen. The dose of cobicistat to be used with darunavir in children less than 12 years of age has not been established.

ART-experienced paediatric patients (3 to 17 years of age and weighing at least 40 kg)

The dose of cobicistat to be used with darunavir in children less than 12 years of age has not been established.

The recommended dose regimens are as follows:

- In ART-experienced patients without DRV-RAMs* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/L (see section 4.1) a regimen of 800 mg once daily with ritonavir 100 mg once daily taken with food or 800 mg once daily with cobicistat 150 mg once daily taken with food (in adolescent patients 12 years of age or older) may be used. Darunavir Krka d.d. 400 mg and 800 mg tablets can be used to construct the once daily 800 mg regimen. The dose of cobicistat to be used with darunavir in children less than 12 years of age has not been established.

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- In all other ART-experienced patients or if HIV-1 genotype testing is not available, the recommended dose regimen is described in the Summary of Product Characteristics for Darunavir Krka d.d. 600 mg tablets.

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

Advice on missed doses
If a once daily dose of darunavir and/or cobicistat or ritonavir is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of darunavir and cobicistat or ritonavir with food as soon as possible. If this is noticed later than 12 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

This guidance is based on the half-life of darunavir in the presence of cobicistat or ritonavir and the recommended dosing interval of approximately 24 hours.

If a patient vomits within 4 hours of taking the medicine, another dose of darunavir with cobicistat or ritonavir should be taken with food as soon as possible. If a patient vomits more than 4 hours after taking the medicine, the patient does not need to take another dose of darunavir with cobicistat or ritonavir until the next regularly scheduled time.

Special populations

Elderly
Limited information is available in this population, and therefore, darunavir should be used with caution in this age group (see sections 4.4 and 5.2).

Hepatic impairment
Darunavir is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, darunavir should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its safety profile. Therefore, darunavir must not be used in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3, 4.4 and 5.2).

Renal impairment
No dose adjustment is required for darunavir/ritonavir in patients with renal impairment (see sections 4.4 and 5.2). Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients.
Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance. Hence, the use of creatinine clearance as an estimate of renal elimination capacity may be misleading. Cobicistat as a pharmacokinetic enhancer of darunavir should, therefore, not be initiated in patients with creatine clearance less than 70 ml/min if any co-administered agent requires dose adjustment based on creatinine clearance: e.g. emtricitabine, lamivudine, tenofovir disoproxil (as fumarate, phosphate or succinate) or adefovir dipovoxil.
For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Paediatric population
Darunavir Krka d.d. should not be used in children
- below 3 years of age, because of safety concerns (see sections 4.4 and 5.3), or,
- less than 15 kg body weight, as the dose for this population has not been established in a sufficient number of patients (see section 5.1).

Darunavir Krka d.d. taken with cobicistat should not be used in children aged 3 to 11 years of age weighing < 40 kg as the dose of cobicistat to be used in these children has not been established (see sections 4.4 and 5.3).

For dosage recommendations in children, see the Summary of Product Characteristics for Darunavir Krka d.d. 600 mg tablets.

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Pregnancy and postpartum
No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. Darunavir/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk (see sections 4.4, 4.6 and 5.2).

Treatment with darunavir/cobicistat 800/150 mg during pregnancy results in low darunavir exposure (see sections 4.4 and 5.2). Therefore, therapy with darunavir/cobicistat should not be initiated during pregnancy, and women who become pregnant during therapy with darunavir/cobicistat should be switched to an alternative regimen (see sections 4.4 and 4.6). Darunavir/ritonavir may be considered as an alternative.

Method of administration

Patients should be instructed to take darunavir with cobicistat or low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir (see sections 4.4, 4.5 and 5.2).

4.3 Contraindications

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

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

Concomitant treatment with any of the following medicinal products given the expected decrease in plasma concentrations of darunavir, ritonavir and cobicistat and the potential for loss of therapeutic effect (see sections 4.4 and 4.5).

Applicable to darunavir boosted with either ritonavir or cobicistat:
- The combination product lopinavir/ritonavir (see section 4.5).
- The strong CYP3A inducers rifampicin and herbal preparations containing St John's wort (Hypericum perforatum). Co-administration is expected to reduce plasma concentrations of darunavir, ritonavir and cobicistat, which could lead to loss of therapeutic effect and possible development of resistance (see sections 4.4 and 4.5).

Applicable to darunavir boosted with cobicistat, not when boosted with ritonavir:
- Darunavir boosted with cobicistat is more sensitive for CYP3A induction than darunavir boosted with ritonavir. Concomitant use with strong CYP3A inducers is contraindicated, since these may reduce the exposure to cobicistat and darunavir leading to loss of therapeutic effect. Strong CYP3A inducers include e.g. carbamazepine, phenobarbital and phenytoin (see sections 4.4 and 4.5).

Darunavir boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the co-administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat). These active substances include e.g.:
- alfuzosin
- amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine
- astemizole, terfenadine
- colchicine when used in patients with renal and/or hepatic impairment (see section
- 4.5)
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- elbasvir/grazoprevir
- cisapride

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– dapoxetine
– domperidone
– naloxegol
– lurasidone, pimozide, quetiapine, sertindole (see section 4.5)
– triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5)
– sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil
– simvastatin, lovastatin and lomitapide (see section 4.5)
– dabigatran, ticagrelor (see section 4.5).

4.4 Special warnings and precautions for use

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

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

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

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

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

ART-experienced patients – once daily dosing

Darunavir used in combination with cobicistat or low dose ritonavir once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10^6/L (see section 4.2). Combinations with optimised background regimen (OBRs) other than ≥ 2 NRTIs have not been studied in this population. Limited data are available in patients with HIV-1 clades other than B (see section 5.1).

Paediatric population

Darunavir is not recommended for use in paediatric patients below 3 years of age or less than 15 kg body weight (see sections 4.2 and 5.3).

Pregnancy

Darunavir/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk.

Caution should be used in pregnant women with concomitant medications which may further decrease darunavir exposure (see sections 4.5 and 5.2).

Treatment with darunavir/cobicistat 800/150 mg once daily during the second and third trimester has been shown to result in low darunavir exposure, with a reduction of around 90% in C_{min} levels (see section 5.2). Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in darunavir exposure may result in virological failure and an increased risk of mother to child transmission of HIV infection. Therefore, therapy with darunavir/cobicistat should not be

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initiated during pregnancy, and women who become pregnant during therapy with darunavir/cobicistat should be switched to an alternative regimen (see sections 4.2 and 4.6). Darunavir given with low dose ritonavir may be considered as an alternative.

Elderly

As limited information is available on the use of darunavir in patients aged 65 and over, caution should be exercised in the administration of darunavir in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy (see sections 4.2 and 5.2).

Severe skin reactions

During the darunavir/ritonavir clinical development program (N=3,063), severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens-Johnson Syndrome has been rarely (< 0.1%) reported, and during post-marketing experience toxic epidermal necrolysis and acute generalised exanthematous pustulosis have been reported. Darunavir should be discontinued immediately if signs or symptoms of severe skin reactions develop. These can include, but are not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

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

Darunavir contains a sulphonamide moiety. Darunavir should be used with caution in patients with a known sulphonamide allergy.

Hepatotoxicity

Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with darunavir. During the darunavir/ritonavir clinical development program (N=3,063), hepatitis was reported in 0.5% of patients receiving combination antiretroviral therapy with darunavir/ritonavir. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

Appropriate laboratory testing should be conducted prior to initiating therapy with darunavir used in combination with cobicistat or low dose 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 used in combination with cobicistat or low dose ritonavir treatment.

If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients using darunavir used in combination with cobicistat or low dose ritonavir, interruption or discontinuation of treatment should be considered promptly.

Patients with coexisting conditions

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

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Renal impairment
No special precautions or dose adjustments for darunavir/ritonavir are required in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis. Therefore, no special precautions or dose adjustments are required in these patients (see sections 4.2 and 5.2). Cobicistat has not been studied in patients receiving dialysis, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients (see section 4.2).

Cobicistat decreases the estimated creatinine clearance due to inhibition of tubular secretion of creatinine. This should be taken into consideration if darunavir with cobicistat is administered to patients in whom the estimated creatinine clearance is used to adjust doses of co-administered medicinal products (see section 4.2 and cobicistat SmPC).

There are currently inadequate data to determine whether co-administration of tenofovir disoproxil and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil without cobicistat.

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

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

Osteonecrosis

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

Immune reconstitution inflammatory syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia caused by Pneumocystis jirovecii (formerly known as Pneumocystis carinii). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. In addition, reactivation of herpes simplex and herpes zoster has been observed in clinical studies with darunavir co-administered with low dose ritonavir.

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

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Interactions with medicinal products
Several of the interaction studies have been performed with darunavir at lower than recommended doses. The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated. For full information on interactions with other medicinal products see section 4.5.

Pharmacokinetic enhancer and concomitant medications
Darunavir has different interaction profiles depending on whether the compound is boosted with ritonavir or cobicistat:

- Darunavir boosted with cobicistat is more sensitive for CYP3A induction: concomitant use of darunavir/cobicistat and strong CYP3A inducers is therefore contraindicated (see section 4.3),and concomitant use with weak to moderate CYP3A inducers is not recommended (see section 4.5). Concomitant use of darunavir/ritonavir and darunavir/cobicistat with lopinavir/ritonavir, rifampicin and herbal products containing St John's wort, Hypericum perforatum, is contraindicated (see section 4.5).
- Unlike ritonavir, cobicistat does not have inducing effects on enzymes or transport proteins (see section 4.5). If switching the pharmacoenhancer from ritonavir to cobicistat, caution is required during the first two weeks of treatment with darunavir/cobicistat, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of ritonavir as a pharmacoenhancer. A dose reduction of the co-administered drug may be needed in these cases.

Efavirenz in combination with boosted darunavir may result in sub-optimal darunavir C_{min}. If efavirenz is to be used in combination with darunavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used. See the Summary of Product Characteristics for Darunavir Krka d.d. 600 mg tablets (see section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

The interaction profile of darunavir may differ depending on whether ritonavir or cobicistat is used as pharmacoenhancer. The recommendations given for concomitant use of darunavir and other medicinal products may therefore differ depending on whether darunavir is boosted with ritonavir or cobicistat (see sections 4.3 and 4.4), and caution is also required during the first time of treatment if switching the pharmacoenhancer from ritonavir to cobicistat (see section 4.4).

Medicinal products that affect darunavir exposure (ritonavir as pharmacoenhancer)

Darunavir and ritonavir are metabolised by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of these compounds and consequently that of darunavir, leading to loss of therapeutic effect and possible development of resistance (see sections 4.3 and 4.4). CYP3A inducers that are contraindicated include rifampicin, St John's wort and lopinavir.

Co-administration of darunavir and ritonavir with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir, which may result in increased plasma concentrations of darunavir and ritonavir. Co-administration with strong CYP3A4 inhibitors is not recommended and caution is warranted, these interactions are described in the interaction table below (e.g. indinavir, azole antifungals like clotrimazole).

Medicinal products that affect darunavir exposure (cobicistat as pharmacoenhancer)

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Darunavir and cobicistat are metabolised by CYP3A, and co-administration with CYP3A inducers may therefore result in subtherapeutic plasma exposure to darunavir. Darunavir boosted with cobicistat is more sensitive to CYP3A induction than ritonavir-boosted darunavir: co-administration of darunavir/cobicistat with medicinal products that are strong inducers of CYP3A (e.g. St John's wort, rifampicin, carbamazepine, phenobarbital, and phenytoin) is contraindicated (see section 4.3). Co-administration of darunavir/cobicistat with weak to moderate CYP3A inducers (e.g. efavirenz, etravirine, nevirapine, fluticasone, and bosentan) is not recommended (see interaction table below).

For co-administration with strong CYP3A4 inhibitors, the same recommendations apply independent of whether darunavir is boosted with ritonavir or with cobicistat (see section above).

Medicinal products that may be affected by darunavir boosted with ritonavir

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

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

Co-administration of boosted darunavir with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect (see the Interaction table below).

The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily. Therefore, darunavir must only be used in combination with a pharmacokinetic enhancer (see sections 4.4 and 5.2).

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

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

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

Medicinal products that may be affected by darunavir boosted with cobicistat

The recommendations for darunavir boosted with ritonavir are adequate also for darunavir boosted with cobicistat with regard to substrates of CYP3A4, CYP2D6, P-glycoprotein, OATP1B1 and OATP1B3 (see contraindications and recommendations presented in the section above). Cobicistat

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150 mg given with darunavir 800 mg once daily enhances darunavir pharmacokinetic parameters in a comparable way to ritonavir (see section 5.2).

Unlike ritonavir, cobicistat does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1. For further information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Interaction table

Interaction studies have only been performed in adults.

Several of the interaction studies (indicated by # in the table below) have been performed at lower than recommended doses of darunavir or with a different dosing regimen (see section 4.2 Posology). The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated.

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer. Darunavir may therefore have different recommendations for concomitant medications depending on whether the compound is boosted with ritonavir or cobicistat. No interaction studies presented in the table have been performed with darunavir boosted with cobicistat. The same recommendations apply, unless specifically indicated. For further information on cobicistat, consult the cobicistat Summary of Product Characteristics.

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 (not determined as "ND").

In the table below the specific pharmacokinetic enhancer is specified when recommendations differ. When the recommendation is the same for darunavir when co-administered with a low dose ritonavir or cobicistat, the term "boosted darunavir" is used.

The below list of examples of drug-drug interactions is not comprehensive and therefore the label of each drug that is co-administered with darunavir should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction** **Geometric mean change (%)**	**Recommendations concerning co-administration**
HIV ANTIRETROVIRALS		
Integrase strand transfer inhibitors		
Dolutegravir	dolutegravir AUC ↓ 22% dolutegravir C_{24h} ↓38% dolutegravir C_{max} ↓ 11% darunavir ↔* * Using cross-study comparisons to historical pharmacokinetic data	Boosted darunavir and dolutegravir can be used without dose adjustment.
Raltegravir	Some clinical studies suggest raltegravir may cause a modest decrease in darunavir plasma concentrations.	At present the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically relevant. Boosted darunavir and raltegravir can be used without dose adjustments.
Nucleo(s/t)ide reverse transcriptase inhibitors (NRTIs)		
Didanosine 400 mg once daily	didanosine AUC ↓ 9% didanosine C_{min} ND	Boosted darunavir and didanosine can be used without dose

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	didanosine C_{max} ↓ 16% darunavir AUC ↔ darunavir C_{min} ↔ darunavir C_{max} ↔	adjustments. Didanosine is to be administered on an empty stomach, thus it should be administered 1 hour before or 2 hours after boosted darunavir given with food.
Tenofovir disoproxil 245 mg once daily	tenofovir AUC ↑ 22% tenofovir C_{min} ↑ 37% tenofovir C_{max} ↑ 24% #darunavir AUC ↑ 21% #darunavir C_{min} ↑ 24% #darunavir C_{max} ↑ 16% (↑ tenofovir from effect on MDR-1 transport in the renal tubules)	Monitoring of renal function may be indicated when boosted darunavir is given in combination with tenofovir disoproxil, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents. Darunavir co-administered with cobicistat lowers the creatinine clearance. Refer to section 4.4 if creatinine clearance is used for dose adjustment of tenofovir disoproxil.
Emtricitabine/tenofovir alafenamide	Tenofovir alafenamide ↔ Tenofovir ↑	The recommended dose of emtricitabine/tenofovir alafenamide is 200/10 mg once daily when used with boosted darunavir.
Abacavir Emtricitabine Lamivudine Stavudine Zidovudine	Not studied. Based on the different elimination pathways of the other NRTIs zidovudine, emtricitabine, stavudine, lamivudine, that are primarily renally excreted, and abacavir for which metabolism is not mediated by CYP450, no interactions are expected for these medicinal compounds and boosted darunavir.	Boosted darunavir can be used with these NRTIs without dose adjustment. Darunavir co-administered with cobicistat lowers the creatinine clearance. Refer to section 4.4 if creatinine clearance is used for dose adjustment of emtricitabine or lamivudine.
Non-nucleo(s/t)ide reverse transcriptase inhibitors (N(t)NRTIs)		
Efavirenz 600 mg once daily	efavirenz AUC ↑ 21% efavirenz C_{min} ↑ 17% efavirenz C_{max} ↑ 15% #darunavir AUC ↓ 13% #darunavir C_{min} ↓ 31% #darunavir C_{max} ↓ 15% (↑ efavirenz from CYP3A inhibition) (↓ darunavir from CYP3A induction)	Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when darunavir co-administered with low dose ritonavir is given in combination with efavirenz. Efavirenz in combination with darunavir /ritonavir 800/100 mg once daily may result in sub-optimal darunavir C_{min}. If efavirenz is to be used in combination with darunavir /ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used (see section 4.4). Co-administration with darunavir co-administered with cobicistat is not recommended (see section 4.4).
Etravirine 100 mg twice daily	etravirine AUC ↓ 37% etravirine C_{min} ↓ 49% etravirine C_{max} ↓ 32% darunavir AUC ↑ 15% darunavir C_{min} ↔ darunavir C_{max} ↔	Darunavir co-administered with low dose ritonavir and etravirine 200 mg twice daily can be used without dose adjustments. Co-administration with darunavir co-administered with cobicistat is not recommended (see section 4.4).
Nevirapine 200 mg twice daily	nevirapine AUC ↑ 27% nevirapine C_{min} ↑ 47% nevirapine C_{max} ↑ 18%	Darunavir co-administered with low dose ritonavir and nevirapine can be used without dose adjustments.

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	#darunavir: concentrations were consistent with historical data (↑ nevirapine from CYP3A inhibition)	Co-administration with darunavir co-administered with cobicistat is not recommended (see section 4.4).
Rilpivirine 150 mg once daily	rilpivirine AUC ↑ 130% rilpivirine C_{min} ↑ 178% rilpivirine C_{max} ↑ 79% darunavir AUC ↔ darunavir C_{min} ↓ 11% darunavir C_{max} ↔	Boosted darunavir and rilpivirine can be used without dose adjustments.
HIV Protease inhibitors (PIs) - without additional co-administration of low dose ritonavir†		
Atazanavir 300 mg once daily	atazanavir AUC ↔ atazanavir C_{min} ↑ 52% atazanavir C_{max} ↓ 11% #darunavir AUC ↔ #darunavir C_{min} ↔ #darunavir C_{max} ↔ Atazanavir: comparison of atazanavir/ritonavir 300/100 mg once daily vs. atazanavir 300 mg once daily in combination with darunavir/ritonavir 400/100 mg twice daily. Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg twice daily in combination with atazanavir 300 mg once daily.	Darunavir co-administered with low dose ritonavir and atazanavir can be used without dose adjustments. Darunavir co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5).
Indinavir 800 mg twice daily	indinavir AUC ↑ 23% indinavir C_{min} ↑ 125% indinavir C_{max} ↔ #darunavir AUC ↑ 24% #darunavir C_{min} ↑ 44% #darunavir C_{max} ↑ 11% Indinavir: comparison of indinavir/ritonavir 800/100 mg twice daily vs. indinavir/darunavir/ritonavir 800/400/100 mg twice daily. Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with indinavir 800 mg twice daily.	When used in combination with darunavir co-administered with low dose ritonavir, dose adjustment of indinavir from 800 mg twice daily to 600 mg twice daily may be warranted in case of intolerance. Darunavir co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5).
Saquinavir 1,000 mg twice daily	#darunavir AUC ↓ 26% #darunavir C_{min} ↓ 42% #darunavir C_{max} ↓ 17% saquinavir AUC ↓ 6% saquinavir C_{min} ↓ 18% saquinavir C_{max} ↓ 6% Saquinavir: comparison of saquinavir/ritonavir 1,000/100 mg twice daily vs. saquinavir/darunavir/ritonavir 1,000/400/100 mg twice daily Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with saquinavir 1,000 mg twice daily.	It is not recommended to combine darunavir co-administered with low dose ritonavir with saquinavir. Darunavir co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5).
HIV Protease inhibitors (PIs) - with co-administration of low dose ritonavir†		
Lopinavir/ritonavir 400/100 mg twice daily	lopinavir AUC ↑ 9% lopinavir C_{min} ↑ 23% lopinavir C_{max} ↓ 2%	Due to a decrease in the exposure (AUC) of darunavir by 40%, appropriate doses of the combination

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Lopinavir/ritonavir 533/133.3 mg twice daily	darunavir AUC ↓ 38%‡ darunavir C_{min} ↓ 51%‡ darunavir C_{max} ↓ 21%‡ lopinavir AUC ↔ lopinavir C_{min} ↑ 13% lopinavir C_{max} ↑ 11% darunavir AUC ↓ 41% darunavir C_{min} ↓ 55% darunavir C_{max} ↓ 21% ‡ based upon non dose normalised values	have not been established. Hence, concomitant use of boosted darunavir and the combination product lopinavir/ritonavir is contraindicated (see section 4.3).
CCR5 ANTAGONIST		
Maraviroc 150 mg twice daily	maraviroc AUC ↑ 305% maraviroc C_{min} ND maraviroc C_{max} ↑ 129% darunavir, ritonavir concentrations were consistent with historical data	The maraviroc dose should be 150 mg twice daily when co-administered with boosted darunavir.
α1-ADRENORECEPTOR ANTAGONIST		
Alfuzosin	Based on theoretical considerations darunavir is expected to increase alfuzosin plasma concentrations. (CYP3A inhibition)	Co-administration of boosted darunavir and alfuzosin is contraindicated (see section 4.3).
ANAESTHETIC		
Alfentanil	Not studied. The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by boosted darunavir.	The concomitant use with boosted darunavir may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.
ANTIANGINA/ANTIARRHYTHMIC		
Disopyramide Flecainide Lidocaine (systemic) Mexiletine Propafenone	Not studied. Boosted darunavir is expected to increase these antiarrhythmic plasma concentrations. (CYP3A and/or CYP2D6 inhibition)	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with boosted darunavir.
Amiodarone Bepridil Dronedarone Ivabradine Quinidine Ranolazine		Co-administration of boosted darunavir and amiodarone, bepridil, dronedarone, ivabradine, quinidine, or ranolazine is contraindicated (see section 4.3).
Digoxin 0.4 mg single dose	digoxin AUC ↑ 61% digoxin C_{min} ND digoxin C_{max} ↑ 29% (↑ digoxin from probable inhibition of P-gp)	Given that digoxin has a narrow therapeutic index, it is recommended that the lowest possible dose of digoxin should initially be prescribed in case digoxin is given to patients on boosted darunavir therapy. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject.
ANTIBIOTIC		
Clarithromycin 500 mg twice daily	clarithromycin AUC ↑ 57% clarithromycin C_{min} ↑ 174% clarithromycin C_{max} ↑ 26% #darunavir AUC ↓ 13% #darunavir C_{min} ↑ 1% #darunavir C_{max} ↓ 17% 14-OH-clarithromycin concentrations were	Caution should be exercised when clarithromycin is combined with boosted darunavir. For patients with renal impairment the Summary of Product Characteristics for clarithromycin should be consulted for the

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	not detectable when combined with darunavir/ritonavir. (↑ clarithromycin from CYP3A inhibition and possible P-gp inhibition)	recommended dose.
ANTICOAGULANT/PLATELET AGGREGATION INHIBITOR		
Apixaban Edoxaban Rivaroxaban	Not studied. Co-administration of boosted darunavir with these anticoagulants may increase concentrations of the anticoagulant, which may lead to an increased bleeding risk. (CYP3A and/or P-gp inhibition)	The use of boosted darunavir and these anticoagulants is not recommended.
Dabigatran Ticagrelor Clopidogrel	Not studied. Co-administration with boosted darunavir may lead to a substantial increase in exposure to dabigatran or ticagrelor. Not studied. Co-administration of clopidogrel with boosted darunavir is expected to decrease clopidogrel active metabolite plasma concentration, which may reduce the antiplatelet activity of clopidogrel	Concomitant administration of boosted darunavir with dabigatran or ticagrelor is contraindicated (see section 4.3). Co-administration of clopidogrel with boosted darunavir 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 boosted darunavir.	It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with boosted darunavir.
ANTICONVULSANTS		
Phenobarbital Phenytoin	Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir and its pharmacoenhancer. (induction of CYP450 enzymes)	Darunavir co-administered with low dose ritonavir should not be used in combination with these medicines. The use of these medicines with darunavir/cobicistat is contraindicated (see section 4.3).
Carbamazepine 200 mg twice daily	carbamazepine AUC ↑ 45% carbamazepine C_{min} ↑ 54% carbamazepine C_{max} ↑ 43% darunavir AUC ↔ darunavir C_{min} ↓ 15% darunavir C_{max} ↔	No dose adjustment for darunavir /ritonavir is recommended. If there is a need to combine darunavir/ritonavir and carbamazepine, patients should be monitored for potential carbamazepine-related adverse events. Carbamazepine concentrations should be monitored and its dose should be titrated for adequate response. Based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of darunavir/ritonavir. The use of carbamazepine with darunavir co-administered with cobicistat is contraindicated (see section 4.3).
Clonazepam	Not studied. Co-administration of boosted darunavir with clonazepam may increase concentrations of clonazepam. (CYP3A inhibition)	Clinical monitoring is recommended when co-administering boosted darunavir with clonazepam.

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ANTIDEPRESSANTS		
Paroxetine 20 mg once daily Sertraline 50 mg once daily Amitriptyline Desipramine Imipramine Nortriptyline Trazodone	paroxetine AUC ↓ 39% paroxetine C_{min} ↓ 37% paroxetine C_{max} ↓ 36% #darunavir AUC ↔ #darunavir C_{min} ↔ #darunavir C_{max} ↔ sertraline AUC ↓ 49% sertraline C_{min} ↓ 49% sertraline C_{max} ↓ 44% #darunavir AUC ↔ #darunavir C_{min} ↓ 6% #darunavir C_{max} ↔ In contrast to these data with darunavir /ritonavir, darunavir/cobicistat may increase these antidepressant plasma concentrations (CYP2D6 and/or CYP3A inhibition). Concomitant use of boosted darunavir and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or CYP3A inhibition)	If antidepressants are co-administered with boosted darunavir, the recommended approach is a dose titration of the antidepressant based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of these antidepressants who start treatment with boosted darunavir should be monitored for antidepressant response. Clinical monitoring is recommended when co-administering boosted darunavir with these antidepressants and a dose adjustment of the antidepressant may be needed.
ANTI-DIABETICS		
Metformin	Not studied. Based on theoretical considerations darunavir co-administered with cobicistat is expected to increase metformin plasma concentrations. (MATE1 inhibition)	Careful patient monitoring and dose adjustment of metformin is recommended in patients who are taking darunavir co-administered with cobicistat. (not applicable for darunavir co-administered with ritonavir)
ANTIEMETICS		
Domperidone	Not studied.	Co-administration of domperidone with boosted darunavir is contraindicated.
ANTIFUNGALS		
Voriconazole	Not studied. Ritonavir may decrease plasma concentrations of voriconazole. (induction of CYP450 enzymes) Concentrations of voriconazole may increase or decrease when co-administered with darunavir co-administered with cobicistat. (inhibition of CYP450 enzymes)	Voriconazole should not be combined with boosted darunavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Fluconazole Isavuconazole Itraconazole Posaconazole Clotrimazole	Not studied. Boosted darunavir may increase antifungal plasma concentrations and posaconazole, isavuconazole, itraconazole or fluconazole may increase darunavir concentrations. (CYP3A and/or P-gp inhibition) Not studied. Concomitant systemic use of clotrimazole and boosted darunavir may increase plasma concentrations of darunavir and/or clotrimazole. darunavir AUC_{24h} ↑ 33% (based on population pharmacokinetic model)	Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of itraconazole should not exceed 200 mg.
ANTIGOUT MEDICINES		

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Colchicine	Not studied. Concomitant use of colchicine and boosted darunavir may increase the exposure to colchicine. (CYP3A and/ or P-gp inhibition)	A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with boosted darunavir is required. For patients with renal or hepatic impairment colchicine with boosted darunavir is contraindicated (see sections 4.3 and 4.4).
ANTIMALARIALS		
Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	artemether AUC ↓ 16% artemether C_{min} ↔ artemether C_{max} ↓ 18% dihydroartemisinin AUC ↓ 18% dihydroartemisinin C_{min} ↔ dihydroartemisinin C_{max} ↓ 18% lumefantrine AUC ↑ 175% lumefantrine C_{min} ↑ 126% lumefantrine C_{max} ↑ 65% darunavir AUC ↔ darunavir C_{min} ↓ 13% darunavir C_{max} ↔	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.
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Not studied. Rifapentine and rifampicin are strong CYP3A inducers and have been shown to cause profound decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction). During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with low dose ritonavir, a high frequency of liver reactions was seen with rifampicin.	The combination of rifapentine and boosted darunavir is not recommended. The combination of rifampicin and boosted darunavir is contraindicated (see section 4.3).
Rifabutin 150 mg once every other day	rifabutin AUC** ↑ 55% rifabutin C_{min}** ↑ ND rifabutin C_{max}** ↔ darunavir AUC ↑ 53% darunavir C_{min} ↑ 68% darunavir C_{max} ↑ 39% ** sum of active moieties of rifabutin (parent drug + 25-*O*-desacetyl metabolite) The interaction trial showed a comparable daily systemic exposure for rifabutin between treatment at 300 mg once daily alone and 150 mg once every other day in combination with darunavir/ritonavir (600/100 mg twice daily) with an about 10-fold increase in the daily exposure to the active metabolite 25-*O*-desacetylrifabutin. Furthermore, AUC of the sum of active moieties of rifabutin (parent drug + 25-*O*-desacetyl metabolite) was increased 1.6-fold, while C_{max} remained comparable. Data on comparison with a 150 mg once daily reference dose is lacking. (Rifabutin is an inducer and substrate of CYP3A.) An increase of systemic exposure to darunavir was observed when darunavir co-administered with 100 mg ritonavir was co-administered with rifabutin (150 mg	A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg once every other day) and increased monitoring for rifabutin related adverse events is warranted in patients receiving the combination with darunavir co-administered with ritonavir. In case of safety issues, a further increase of the dosing interval for rifabutin and/or monitoring of rifabutin levels should be considered. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients. Based upon the safety profile of darunavir/ritonavir, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for darunavir/ritonavir. Based on pharmacokinetic modeling, this dosage reduction of 75% is also applicable if patients receive rifabutin at doses other than 300 mg/day. Co-administration of darunavir co-administered with cobicistat and

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	once every other day).	rifabutin is not recommended.
ANTINEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine Everolimus Irinotecan	Not studied. Boosted darunavir is expected to increase these antineoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when co-administered with boosted darunavir resulting in the potential for increased adverse events usually associated with these agents. Caution should be exercised when combining one of these antineoplastic agents with boosted darunavir. Concomitant use of everolimus or irinotecan and boosted darunavir is not recommended.
ANTIPSYCHOTICS/NEUROLEPTICS		
Quetiapine	Not studied. Boosted darunavir is expected to increase these antipsychotic plasma concentrations. (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 these antipsychotic plasma concentrations. (CYP3A, CYP2D6 and/or P-gp inhibition)	A dose decrease may be needed for these drugs when co-administered with boosted darunavir. Concomitant administration of boosted darunavir and lurasidone, pimozide or sertindole is contraindicated (see section 4.3).
β-BLOCKERS		
Carvedilol Metoprolol Timolol	Not studied. Boosted darunavir is expected to increase these β-blocker plasma concentrations. (CYP2D6 inhibition)	Clinical monitoring is recommended when co-administering boosted darunavir with β-blockers. A lower dose of the β-blocker should be considered.
CALCIUM CHANNEL BLOCKERS		
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Not studied. Boosted darunavir can be expected to increase the plasma concentrations of calcium channel blockers. (CYP3A and/or CYP2D6 inhibition)	Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with boosted darunavir.
CORTICOSTEROIDS		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone)	Fluticasone: in a clinical study where ritonavir 100 mg capsules twice daily were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, fluticasone propionate plasma concentrations increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% CI 82-89%). Greater effects may be expected when fluticasone is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone. The	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. Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid

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	effects of high fluticasone systemic exposure on ritonavir plasma levels are unknown. Other corticosteroids: interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with boosted darunavir, resulting in reduced serum cortisol concentrations.	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 and low dose ritonavir, the patient's tolerability of bosentan should be monitored. Co administration of darunavir co-administered with cobicistat and bosentan is not recommended.
HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS		
NS3-4A protease inhibitors		
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	Based on theoretical considerations, boosted darunavir may increase the exposure to glecaprevir and pibrentasvir. (P-gp, BCRP and/or OATP1B1/3 inhibition)	It is not recommended to co-administer boosted darunavir with glecaprevir/pibrentasvir.
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 (*Hypericum perforatum*) (see section 4.3). If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Darunavir exposure (and also ritonavir exposure) may increase on stopping St John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort.
HMG CO-A REDUCTASE INHIBITORS		
Lovastatin Simvastatin	Not studied. Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with 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 10 mg once daily	atorvastatin AUC ↑ 3-4 fold atorvastatin C_{min} ↑ ≈5.5-10 fold atorvastatin C_{max} ↑ ≈2 fold [#]darunavir/ritonavir	When administration of atorvastatin and boosted darunavir is desired, it is recommended to start with an atorvastatin dose of 10 mg once daily. A gradual dose increase of

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	atorvastatin AUC ↑ 290%[Ω] atorvastatin C_{max} ↑ 319%[Ω] atorvastatin C_{min} ND[Ω] [Ω] with darunavir/cobicistat 800/150 mg	atorvastatin may be tailored to the clinical response.
Pravastatin 40 mg single dose	pravastatin AUC ↑ 81%[¶] pravastatin C_{min} ND pravastatin C_{max} ↑ 63% [¶] an up to five-fold increase was seen in a limited subset of subjects	When administration of pravastatin and boosted darunavir is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effect while monitoring for safety.
Rosuvastatin 10 mg once daily	rosuvastatin AUC ↑ 48%[‖] rosuvastatin C_{max} ↑ 144%[‖] [‖] based on published data with darunavir/ritonavir rosuvastatin AUC ↑ 93%[§] rosuvastatin C_{max} ↑ 277%[§] rosuvastatin C_{min} ND[§] [§] with darunavir/cobicistat 800/150 mg	When administration of rosuvastatin and boosted darunavir is required, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.
OTHER LIPID MODIFYING AGENTS		
Lomitapide	Based on theoretical considerations boosted darunavir is expected to increase the exposure of lomitapide when co-administered. (CYP3A inhibition)	Co-administration is contraindicated (see section 4.3).
H_2-RECEPTOR ANTAGONISTS		
Ranitidine 150 mg twice daily	[#]darunavir AUC ↔ [#]darunavir C_{min} ↔ [#]darunavir C_{max} ↔	Boosted darunavir can be co-administered with H_2-receptor antagonists 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 immunosuppressive agent must be done when co-administration occurs. Concomitant use of everolimus and boosted darunavir is not recommended.
INHALED BETA AGONISTS		
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 result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS / TREATMENT OF OPIOID DEPENDENCE		
Methadone individual dose ranging from 55 mg to 150 mg once daily	R(-) methadone AUC ↓ 16% R(-) methadone C_{min} ↓ 15% R(-) methadone C_{max} ↓ 24% darunavir /cobicistat may, in contrast, increase methadone plasma concentrations (see cobicistat SmPC).	No adjustment of methadone dosage is required when initiating co-administration with boosted darunavir. However, adjustment of the methadone dose may be necessary when concomitantly administered for a longer period of time. Therefore, clinical monitoring is recommended, as maintenance therapy may need to be adjusted in some patients.

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Buprenorphine/naloxone 8/2 mg–16/4 mg once daily	buprenorphine AUC ↓ 11% buprenorphine C_{min} ↔ buprenorphine C_{max} ↓ 8% norbuprenorphine AUC ↑ 46% norbuprenorphine C_{min} ↑ 71% norbuprenorphine C_{max} ↑ 36% naloxone AUC ↔ naloxone C_{min} ND naloxone C_{max} ↔	The clinical relevance of the increase in norbuprenorphine pharmacokinetic parameters has not been established. Dose adjustment for buprenorphine may not be necessary when co-administered with boosted darunavir but a careful clinical monitoring for signs of opiate toxicity is recommended.
Fentanyl Oxycodone Tramadol	Based on theoretical considerations boosted darunavir may increase plasma concentrations of these analgesics. (CYP2D6 and/or CYP3A inhibition)	Clinical monitoring is recommended when co-administering boosted darunavir with these analgesics.
OESTROGEN-BASED CONTRACEPTIVES		
Drospirenone Ethinylestradiol (3 mg/0.02 mg once daily)	drospirenone AUC ↑ 58%[€] drospirenone C_{min} ND[€] drospirenone C_{max} ↑ 15%[€] ethinylestradiol AUC ↓ 30%[€] ethinylestradiol C_{min} ND[€] ethinylestradiol C_{max} ↓ 14%[€] [€] with darunavir/cobicistat	When darunavir is coadministered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalaemia.
Ethinylestradiol Norethindrone 35 µg/1 mg once daily	ethinylestradiol AUC ↓ 44%[β] ethinylestradiol C_{min} ↓ 62%[β] ethinylestradiol C_{max} ↓ 32%[β] norethindrone AUC ↓ 14%[β] norethindrone C_{min} ↓ 30%[β] norethindrone C_{max} ↔[β] [β] with darunavir/ritonavir	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.
OPIOID ANTAGONIST		
Naloxegol	Not studied.	Co-administration of boosted darunavir and naloxegol is contraindicated.
PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS		
For the treatment of erectile dysfunction Avanafil Sildenafil Tadalafil Vardenafil	In an interaction study [#], a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with darunavir and low dose ritonavir.	The combination of avanafil and boosted darunavir is contraindicated (see section 4.3). Concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with boosted darunavir should be done with caution. 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 the treatment of 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-

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		administration of boosted darunavir and sildenafil when used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3). Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with boosted darunavir is not recommended.
PROTON PUMP INHIBITORS		
Omeprazole 20 mg once daily	[#]darunavir AUC ↔ [#]darunavir C_{min} ↔ [#]darunavir C_{max} ↔	Boosted darunavir can be co-administered with proton pump inhibitors without dose adjustments.
SEDATIVES/HYPNOTICS		
Buspirone Clorazepate Diazepam Estazolam Flurazepam Midazolam (parenteral) Zoldipem	Not studied. Sedative/hypnotics are extensively metabolised by CYP3A. Co-administration with boosted darunavir may cause a large increase in the concentration of these medicines.	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 may cause a large increase in the concentration of this benzodiazepine. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.	If parenteral midazolam is co-administered with boosted darunavir, it should be done in an intensive care unit (ICU) or similar setting, which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
Midazolam (oral) Triazolam		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 have been performed at lower than recommended doses of darunavir or with a different dosing regimen (see section 4.2 Posology).

[1] The efficacy and safety of the use of darunavir with 100 mg ritonavir and any other HIV PI (e.g. (fos)amprenavir and tipranavir) has not been established in HIV patients. According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended.

[‡] Study was conducted with tenofovir disoproxil fumarate 300 mg once daily.

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4.6 Fertility, pregnancy and lactation

Pregnancy

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

There are no adequate and well controlled studies on pregnancy outcome with darunavir in pregnant women. Studies in animals do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Darunavir co-administered with low dose ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk.

Treatment with darunavir/cobicistat 800/150 mg 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 darunavir/cobicistat should not be initiated during pregnancy, and women who become pregnant during therapy with darunavir/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. Because of both the potential for HIV transmission and the potential for adverse reactions in breast-fed infants, mothers should be instructed not to breast-feed under any circumstances if they are receiving Darunavir Krka d.d..

Fertility

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

4.7 Effects on ability to drive and use machines

Darunavir in combination with cobicistat or ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing darunavir co-administered with cobicistat or low dose ritonavir and should be borne in mind when considering a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

During the clinical development program (N=2,613 treatment-experienced subjects who initiated therapy with darunavir/ritonavir 600/100 mg twice daily), 51.3% of subjects experienced at least one adverse reaction. The total mean treatment duration for subjects was 95.3 weeks. The most frequent adverse reactions reported in clinical trials and as spontaneous reports are diarrhoea, nausea, rash, headache and vomiting. The most frequent serious reactions are acute renal failure, myocardial infarction, immune reconstitution inflammatory syndrome, thrombocytopenia, osteonecrosis, diarrhoea, hepatitis and pyrexia.

In the 96 week analysis, the safety profile of darunavir/ritonavir 800/100 mg once daily in treatment-naïve subjects was similar to that seen with darunavir/ritonavir 600/100 mg twice daily in treatment-experienced subjects except for nausea which was observed more frequently in treatment-naïve subjects. This was driven by mild intensity nausea. No new safety findings were identified in the 192 week analysis of the treatment-naïve subjects in which the mean treatment duration of darunavir/ritonavir 800/100 mg once daily was 162.5 weeks.

During the Phase III clinical trial GS-US-216-130 with darunavir/cobicistat (N=313 treatment-naïve and treatment-experienced subjects), 66.5% of subjects experienced at least one adverse reaction. The mean treatment duration was 58.4 weeks. The most frequent adverse reactions reported were diarrhoea (28%), nausea (23%), and rash (16%). Serious adverse reactions are diabetes mellitus, (drug)

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hypersensitivity, immune reconstitution inflammatory syndrome, rash and vomiting.

For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Tabulated list of adverse reactions

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

Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing

MedDRA system organ class Frequency category	Adverse reaction
Infections and infestations	
uncommon	herpes simplex
Blood and lymphatic system disorders	
uncommon	thrombocytopenia, neutropenia, anaemia, leukopenia
rare	increased eosinophil count
Immune system disorders	
uncommon	immune reconstitution inflammatory syndrome, (drug) hypersensitivity
Endocrine disorders	
uncommon	hypothyroidism, increased blood thyroid stimulating hormone
Metabolism and nutrition disorders	
common	diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia
uncommon	gout, anorexia, decreased appetite, decreased weight, increased weight, hyperglycaemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase
Psychiatric disorders	
common	insomnia
uncommon	depression, disorientation, anxiety, sleep disorder, abnormal dreams, nightmare, decreased libido
rare	confusional state, altered mood, restlessness
Nervous system disorders	
common	headache, peripheral neuropathy, dizziness
uncommon	lethargy, paraesthesia, hypoaesthesia, dysgeusia, disturbance in attention, memory impairment, somnolence
rare	syncope, convulsion, ageusia, sleep phase rhythm disturbance
Eye disorders	
uncommon	conjunctival hyperaemia, dry eye
rare	visual disturbance
Ear and labyrinth disorders	
uncommon	vertigo
Cardiac disorders	

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uncommon	myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia
rare	acute myocardial infarction, sinus bradycardia, palpitations
Vascular disorders	
uncommon	hypertension, flushing
Respiratory, thoracic and mediastinal disorders	
uncommon	dyspnoea, cough, epistaxis, throat irritation
rare	rhinorrhoea
Gastrointestinal disorders	
very common	diarrhoea
common	vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence
uncommon	pancreatitis, gastritis, gastrooesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia
rare	stomatitis, haematemesis, cheilitis, dry lip, coated tongue
Hepatobiliary disorders	
common	increased alanine aminotransferase
uncommon	hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-glutamyltransferase
Skin and subcutaneous tissue disorders	
common	rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus
uncommon	angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation
rare	DRESS, Stevens-Johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma
not known	toxic epidermal necrolysis, acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	
uncommon	myalgia, osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphokinase
rare	musculoskeletal stiffness, arthritis, joint stiffness
Renal and urinary disorders	
uncommon	acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria
rare	decreased creatinine renal clearance
Reproductive system and breast disorders	
uncommon	erectile dysfunction, gynaecomastia
General disorders and administration site conditions	
common	asthenia, fatigue
uncommon	pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain

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rare	chills, abnormal feeling, xerosis

Adverse reactions observed with darunavir/cobicistat in adult patients

MedDRA system organ class Frequency category	Adverse reaction
Immune system disorders	
common	(drug) hypersensitivity
uncommon	immune reconstitution inflammatory syndrome
Metabolism and nutrition disorders	
common	anorexia, diabetes mellitus, hypercholesterolaemia, hypertriglyceridaemia, hyperlipidaemia
Psychiatric disorders	
common	abnormal dreams
Nervous system disorders	
very common	headache
Gastrointestinal disorders	
very common	diarrhoea, nausea
common	vomiting, abdominal pain, abdominal distension, dyspepsia, flatulence, pancreatic enzymes increased
uncommon	pancreatitis acute
Hepatobiliary disorders	
common	hepatic enzyme increased
uncommon	hepatitis*, cytolytic hepatitis*
Skin and subcutaneous tissue disorders	
very common	rash (including macular, maculopapular, papular, erythematous, pruritic rash, generalised rash, and allergic dermatitis)
common	angioedema, pruritus, urticaria
rare	drug reaction with eosinophilia and systemic symptoms*, Stevens-Johnson syndrome*
not known	toxic epidermal necrolysis*, acute generalised exanthematous pustulosis*
Musculoskeletal and connective tissue disorders	
common	myalgia
uncommon	osteonecrosis*
Reproductive system and breast disorders	
uncommon	gynaecomastia*
General disorders and administration site conditions	
common	fatigue
uncommon	asthenia
Investigations	
common	increased blood creatinine

* these adverse drug reactions have not been reported in clinical trial experience with darunavir/cobicistat but have been noted with darunavir/ritonavir treatment and could be expected with darunavir/cobicistat too.

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Description of selected adverse reactions

Rash
In clinical trials, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In cases of severe skin reaction see the warning in section 4.4. In a single arm trial investigating darunavir 800 mg once daily in combination with cobicistat 150 mg once daily and other antiretrovirals 2.2% of patients discontinued treatment due to rash.

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

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

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

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

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

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

Paediatric population
The safety assessment of darunavir with ritonavir in paediatric patients is based on the 48-week analysis of safety data from three Phase II trials. The following patient populations were evaluated (see section 5.1):

- 80 ART-experienced HIV-1 infected paediatric patients aged from 6 to 17 years and weighing at least 20 kg who received darunavir tablets with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 21 ART-experienced HIV-1 infected paediatric patients aged from 3 to < 6 years and weighing 10 kg to < 20 kg (16 participants from 15 kg to < 20 kg) who received darunavir oral suspension with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 12 ART-naïve HIV-1 infected paediatric patients aged from 12 to 17 years and weighing at least 40 kg who received darunavir tablets with low dose ritonavir once daily in combination with other antiretroviral agents (see section 5.1).

Overall, the safety profile in these paediatric patients was similar to that observed in the adult population.

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The safety assessment of darunavir with cobicistat in paediatric patients was evaluated in adolescents aged 12 to less than 18 years, weighing at least 40 kg through the clinical trial GS-US-216-0128 (treatment-experienced, virologically suppressed, N=7). Safety analyses of this study in adolescent subjects did not identify new safety concerns compared to the known safety profile of darunavir and cobicistat in adult subjects.

Other special populations

Patients co-infected with hepatitis B and/or hepatitis C virus

Among 1,968 treatment-experienced patients receiving darunavir co-administered with ritonavir 600/100 mg twice daily, 236 patients were co-infected with hepatitis B or C. Co-infected patients were more likely to have baseline and treatment emergent hepatic transaminase elevations than those without chronic viral hepatitis (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Human experience of acute overdose with darunavir co-administered with cobicistat or low dose ritonavir is limited. Single doses up to 3,200 mg of darunavir as oral solution alone and up to 1,600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Antiviral activity *in vitro*

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

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

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Resistance

In vitro selection of darunavir-resistant virus from wild type HIV-1 was lengthy (> 3 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23-50-fold) harboured 2 to 4 amino acid substitutions in the protease gene. The decreased susceptibility to darunavir of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations.

The clinical trial data from ART-experienced patients (*TITAN* trial and the pooled analysis of the *POWER* 1, 2 and 3 and *DUET* 1 and 2 trials) showed that virologic response to darunavir co-administered with low dose ritonavir was decreased when 3 or more darunavir RAMs (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) were present at baseline or when these mutations developed during treatment.

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

Viruses isolated from patients on darunavir/ritonavir 600/100 mg twice daily experiencing virologic failure by rebound that were susceptible to tipranavir at baseline remained susceptible to tipranavir after treatment in the vast majority of cases.

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

The table below shows the development of HIV-1 protease mutations and loss of susceptibility to PIs in virologic failures at endpoint in the *ARTEMIS*, *ODIN* and *TITAN* trials.

	ARTEMIS Week 192	ODIN Week 48		TITAN Week 48
	Darunavir/ritonavir 800/100 mg once daily N=343	Darunavir/ritonavir 800/100 mg once daily N=294	darunavir/ritonavir 600/100 mg twice daily N=296	darunavir/ritonavir 600/100 mg twice daily N=298
Total number of virologic failures[a], n (%)	55 (16.0%)	65 (22.1%)	54 (18.2%)	31 (10.4%)
Rebounders	39 (11.4%)	11 (3.7%)	11 (3.7%)	16 (5.4%)
Never suppressed subjects	16 (4.7%)	54 (18.4%)	43 (14.5%)	15 (5.0%)
Number of subjects with virologic failure and paired baseline/endpoint genotypes, developing mutations[b] at endpoint, n/N				
Primary (major) PI mutations	0/43	1/60	0/42	6/28
PI RAMs	4/43	7/60	4/42	10/28
Number of subjects with virologic failure and paired baseline/endpoint phenotypes, showing loss of susceptibility to PIs at endpoint compared to baseline, n/N				
PI				
darunavir	0/39	1/58	0/41	3/26
amprenavir	0/39	1/58	0/40	0/22
atazanavir	0/39	2/56	0/40	0/22
indinavir	0/39	2/57	0/40	1/24
lopinavir	0/39	1/58	0/40	0/23

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saquinavir	0/39	0/56	0/40	0/22
tipranavir	0/39	0/58	0/41	1/25

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

Low rates of developing resistant HIV-1 virus were observed in ART-naïve patients who are treated for the first time with darunavir/cobicistat once daily in combination with other ART, and in ART-experienced patients with no darunavir RAMs receiving darunavir/cobicistat in combination with other ART. The table below shows the development of HIV-1 protease mutations and resistance to PIs in virologic failures at endpoint in the GS-US-216-130 trial.

	GS-US-216-130 Week 48	
	Treatment-naïve darunavir/cobicistat 800/150 mg once daily N=295	Treatment-experienced darunavir/cobicistat 800/150 mg once daily N=18
Number of subjects with virologic failure[a] and genotype data that develop mutations[b] at endpoint, n/N		
Primary (major) PI mutations	0/8	1/7
PI RAMs	2/8	1/7
Number of subjects with virologic failure[a] and phenotype data that show resistance to PIs at endpoint[c], n/N		
HIV PI		
darunavir	0/8	0/7
amprenavir	0/8	0/7
atazanavir	0/8	0/7
indinavir	0/8	0/7
lopinavir	0/8	0/7
saquinavir	0/8	0/7
tipranavir	0/8	0/7

[a] Virogic failures were defined as: never suppressed: confirmed HIV-1 RNA < 1 $\log_{10}$ reduction from baseline and ≥ 50 copies/ml at the week-8; rebound: HIV-1 RNA ≥ 50 copies/ml followed by confirmed HIV-1 RNA to ≥ 400 copies/ml or confirmed > 1 $\log_{10}$ HIV-1 RNA increase from the nadir; discontinuations with HIV-1 RNA ≥ 400 copies/ml at last visit
[b] IAS-USA lists
[c] In GS-US216-130 baseline phenotype was not available

Cross-resistance
Darunavir FC was less than 10 for 90% of 3,309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to most PIs remain susceptible to darunavir.

In the virologic failures of the *ARTEMIS* trial no cross-resistance with other PIs was observed.
In the virologic failures of the GS-US-216-130 trial no cross-resistance with other HIV PIs was observed.

Clinical results
The pharmacokinetic enhancing effect of cobicistat on darunavir was evaluated in a Phase I study in healthy subjects that were administered darunavir 800 mg with either cobicistat at 150 mg or ritonavir at 100 mg once daily. The steady-state pharmacokinetic parameters of darunavir were comparable when boosted with cobicistat versus ritonavir. For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Adult patients

Efficacy of darunavir 800 mg once daily co-administered with 150 mg cobicistat once daily in ART-

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naïve and ART-experienced patients

GS-US-216-130 is a single arm, open-label, Phase III trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with cobicistat in 313 HIV-1 infected adult patients (295 treatment-naïve and 18 treatment-experienced). These patients received darunavir 800 mg once daily in combination with cobicistat 150 mg once daily with an investigator selected background regimen consisting of 2 active NRTIs.

HIV-1 infected patients who were eligible for this trial had a screening genotype showing no darunavir RAMs and plasma HIV-1 RNA ≥ 1,000 copies/ml. The table below shows the efficacy data of the 48 week analyses from the GS-US-216-130 trial:

	GS-US-216-130		
Outcomes at Week 48	Treatment-naïve darunavir/cobicistat 800/150 mg once daily + OBR N=295	Treatment-experienced darunavir/cobicistat 800/150 mg once daily + OBR N=18	All subjects darunavir/cobicistat 800/150 mg once daily + OBR N=313
HIV-1 RNA < 50 copies/ml[a]	245 (83.1%)	8 (44.4%)	253 (80.8%)
mean HIV-1 RNA log change from baseline (log_{10} copies/ml)	-3.01	-2.39	-2.97
CD4+ cell count mean change from baseline[b]	+174	+102	+170

[a] Imputations according to the TLOVR algorithm
[b] Last Observation Carried Forward imputation

Efficacy of darunavir 800 mg once daily co-administered with 100 mg ritonavir once daily in ART-naïve patients

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

The table below shows the efficacy data of the 48 week and 96 week analyses from the *ARTEMIS* trial:

ARTEMIS						
	Week 48[a]			Week 96[b]		
Outcomes	Darunavir/ritonavir 800/100 mg once daily N=343	Lopinavir/ ritonavir 800/200 mg per day N=346	Treatment difference (95% CI of difference)	Darunavir/ritonavir 800/100 mg once daily N=343	Lopinavir/ ritonavir 800/200 mg per day N=346	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[c] All patients	83.7% (287)	78.3% (271)	5.3% (-0.5; 11.2)[d]	79.0% (271)	70.8% (245)	8.2% (1.7; 14.7)[d]
With baseline HIV-RNA < 100,000	85.8% (194/226)	84.5% (191/226)	1.3% (-5.2; 7.9)[d]	80.5% (182/226)	75.2% (170/226)	5.3% (-2.3; 13.0)[d]
With baseline HIV-RNA ≥ 100,000	79.5% (93/117)	66.7% (80/120)	12.8% (1.6; 24.1)[d]	76.1% (89/117)	62.5% (75/120)	13.6% (1.9; 25.3)[d]
With baseline CD4+ cell count < 200	79.4% (112/141)	70.3% (104/148)	9.2% (-0.8; 19.2)[d]	78.7% (111/141)	64.9% (96/148)	13.9% (3.5; 24.2)[d]

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With baseline CD4+ cell count ≥ 200	86.6% (175/202)	84.3% (167/198)	2.3% (-4.6; 9.2)[d]	79.2% (160/202)	75.3% (149/198)	4.0% (-4.3; 12.2)[d]
median CD4+ cell count change from baseline (x 10^6/L)[e]	137	141		171	188	

[a] Data based on analyses at week 48
[b] Data based on analyses at week 96
[c] Imputations according to the TLOVR algorithm
[d] Based on normal approximation to the difference in % response
[e] Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0

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, was demonstrated (at the pre-defined 12% non-inferiority margin) for both Intent-To-Treat (ITT) and On Protocol (OP) populations in the 48 week analysis. These results were confirmed in the analyses of data at 96 weeks of treatment in the *ARTEMIS* trial. These results were sustained up to 192 weeks of treatment in the ARTEMIS trial.

Efficacy of darunavir 800 mg once daily co-administered with 100 mg ritonavir once daily in ART-experienced patients

ODIN is a Phase III, randomised, open-label trial comparing darunavir/ritonavir 800/100 mg once daily versus darunavir/ritonavir 600/100 mg twice daily in ART-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMS (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a screening HIV-1 RNA > 1,000 copies/ml. Efficacy analysis is based on 48 weeks of treatment (see table below). Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs.

ODIN			
Outcomes	Darunavir/ritonavir 800/100 mg once daily + OBR N=294	Darunavir/ritonavir 600/100 mg twice daily + OBR N=296	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[a]	72.1% (212)	70.9% (210)	1.2% (-6.1; 8.5)[b]
With Baseline HIV-1 RNA (copies/ml) < 100,000 ≥ 100,000	 77.6% (198/255) 35.9% (14/39)	 73.2% (194/265) 51.6% (16/31)	 4.4% (-3.0; 11.9) -15.7% (-39.2; 7.7)
With Baseline CD4+ cell count (x 10^6/L) ≥ 100 < 100	 75.1% (184/245) 57.1% (28/49)	 72.5% (187/258) 60.5% (23/38)	 2.6% (-5.1; 10.3) -3.4% (-24.5; 17.8)
With HIV-1 clade Type B Type AE Type C Other[c]	 70.4% (126/179) 90.5% (38/42) 72.7% (32/44) 55.2% (16/29)	 64.3% (128/199) 91.2% (31/34) 78.8% (26/33) 83.3% (25/30)	 6.1% (-3.4; 15.6) -0.7% (-14.0; 12.6) -6.1% (-2.6; 13.7) -28.2% (-51.0; -5.3)
Mean CD4+ cell count change from baseline (x 10^6/L)[e]	108	112	-5[d] (-25; 16)

[a] Imputations according to the TLOVR algorithm
[b] Based on a normal approximation of the difference in % response
[c] Clades A1, D, F1, G, K, CRF02_AG, CRF12_BF, and CRF06_CPX
[d] Difference in means
[e] Last Observation Carried Forward imputation

At 48 weeks, virologic response, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/ml, with darunavir/ritonavir 800/100 mg once daily treatment was demonstrated to be non-inferior (at the pre-defined 12% non-inferiority margin) compared to darunavir/ritonavir 600/100

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mg twice daily for both ITT and OP populations.

Darunavir/ritonavir 800/100 mg once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10^6/L (see section 4.2 and 4.4). Limited data is available in patients with HIV-1 clades other than B.

Paediatric patients

ART-naïve paediatric patients from the age of 12 years to < 18 years, and weighing at least 40 kg
DIONE is an open-label, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with low dose ritonavir in 12 ART-naïve HIV-1 infected paediatric patients aged 12 to less than 18 years and weighing at least 40 kg. These patients received darunavir/ritonavir 800/100 mg once daily in combination with other antiretroviral agents. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 $\log_{10}$ versus baseline.

DIONE	
Outcomes at week 48	Darunavir/ritonavir N=12
HIV-1 RNA < 50 copies/ml[a]	83.3% (10)
CD4+ percent change from baseline[b]	14
CD4+ cell count mean change from baseline[b]	221
≥ 1.0 $\log_{10}$ decrease from baseline in plasma viral load	100%

[a] Imputations according to the TLOVR algorithm.
[b] Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0.

In the open-label, Phase II/III trial GS-US-216-0128, the efficacy, safety, and pharmacokinetics of darunavir 800 mg and cobicistat 150 mg (administered as separate tablets) and at least 2 NRTIs were evaluated in 7 HIV-1 infected, treatment-experienced, virologically suppressed adolescents weighing at least 40 kg. Patients were on a stable antiretroviral regimen (for at least 3 months), consisting of darunavir administered with ritonavir, combined with 2 NRTIs. They were switched from ritonavir to cobicistat 150 mg once daily and continued darunavir (N=7) and 2 NRTIs.

Virologic outcome in ART-experienced, virologically suppressed adolescents at week 48	
GS-US-216-0128	
Outcomes at Week 48	Darunavir/cobicistat + at least 2 NRTIs (N=7)
HIV-1 RNA < 50 copies/mL per FDA Snapshot Approach	85.7% (6)
CD4+ percent median change from baseline[a]	-6.1%
CD4+ cell count median change from baseline[a]	-342 cells/mm³

[a] No imputation (observed data).

For additional clinical study results in ART-experienced adults and paediatric patients, refer to the Summary of Product Characteristics for Darunavir Krka d.d. 600 mg tablets.

Pregnancy and postpartum
Darunavir/ritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 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 subjects who stayed on the antiretroviral treatment through delivery. There were no new clinically relevant safety findings compared with the known safety profile of darunavir/ritonavir in HIV-1 infected adults (see sections 4.2, 4.4 and 5.2).

5.2 Pharmacokinetic properties

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The pharmacokinetic properties of darunavir, co-administered with cobicistat or ritonavir, have been evaluated in healthy adult volunteers and in HIV-1 infected patients. Exposure to darunavir was higher in HIV-1 infected patients than in healthy subjects. The increased exposure to darunavir in HIV-1 infected patients compared to healthy subjects may be explained by the higher concentrations of α_1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG and, therefore, higher plasma concentrations.

Darunavir is primarily metabolised by CYP3A. Cobicistat and ritonavir inhibit CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

For information on cobicistat pharmacokinetic properties, consult the cobicistat Summary of Product Characteristics.

Absorption
Darunavir was rapidly absorbed following oral administration. Maximum plasma concentration of darunavir in the presence of low dose ritonavir is generally achieved within 2.5-4.0 hours.

The absolute oral bioavailability of a single 600 mg dose of darunavir alone was approximately 37% and increased to approximately 82% in the presence of 100 mg twice daily ritonavir. The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily (see section 4.4).

When administered without food, the relative bioavailability of darunavir in the presence of cobicistat or low dose ritonavir is lower as compared to intake with food. Therefore, darunavir tablets should be taken with cobicistat or ritonavir and with food. The type of food does not affect exposure to darunavir.

Distribution
Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma α_1-acid glycoprotein.

Following intravenous administration, the volume of distribution of darunavir alone was 88.1 ± 59.0 l (Mean ± SD) and increased to 131 ± 49.9 l (Mean ± SD) in the presence of 100 mg twice-daily ritonavir.

Biotransformation
In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolised by the hepatic CYP system and almost exclusively by isozyme CYP3A4. A ^{14}C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir with ritonavir dose was due to the parent active substance. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 10-fold less than the activity of darunavir against wild type HIV.

Elimination
After a 400/100 mg ^{14}C-darunavir with ritonavir dose, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir could be retrieved in faeces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in faeces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir.
The intravenous clearance of darunavir alone (150 mg) and in the presence of low dose ritonavir was 32.8 l/h and 5.9 l/h, respectively.

Special populations

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Paediatric population
The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 74 treatment-experienced paediatric patients, aged 6 to 17 years and weighing at least 20 kg, showed that the administered weight-based doses of darunavir /ritonavir resulted in darunavir exposure comparable to that in adults receiving darunavir /ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 14 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 15 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving darunavir /ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 12 ART-naïve paediatric patients, aged 12 to < 18 years and weighing at least 40 kg, showed that darunavir /ritonavir 800/100 mg once daily results in darunavir exposure that was comparable to that achieved in adults receiving darunavir /ritonavir 800/100 mg once daily. Therefore the same once daily dosage may be used in treatment-experienced adolescents aged 12 to < 18 years and weighing at least 40 kg without darunavir resistance associated mutations (DRV-RAMs)* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/L (see section 4.2).
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 10 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 14 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving darunavir/ritonavir 800/100 mg once daily (see section 4.2). In addition, pharmacokinetic modeling and simulation of darunavir exposures in paediatric patients across the ages of 3 to < 18 years confirmed the darunavir exposures as observed in the clinical studies and allowed the identification of weight-based darunavir/ritonavir once daily dosing regimens for paediatric patients weighing at least 15 kg that are either ART-naïve or treatment-experienced paediatric patients without DRV-RAMs* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/L (see section 4.2).
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The pharmacokinetics of darunavir 800 mg co-administered with cobicistat 150 mg in paediatric patients have been studied in 7 adolescents aged 12 to less than 18 years, weighing at least 40 kg in Study GS-US-216-0128. The geometric mean adolescent exposure (AUC_{tau}) was similar for darunavir and increased 19% for cobicistat compared to exposures achieved in adults who received darunavir 800 mg co-administered with cobicistat 150 mg in Study GS-US-216-0130. The difference observed for cobicistat was not considered clinically relevant.

	Adults in Study GS-US-216-0130, week 24 (Reference)[a] Mean (%CV) GLSM	**Adolescents in Study GS-US-216-0128, day 10 (Test)[b] Mean (%CV) GLSM**	**GLSM Ratio (90% CI) (Test/Reference)**
N	60[c]	7	
DRV PK Parameter			
AUC_{tau} (h.ng/mL)[d]	81,646 (32.2) 77,534	80,877 (29.5) 77,217	1.00 (0.79-1.26)
C_{max} (ng/mL)	7,663 (25.1) 7,422	7,506 (21.7) 7,319	0.99 (0.83-1.17)
C_{tau} (ng/mL)[d]	1,311 (74.0) 947	1,087 (91.6) 676	0.71 (0.34-1.48)

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COBI PK Parameter			
AUC_{tau} (h.ng/mL)[d]	7,596 (48.1) 7,022	8,741 (34.9) 8,330	1.19 (0.95-1.48)
C_{max} (ng/mL)	991 (33.4) 945	1,116 (20.0) 1,095	1.16 (1.00-1.35)
C_{tau} (ng/mL)[d]	32.8 (289.4) 17.2[e]	28.3 (157.2) 22.0[e]	1.28 (0.51-3.22)

[a] Week 24 intensive PK data from subjects who received DRV 800 mg + COBI 150 mg.

[b] Day 10 intensive PK data from subjects who received DRV 800 mg + COBI 150 mg.

[c] N=59 for AUC_{tau} and C_{tau}.

[d] Concentration at predose (0 hours) was used as surrogate for concentration at 24 hours for the purposes of estimating AUC_{tau} and C_{tau} in Study GS-US-216-0128.

[e] N=57 and N=5 for GLSM of C_{tau} in Study GS-US-216-0130 and Study GS-US-216-0128, respectively.

Elderly
Population pharmacokinetic analysis in HIV infected patients showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV infected patients (n=12, age ≥ 65) (see section 4.4). However, only limited data were available in patients above the age of 65 year.

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

Renal impairment
Results from a mass balance study with ^{14}C-darunavir with ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine unchanged.
Although darunavir has not been studied in patients with renal impairment, population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected patients with moderate renal impairment (CrCl between 30-60 ml/min, n=20) (see sections 4.2 and 4.4).

Hepatic impairment
Darunavir is primarily metabolised and eliminated by the liver. In a multiple dose study with darunavir co-administered with ritonavir (600/100 mg) twice daily, it was demonstrated that the total plasma concentrations of darunavir in subjects with mild (Child-Pugh Class A, n=8) and moderate (Child-Pugh Class B, n=8) hepatic impairment were comparable with those in healthy subjects. However, unbound darunavir concentrations were approximately 55% (Child-Pugh Class A) and 100% (Child-Pugh Class B) higher, respectively. The clinical relevance of this increase is unknown therefore, darunavir should be used with caution. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see sections 4.2, 4.3 and 4.4).

Pregnancy and postpartum
The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 600/100 mg twice daily and darunavir/ritonavir 800/100 mg once daily as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum. However, for unbound (i.e. active) darunavir, the pharmacokinetic parameters were less reduced during pregnancy compared to postpartum, due to an increase in the unbound fraction of darunavir during pregnancy compared to postpartum.

Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 600/100 mg twice daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum			
Pharmacokinetics of total darunavir (mean ± SD)	Second trimester of pregnancy (n=12)[a]	Third trimester of pregnancy (n=12)	Postpartum (6-12 weeks) (n=12)

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C_{max}, ng/ml	4,668 ± 1,097	5,328 ± 1,631	6,659 ± 2,364
AUC_{12h}, ng.h/ml	39,370 ± 9,597	45,880 ± 17,360	56,890 ± 26,340
C_{min}, ng/ml	1,922 ± 825	2,661 ± 1,269	2,851 ± 2,216

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

Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 800/100 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum			
Pharmacokinetics of total darunavir (mean ± SD)	Second trimester of pregnancy (n=17)	Third Trimester of pregnancy (n=15)	Postpartum (6-12 weeks) (n=16)
C_{max}, ng/ml	4,964 ± 1,505	5,132 ± 1,198	7,310 ± 1,704
AUC_{24h}, ng.h/ml	62,289 ± 16,234	61,112 ± 13,790	92,116 ± 29,241
C_{min}, ng/ml	1,248 ± 542	1,075 ± 594	1,473 ± 1,141

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

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

Treatment with darunavir/cobicistat 800/150 mg once daily during pregnancy results in low darunavir exposure. In women receiving darunavir/cobicistat during the second trimester of pregnancy, mean intra-individual values for total darunavir C_{max}, AUC_{24h} and C_{min} were 49%, 56% and 92% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir C_{max}, AUC_{24h} and C_{min} values were 37%, 50% and 89% lower, respectively, as compared with postpartum. The unbound fraction was also substantially reduced, including around 90% reductions of C_{min} levels. The main cause of these low exposures is a marked reduction in cobicistat exposure as a consequence of pregnancy-associated enzyme induction (see below).

Pharmacokinetic results of total darunavir after administration of darunavir/cobicistat 800/150 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy, and postpartum			
Pharmacokinetics of total darunavir (mean ± SD)	**Second trimester of pregnancy (n=7)**	**Third trimester of pregnancy (n=6)**	**Postpartum (6-12 weeks) (n=6)**
C_{max}, ng/mL	4,340 ± 1,616	4,910 ± 970	7,918 ± 2,199
AUC_{24h}, ng.h/mL	47,293 ± 19,058	47,991 ± 9,879	99,613 ± 34,862
C_{min}, ng/mL	168 ± 149	184 ± 99	1,538 ± 1,344

The exposure to cobicistat was lower during pregnancy, potentially leading to suboptimal boosting of darunavir. During the second trimester of pregnancy, cobicistat C_{max}, AUC_{24h}, and C_{min} were 50%, 63%, and 83% lower, respectively, as compared with postpartum. During the third trimester of pregnancy, cobicistat C_{max}, AUC_{24h}, and C_{min}, were 27%, 49%, and 83% lower, respectively, as compared with postpartum.

5.3 Preclinical safety data

Animal toxicology studies have been conducted at exposures up to clinical exposure levels with

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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*

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micronucleus test in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose, microcrystalline
Crospovidone
Hydroxypropylcellulose
Silica, colloidal anhydrous
Silicified microcrystalline cellulose (Cellulose, microcrystalline; Silica, colloidal anhydrous)
Magnesium stearate (E470b)

Film coating:

Poly(vinyl alcohol)
Macrogol
Titanium dioxide (E171)
Talc (E553b)
Iron oxide, yellow (E172) – *only for 400 mg film-coated tablets*
Iron oxide, red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Shelf life after first opening: 3 months.

6.4 Special precautions for storage

Keep the bottle tightly closed in order to protect from moisture.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

400 mg film-coated tablets:
Bottle (HDPE), child resistant tamper evident PP closure with a desiccant:
- 30 tablets: 1 bottle of 30 film-coated tablets,
- 60 tablets: 2 bottles of 30 film-coated tablets,
- 90 tablets: 3 bottles of 30 film-coated tablets,
- 180 tablets: 6 bottles of 30 film-coated tablets.

800 mg film-coated tablets:
Bottle (HDPE), child resistant tamper evident PP closure with a desiccant:
- 30 tablets: 1 bottle of 30 film-coated tablets,
- 90 tablets: 3 bottles of 30 film-coated tablets.

Not all pack sizes may be marketed.

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6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

400 mg film-coated tablets:

30 film-coated tablets: EU/1/17/1248/001
60 film-coated tablets: EU/1/17/1248/002
90 film-coated tablets: EU/1/17/1248/003
180 film-coated tablets: EU/1/17/1248/004

800 mg film-coated tablets:

30 film-coated tablets: EU/1/17/1248/009
90 film-coated tablets: EU/1/17/1248/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 January 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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1. NAME OF THE MEDICINAL PRODUCT

Darunavir Krka d.d. 600 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg darunavir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Orangish brown, oval, biconvex film-coated tablets, engraved with a mark S2 on one side. Tablet dimension: 19.5 x 10 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Darunavir Krka d.d., co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection (see section 4.2).

Darunavir Krka d.d. 600 mg tablets may be used to provide suitable dose regimens (see section 4.2):

- For the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced adult patients, including those that have been highly pre-treated.
- For the treatment of HIV-1 infection in paediatric patients from the age of 3 years and at least 15 kg body weight.

In deciding to initiate treatment with darunavir co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of darunavir (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a healthcare provider experienced in the management of HIV infection. After therapy with darunavir has been initiated, patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their healthcare provider.

Posology

Darunavir must always be given orally with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of ritonavir must, therefore, be consulted prior to initiation of therapy with darunavir.

Darunavir Krka d.d. 600 mg film coated tablets must not be chewed or crushed. This strength is not suitable for dosages below 600 mg. It is not possible to administer all paediatric dosages with this product. Other tablet strengths and formulations of darunavir are available.

ART-experienced adult patients
The recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. Darunavir Krka d.d. 600 mg tablets can be used to construct the twice daily 600 mg

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regimen.

ART-naïve adult patients
For dosage recommendations in ART-naïve patients see the Summary of Product Characteristics for Darunavir Krka d.d. 400 mg and 800 mg tablets.

ART-naïve paediatric patients (3 to 17 years of age and weighing at least 15 kg)
The weight-based dose of darunavir and ritonavir in paediatric patients is provided in the table below.

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

[a] ritonavir oral solution: 80 mg/ml

ART-experienced paediatric patients (3 to 17 years of age and weighing at least 15 kg)
Darunavir twice daily taken with ritonavir taken with food is usually recommended.

A once daily dose regimen of darunavir taken with ritonavir taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without darunavir resistance associated mutations (DRV-RAMs)* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/L.
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

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

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

[a] ritonavir oral solution: 80 mg/ml

For ART-experienced paediatric patients HIV genotypic testing is recommended. However, when HIV genotypic testing is not feasible, the darunavir/ritonavir once daily dosing regimen is recommended in HIV-protease inhibitor-naïve paediatric patients and the twice daily dosing regimen is recommended in HIV protease inhibitor-experienced patients.

Advice on missed doses
In case a dose of darunavir and/or ritonavir is missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of darunavir and ritonavir with food as soon as possible. If this is noticed later than 6 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

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

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If a patient vomits within 4 hours of taking the medicine, another dose of darunavir with ritonavir should be taken with food as soon as possible. If a patient vomits more than 4 hours after taking the medicine, the patient does not need to take another dose of darunavir with ritonavir until the next regularly scheduled time.

Special populations

Elderly
Limited information is available in this population, and therefore, darunavir should be used with caution in this age group (see sections 4.4 and 5.2).

Hepatic impairment
Darunavir is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, darunavir should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its safety profile. Therefore, darunavir must not be used in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3, 4.4 and 5.2).

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

Paediatric population
Darunavir/ritonavir should not be used in children with a body weight of less than 15 kg as the dose for this population has not been established in a sufficient number of patients (see section 5.1). Darunavir/ritonavir should not be used in children below 3 years of age because of safety concerns (see sections 4.4 and 5.3).

The weight-based dose regimen for darunavir and ritonavir is provided in the tables above.

Pregnancy and postpartum
No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. Darunavir/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk (see sections 4.4, 4.6 and 5.2).

Method of administration

Patients should be instructed to take darunavir with low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir (see sections 4.4, 4.5 and 5.2).

4.3 Contraindications

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

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

Combination of rifampicin with darunavir with concomitant low dose ritonavir (see section 4.5).

Co-administration with the combination product lopinavir/ritonavir (see section 4.5).

Co-administration with herbal preparations containing St John's wort (*Hypericum perforatum*) (see section 4.5).

Co-administration of darunavir with low dose ritonavir, with active substances that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These active substances include e.g.:

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

4.4 Special warnings and precautions for use

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

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

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

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

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

ART-experienced patients – once daily dosing

Darunavir used in combination with cobicistat or low dose ritonavir once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10^6/L (see section 4.2). Combinations with optimised background regimen (OBRs) other than ≥ 2 NRTIs have not been studied in this population. Limited data are available in patients with HIV-1 clades other than B (see section 5.1).

Paediatric population

Darunavir is not recommended for use in paediatric patients below 3 years of age or less than 15 kg body weight (see sections 4.2 and 5.3).

Pregnancy

Darunavir/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk. Caution should be used in pregnant women with concomitant medications which may further decrease darunavir exposure (see sections 4.5 and 5.2).

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Elderly

As limited information is available on the use of darunavir in patients aged 65 and over, caution should be exercised in the administration of darunavir in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy (see sections 4.2 and 5.2).

Severe skin reactions

During the darunavir/ritonavir clinical development program (N=3,063), severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens-Johnson Syndrome has been rarely (< 0.1%) reported, and during post-marketing experience toxic epidermal necrolysis and acute generalised exanthematous pustulosis have been reported. Darunavir should be discontinued immediately if signs or symptoms of severe skin reactions develop. These can include, but are not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

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

Darunavir contains a sulphonamide moiety. Darunavir should be used with caution in patients with a known sulphonamide allergy.

Hepatotoxicity

Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with darunavir. During the darunavir/ritonavir clinical development program (N=3,063), hepatitis was reported in 0.5% of patients receiving combination antiretroviral therapy with darunavir/ritonavir. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

Appropriate laboratory testing should be conducted prior to initiating therapy with darunavir/ritonavir and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of darunavir/ritonavir treatment.

If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients using darunavir/ritonavir, interruption or discontinuation of treatment should be considered promptly.

Patients with coexisting conditions

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

Renal impairment
No special precautions or dose adjustments for darunavir/ritonavir are required in patients with renal

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

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

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

Osteonecrosis

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

Immune reconstitution inflammatory syndrome

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

Interactions with medicinal products

Several of the interaction studies have been performed with darunavir at lower than recommended doses. The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated. For full information on interactions with other medicinal products see section 4.5.
Efavirenz in combination with boosted darunavir once daily may result in sub-optimal darunavir C_{min}. If efavirenz is to be used in combination with darunavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used (see section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

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Interaction studies have only been performed in adults.

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

Co-administration of darunavir/ritonavir with drugs that have active metabolite(s) formed by CYP3A 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 co-administered with low dose ritonavir must not be combined with medicinal products that are highly dependent on CYP3A for clearance and for which increased systemic exposure is associated with serious and/or life-threatening events (narrow therapeutic index) (see section 4.3).

The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily. Therefore, darunavir must only be used in combination with low dose ritonavir as a pharmacokinetic enhancer (see sections 4.4 and 5.2).

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

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

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

Medicinal products that affect darunavir/ritonavir exposure
Darunavir and ritonavir are metabolised by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir (e.g. rifampicin, St John's wort, lopinavir). Co-administration of darunavir and ritonavir and other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (e.g. indinavir azole antifungals like clotrimazole). These interactions are described in the interaction table below.

Interaction table

Interactions between darunavir/ritonavir and antiretroviral and non-antiretroviral medicinal products are listed in the table below. 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 (not determined as "ND").

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Several of the interaction studies (indicated by # in the table below) have been performed at lower than recommended doses of darunavir or with a different dosing regimen (see section 4.2 Posology). The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated.

The below list of examples of drug-drug interactions is not comprehensive and therefore the label of each drug that is co-administered with darunavir should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	Interaction Geometric mean change (%)	Recommendations concerning co-administration
HIV ANTIRETROVIRALS		
Integrase strand transfer inhibitors		
Dolutegravir	dolutegravir AUC ↓ 22% dolutegravir C_{24h} ↓38% dolutegravir C_{max} ↓ 11% darunavir ↔* * Using cross-study comparisons to historical pharmacokinetic data	Darunavir co-administered with low dose ritonavir and dolutegravir can be used without dose adjustment.
Raltegravir	Some clinical studies suggest raltegravir may cause a modest decrease in darunavir plasma concentrations.	At present the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically relevant. Darunavir co-administered with low dose ritonavir and raltegravir can be used without dose adjustments.
Nucleo(s/t)ide reverse transcriptase inhibitors (NRTIs)		
Didanosine 400 mg once daily	didanosine AUC ↓ 9% didanosine C_{min} ND didanosine C_{max} ↓16% darunavir AUC ↔ darunavir C_{min} ↔ darunavir C_{max} ↔	Darunavir co-administered with low dose ritonavir and didanosine can be used without dose adjustments. Didanosine is to be administered on an empty stomach, thus it should be administered 1 hour before or 2 hours after darunavir/ritonavir given with food.
Tenofovir disoproxil 245 mg once daily	tenofovir AUC ↑ 22% tenofovir C_{min} ↑ 37% tenofovir C_{max} ↑ 24% #darunavir AUC ↑ 21% #darunavir C_{min} ↑ 24% #darunavir C_{max} ↑ 16% (↑ tenofovir from effect on MDR-1 transport in the renal tubules)	Monitoring of renal function may be indicated when darunavir co-administered with low dose ritonavir is given in combination with tenofovir disoproxil, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.
Emtricitabine/tenofovir alafenamide	Tenofovir alafenamide ↔ Tenofovir ↑	The recommended dose of emtricitabine/tenofovir alafenamide is 200/10 mg once daily when used with darunavir with low dose ritonavir.
Abacavir Emtricitabine Lamivudine Stavudine Zidovudine	Not studied. Based on the different elimination pathways of the other NRTIs zidovudine, emtricitabine, stavudine, lamivudine, that are primarily renally excreted, and abacavir for which metabolism is not mediated by CYP450, no interactions are expected for these medicinal compounds and darunavir co-administered with low dose ritonavir.	Darunavir co-administered with low dose ritonavir can be used with these NRTIs without dose adjustment.

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Non-nucleo(s/t)ide reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily	efavirenz AUC ↑ 21% efavirenz C_{min} ↑ 17% efavirenz C_{max} ↑ 15% [#]darunavir AUC ↓ 13% [#]darunavir C_{min} ↓ 31% [#]darunavir C_{max} ↓ 15% (↑ efavirenz from CYP3A inhibition) (↓ darunavir from CYP3A induction)	Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when darunavir co-administered with low dose ritonavir is given in combination with efavirenz. Efavirenz in combination with darunavir /ritonavir 800/100 mg once daily may result in sub-optimal darunavir C_{min}. If efavirenz is to be used in combination with darunavir /ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used (see section 4.4).
Etravirine 100 mg twice daily	etravirine AUC ↓ 37% etravirine C_{min} ↓ 49% etravirine C_{max} ↓ 32% darunavir AUC ↑ 15% darunavir C_{min} ↔ darunavir C_{max} ↔	Darunavir co-administered with low dose ritonavir and etravirine 200 mg twice daily can be used without dose adjustments.
Nevirapine 200 mg twice daily	nevirapine AUC ↑ 27% nevirapine C_{min} ↑ 47% nevirapine C_{max} ↑ 18% [#]darunavir: concentrations were consistent with historical data (↑ nevirapine from CYP3A inhibition)	Darunavir co-administered with low dose ritonavir and nevirapine can be used without dose adjustments.
Rilpivirine 150 mg once daily	rilpivirine AUC ↑ 130% rilpivirine C_{min} ↑ 178% rilpivirine C_{max} ↑ 79% darunavir AUC ↔ darunavir C_{min} ↓ 11% darunavir C_{max} ↔	Darunavir co-administered with low dose ritonavir and rilpivirine can be used without dose adjustments.
HIV Protease inhibitors (PIs) - without additional co-administration of low dose ritonavir[†]		
Atazanavir 300 mg once daily	atazanavir AUC ↔ atazanavir C_{min} ↑ 52% atazanavir C_{max} ↓ 11% [#]darunavir AUC ↔ [#]darunavir C_{min} ↔ [#]darunavir C_{max} ↔ Atazanavir: comparison of atazanavir/ritonavir 300/100 mg once daily vs. atazanavir 300 mg once daily in combination with darunavir/ritonavir 400/100 mg twice daily. Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg twice daily in combination with atazanavir 300 mg once daily.	Darunavir co-administered with low dose ritonavir and atazanavir can be used without dose adjustments.
Indinavir 800 mg twice daily	indinavir AUC ↑ 23% indinavir C_{min} ↑ 125% indinavir C_{max} ↔ [#]darunavir AUC ↑ 24% [#]darunavir C_{min} ↑ 44% [#]darunavir C_{max} ↑ 11% Indinavir: comparison of indinavir/ritonavir 800/100 mg twice daily vs. indinavir/darunavir/ritonavir	When used in combination with darunavir co-administered with low dose ritonavir, dose adjustment of indinavir from 800 mg twice daily to 600 mg twice daily may be warranted in case of intolerance.

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	800/400/100 mg twice daily. Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with indinavir 800 mg twice daily.	
Saquinavir 1,000 mg twice daily	#darunavir AUC ↓ 26% #darunavir C_{min} ↓ 42% #darunavir C_{max} ↓ 17% saquinavir AUC ↓ 6% saquinavir C_{min} ↓ 18% saquinavir C_{max} ↓ 6% Saquinavir: comparison of saquinavir/ritonavir 1,000/100 mg twice daily vs. saquinavir/darunavir/ritonavir 1,000/400/100 mg twice daily Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with saquinavir 1,000 mg twice daily.	It is not recommended to combine darunavir co-administered with low dose ritonavir with saquinavir.
HIV Protease inhibitors (PIs) - with co-administration of low dose ritonavir†		
Lopinavir/ritonavir 400/100 mg twice daily Lopinavir/ritonavir 533/133.3 mg twice daily	lopinavir AUC ↑ 9% lopinavir C_{min} ↑ 23% lopinavir C_{max} ↓ 2% darunavir AUC ↓ 38%‡ darunavir C_{min} ↓ 51%‡ darunavir C_{max} ↓ 21%‡ lopinavir AUC ↔ lopinavir C_{min} ↑ 13% lopinavir C_{max} ↑ 11% darunavir AUC ↓ 41% darunavir C_{min} ↓ 55% darunavir C_{max} ↓ 21% ‡ based upon non dose normalised values	Due to a decrease in the exposure (AUC) of darunavir by 40%, appropriate doses of the combination have not been established. Hence, concomitant use of darunavir co-administered with low dose ritonavir and the combination product lopinavir/ritonavir is contraindicated (see section 4.3).
CCR5 ANTAGONIST		
Maraviroc 150 mg twice daily	maraviroc AUC ↑ 305% maraviroc C_{min} ND maraviroc C_{max} ↑ 129% darunavir, ritonavir concentrations were consistent with historical data	The maraviroc dose should be 150 mg twice daily when co-administered with darunavir with low dose ritonavir.
α1-ADRENORECEPTOR ANTAGONIST		
Alfuzosin	Based on theoretical considerations darunavir is expected to increase alfuzosin plasma concentrations. (CYP3A inhibition)	Co-administration of darunavir with low dose ritonavir and alfuzosin is contraindicated (see section 4.3).
ANAESTHETIC		
Alfentanil	Not studied. The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by darunavir co-administered with low dose ritonavir.	The concomitant use with darunavir and low dose ritonavir may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.
ANTIANGINA/ANTIARRHYTHMIC		
Disopyramide Flecainide Lidocaine (systemic) Mexiletine Propafenone	Not studied. Darunavir is expected to increase these antiarrhythmic plasma concentrations. (CYP3A and/or CYP2D6 inhibition)	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with darunavir with low

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Amiodarone Bepridil Dronedarone Ivabradine Quinidine Ranolazine		dose ritonavir. Darunavir co-administered with low dose ritonavir and amiodarone, bepridil, dronedarone, ivabradine, quinidine, or ranolazine is contraindicated (see section 4.3).
Digoxin 0.4 mg single dose	digoxin AUC ↑ 61% digoxin C_{min} ND digoxin C_{max} ↑ 29% (↑ digoxin from probable inhibition of P-gp)	Given that digoxin has a narrow therapeutic index, it is recommended that the lowest possible dose of digoxin should initially be prescribed in case digoxin is given to patients on darunavir/ritonavir therapy. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject.
ANTIBIOTIC		
Clarithromycin 500 mg twice daily	clarithromycin AUC ↑ 57% clarithromycin C_{min} ↑ 174% clarithromycin C_{max} ↑ 26% [#]darunavir AUC ↓ 13% [#]darunavir C_{min} ↑ 1% [#]darunavir C_{max} ↓ 17% 14-OH-clarithromycin concentrations were not detectable when combined with darunavir/ritonavir. (↑ clarithromycin from CYP3A inhibition and possible P-gp inhibition)	Caution should be exercised when clarithromycin is combined with darunavir co-administered with low dose ritonavir. For patients with renal impairment the Summary of Product Characteristics for clarithromycin should be consulted for the recommended dose.
ANTICOAGULANT/PLATELET AGGREGATION INHIBITOR		
Apixaban Edoxaban Rivaroxaban	Not studied. Co-administration of darunavir with these anticoagulants may increase concentrations of the anticoagulant, which may lead to an increased bleeding risk. ((CYP3A and/or P-gp inhibition).	The use of boosted darunavir and these anticoagulants is not recommended.
Dabigatran Ticagrelor Clopidogrel	Not studied. Co-administration with boosted darunavir may lead to a substantial increase in exposure to dabigatran or ticagrelor. Not studied. Co-administration of clopidogrel with boosted darunavir is expected to decrease clopidogrel active metabolite plasma concentration, which may reduce the antiplatelet activity of clopidogrel.	Concomitant administration of boosted darunavir with dabigatran or ticagrelor is contraindicated (see section 4.3). Co-administration of clopidogrel with boosted darunavir 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 with low dose ritonavir.	It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with darunavir co-administered with low dose ritonavir.

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ANTICONVULSANTS		
Phenobarbital Phenytoin	Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir and its pharmacoenhancer. (induction of CYP450 enzymes)	Darunavir co-administered with low dose ritonavir should not be used in combination with these medicines.
Carbamazepine 200 mg twice daily	carbamazepine AUC ↑ 45% carbamazepine C_{min} ↑ 54% carbamazepine C_{max} ↑ 43% darunavir AUC ↔ darunavir C_{min} ↓ 15% darunavir C_{max} ↔	No dose adjustment for darunavir /ritonavir is recommended. If there is a need to combine darunavir/ritonavir and carbamazepine, patients should be monitored for potential carbamazepine-related adverse events. Carbamazepine concentrations should be monitored and its dose should be titrated for adequate response. Based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of darunavir/ritonavir.
Clonazepam	Not studied. Co-administration of boosted darunavir with clonazepam may increase concentrations of clonazepam. (CYP3A inhibition)	Clinical monitoring is recommended when co-administering boosted darunavir with clonazepam.
ANTIDEPRESSANTS		
Paroxetine 20 mg once daily Sertraline 50 mg once daily Amitriptyline Desipramine Imipramine Nortriptyline Trazodone	paroxetine AUC ↓ 39% paroxetine C_{min} ↓ 37% paroxetine C_{max} ↓ 36% [#]darunavir AUC ↔ [#]darunavir C_{min} ↔ [#]darunavir C_{max} ↔ sertraline AUC ↓ 49% sertraline C_{min} ↓ 49% sertraline C_{max} ↓ 44% [#]darunavir AUC ↔ [#]darunavir C_{min} ↓ 6% [#]darunavir C_{max} ↔ Concomitant use of darunavir co-administered wirth low dose ritonavir and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or CYP3A inhibition).	If antidepressants are co-administered with darunavir with low dose ritonavir, the recommended approach is a dose titration of the antidepressant based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of these antidepressants who start treatment with darunavir with low dose ritonavir should be monitored for antidepressant response. Clinical monitoring is recommended when co-administering darunavir with low dose ritonavir with these antidepressants and a dose adjustment of the antidepressant may be needed.
ANTIEMETICS		
Domperidone	Not studied.	Co-administration of domperidone with boosted darunavir is contraindicated.
ANTIFUNGALS		
Voriconazole	Not studied. Ritonavir may decrease plasma concentrations of voriconazole. (induction of CYP450 enzymes)	Voriconazole should not be combined with darunavir co-administered with low dose ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.

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Fluconazole Isavuconazole Itraconazole Posaconazole Clotrimazole	Not studied. Darunavir may increase antifungal plasma concentrations and posaconazole, isavuconazole, itraconazole, or fluconazole may increase darunavir concentrations. (CYP3A and/or P-gp inhibition) Not studied. Concomitant systemic use of clotrimazole and darunavir co-administered with low dose ritonavir may increase plasma concentrations of darunavir and/or clotrimazole. darunavir AUC_{24h} ↑ 33% (based on population pharmacokinetic model)	Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of itraconazole should not exceed 200 mg.
ANTIGOUT MEDICINES		
Colchicine	Not studied. Concomitant use of colchicine and darunavir co-administered with low dose ritonavir may increase the exposure to colchicine. (CYP3A and/ or P-gp inhibition)	A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with darunavir co-administered with low dose ritonavir is required. For patients with renal or hepatic impairment colchicine with darunavir co-administered with low dose ritonavir is contraindicated (see sections 4.3 and 4.4).
ANTIMALARIALS		
Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	artemether AUC ↓ 16% artemether C_{min} ↔ artemether C_{max} ↓ 18% dihydroartemisinin AUC ↓ 18% dihydroartemisinin C_{min} ↔ dihydroartemisinin C_{max} ↓ 18% lumefantrine AUC ↑ 175% lumefantrine C_{min} ↑ 126% lumefantrine C_{max} ↑ 65% darunavir AUC ↔ darunavir C_{min} ↓ 13% darunavir C_{max} ↔	The combination of darunavir and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Not studied. Rifapentine and rifampicin are strong CYP3A inducers and have been shown to cause profound decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction). During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with low dose ritonavir, a high frequency of liver reactions was seen with rifampicin.	The combination of rifapentine and darunavir with concomitant low dose ritonavir is not recommended. The combination of rifampicin and darunavir with concomitant low dose ritonavir is contraindicated (see section 4.3).
Rifabutin 150 mg once every other day	rifabutin AUC** ↑ 55% rifabutin C_{min}** ↑ ND rifabutin C_{max}** ↔ darunavir AUC ↑ 53% darunavir C_{min} ↑ 68% darunavir C_{max} ↑ 39% ** sum of active moieties of rifabutin (parent drug + 25-*O*-desacetyl metabolite) The interaction trial showed a comparable	A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg once every other day) and increased monitoring for rifabutin related adverse events is warranted in patients receiving the combination with darunavir co-administered with ritonavir. In case of safety issues, a further

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	daily systemic exposure for rifabutin between treatment at 300 mg once daily alone and 150 mg once every other day in combination with darunavir/ritonavir (600/100 mg twice daily) with an about 10-fold increase in the daily exposure to the active metabolite 25-*O*-desacetylrifabutin. Furthermore, AUC of the sum of active moieties of rifabutin (parent drug + 25-*O*-desacetyl metabolite) was increased 1.6-fold, while C_{max} remained comparable. Data on comparison with a 150 mg once daily reference dose is lacking. (Rifabutin is an inducer and substrate of CYP3A.) An increase of systemic exposure to darunavir was observed when darunavir co-administered with 100 mg ritonavir was co-administered with rifabutin (150 mg once every other day).	increase of the dosing interval for rifabutin and/or monitoring of rifabutin levels should be considered. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients. Based upon the safety profile of darunavir/ritonavir, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for darunavir/ritonavir. Based on pharmacokinetic modeling, this dosage reduction of 75% is also applicable if patients receive rifabutin at doses other than 300 mg/day.
ANTINEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine	Not studied. Darunavir is expected to increase these antineoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when co-administered with darunavir with low dose ritonavir resulting in the potential for increased adverse events usually associated with these agents. Caution should be exercised when combining one of these antineoplastic agents with darunavir with low dose ritonavir.
Everolimus Irinotecan		Concomitant use of everolimus or irinotecan and darunavir co-administered with low dose ritonavir is not recommended.
ANTIPSYCHOTICS/NEUROLEPTICS		
Quetiapine	Not studied. Darunavir is expected to increase these antipsychotic plasma concentrations. (CYP3A inhibition)	Concomitant administration of darunavir with low dose ritonavir and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased concentrations of quetiapine may lead to coma (see section 4.3).
Perphenazine Risperidone Thioridazine	Not studied. Darunavir is expected to increase these antipsychotic plasma concentrations. (CYP3A, CYP2D6 and/or P-gp inhibition)	A dose decrease may be needed for these drugs when co-administered with darunavir co-administered with low dose ritonavir.
Lurasidone Pimozide Sertindole		Concomitant administration of darunavir with low dose ritonavir and lurasidone, pimozide or sertindole is contraindicated (see section 4.3).
β-BLOCKERS		
Carvedilol Metoprolol Timolol	Not studied. Darunavir is expected to increase these β-blocker plasma concentrations. (CYP2D6 inhibition)	Clinical monitoring is recommended when co-administering darunavir with β-blockers. A lower dose of the β-blocker should be considered.
CALCIUM CHANNEL BLOCKERS		
Amlodipine Diltiazem	Not studied. Darunavir co-administered with low dose ritonavir can be expected to	Clinical monitoring of therapeutic and adverse effects is recommended

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Felodipine Nicardipine Nifedipine Verapamil	increase the plasma concentrations of calcium channel blockers. (CYP3A and/or CYP2D6 inhibition)	when these medicines are concomitantly administered with darunavir with low dose ritonavir.
CORTICOSTEROIDS		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone)	Fluticasone: in a clinical study where ritonavir 100 mg capsules twice daily were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, fluticasone propionate plasma concentrations increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% CI 82-89%). Greater effects may be expected when fluticasone is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone. The effects of high fluticasone systemic exposure on ritonavir plasma levels are unknown. Other corticosteroids: interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with darunavir with low dose ritonavir, resulting in reduced serum cortisol concentrations.	Concomitant use of darunavir with low dose ritonavir 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. Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone should be considered, particularly for long term use.
Dexamethasone (systemic)	Not studied. Dexamethasone may decrease plasma concentrations of darunavir. (CYP3A induction)	Systemic dexamethasone should be used with caution when combined with darunavir co-administered with low dose ritonavir.
ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Not studied. Concomitant use of bosentan and darunavir co-administered with low dose ritonavir may increase plasma concentrations of bosentan. Bosentan is expected to decrease plasma concentrations of darunavir and/or its pharmacoenhancer. (CYP3A induction)	When administered concomitantly with darunavir A and low dose ritonavir, the patient's tolerability of bosentan should be monitored.
HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS		
NS3-4A protease inhibitors		
Elbasvir/grazoprevir	Darunavir with low dose ritonavir may increase the exposure to grazoprevir. (CYP3A and OATP1B inhibition)	Concomitant use of darunavir with low dose ritonavir and elbasvir/grazoprevir is contraindicated (see section 4.3).
Glecaprevir/pibrentasvir	Based on theoretical considerations boosted darunavir may increase the exposure to glecaprevir and pibrentasvir. (P-gp, BCRP and/or OATP1B1/3 inhibition)	It is not recommended to co-administer boosted darunavir with glecaprevir/pibrentasvir.
HERBAL PRODUCTS		
St John's wort *(Hypericum perforatum)*	Not studied. St John's wort is expected to decrease the plasma concentrations of darunavir and ritonavir.	Darunavir co-administered with low dose ritonavir must not be used concomitantly with products

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	(CYP450 induction)	containing St John's wort (*Hypericum perforatum*) (see section 4.3). If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Darunavir exposure (and also ritonavir exposure) may increase on stopping St John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort.
HMG CO-A REDUCTASE INHIBITORS		
Lovastatin Simvastatin	Not studied. Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with darunavir co-administered with low dose ritonavir. (CYP3A inhibition)	Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of darunavir co-administered with low dose ritonavir with lovastatin and simvastatin is therefore contraindicated (see section 4.3).
Atorvastatin 10 mg once daily	atorvastatin AUC ↑ 3-4 fold atorvastatin C_{min} ↑ ≈5.5-10 fold atorvastatin C_{max} ↑ ≈2 fold [#]darunavir/ritonavir	When administration of atorvastatin and darunavir co-administered with low dose ritonavir is desired, it is recommended to start with an atorvastatin dose of 10 mg once daily. A gradual dose increase of atorvastatin may be tailored to the clinical response.
Pravastatin 40 mg single dose	pravastatin AUC ↑ 81%[¶] pravastatin C_{min} ND pravastatin C_{max} ↑ 63% [¶] an up to five-fold increase was seen in a limited subset of subjects	When administration of pravastatin and darunavir co-administered with low dose ritonavir is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effect while monitoring for safety.
Rosuvastatin 10 mg once daily	rosuvastatin AUC ↑ 48%[‖] rosuvastatin C_{max} ↑ 144%[‖] [‖] based on published data with darunavir/ritonavir	When administration of rosuvastatin and darunavir co-administered with low dose ritonavir is required, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.
OTHER LIPID MODIFYING AGENTS		
Lomitapide	Based on theoretical considerations boosted darunavir is expected to increase the exposure of lomitapide when co-administered. (CYP3A inhibition)	Co-administration is contraindicated (see section 4.3).
H_2-RECEPTOR ANTAGONISTS		
Ranitidine 150 mg twice daily	[#]darunavir AUC ↔ [#]darunavir C_{min} ↔ [#]darunavir C_{max} ↔	Darunavir co-administered with low dose ritonavir can be co-administered with H_2-receptor antagonists without dose adjustments.
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus	Not studied. Exposure to these immunosuppressants will be increased when co-administered with darunavir co-administered with low dose ritonavir. (CYP3A inhibition)	Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs. Concomitant use of everolimus and darunavir co-administered with low

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		dose ritonavir is not recommended.
INHALED BETA AGONISTS		
Salmeterol	Not studied. Concomitant use of salmeterol and darunavir co-administered with low dose ritonavir may increase plasma concentrations of salmeterol.	Concomitant use of salmeterol and darunavir co-administered with low dose ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS / TREATMENT OF OPIOID DEPENDENCE		
Methadone individual dose ranging from 55 mg to 150 mg once daily	R(-) methadone AUC ↓ 16% R(-) methadone C_{min} ↓ 15% R(-) methadone C_{max} ↓ 24%	No adjustment of methadone dosage is required when initiating co-administration with darunavir /ritonavir. However, increased methadone dose may be necessary when concomitantly administered for a longer period of time due to induction of metabolism by ritonavir. Therefore, clinical monitoring is recommended, as maintenance therapy may need to be adjusted in some patients.
Buprenorphine/naloxone 8/2 mg–16/4 mg once daily	buprenorphine AUC ↓ 11% buprenorphine C_{min} ↔ buprenorphine C_{max} ↓ 8% norbuprenorphine AUC ↑ 46% norbuprenorphine C_{min} ↑ 71% norbuprenorphine C_{max} ↑ 36% naloxone AUC ↔ naloxone C_{min} ND naloxone C_{max} ↔	The clinical relevance of the increase in norbuprenorphine pharmacokinetic parameters has not been established. Dose adjustment for buprenorphine may not be necessary when co-administered with darunavir/ritonavir but a careful clinical monitoring for signs of opiate toxicity is recommended.
Fentanyl Oxycodone Tramadol	Based on theoretical considerations boosted darunavir may increase plasma concentrations of these analgesics. (CYP2D6 and/or CYP3A inhibition)	Clinical monitoring is recommended when co-administering boosted darunavir with these analgesics.
OESTROGEN-BASED CONTRACEPTIVES		
Drospirenone Ethinylestradiol (3 mg/0.02 mg once daily)	Not studied with darunavir/ritonavir.	When darunavir is coadministered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalaemia.
Ethinylestradiol Norethindrone 35 µg/1 mg once daily	ethinylestradiol AUC ↓ 44%[β] ethinylestradiol C_{min} ↓ 62%[β] ethinylestradiol C_{max} ↓ 32%[β] norethindrone AUC ↓ 14%[β] norethindrone C_{min} ↓ 30%[β] norethindrone C_{max} ↔[β] [β] with darunavir/ritonavir	Alternative or additional contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with darunavir and low dose ritonavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.
OPIOID ANTAGONIST		
Naloxegol	Not studied.	Co-administration of boosted darunavir and naloxegol is contraindicated.
PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS		

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For the treatment of erectile dysfunction Avanafil Sildenafil Tadalafil Vardenafil	In an interaction study [#], a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with darunavir and low dose ritonavir.	The combination of avanafil and darunavir with low dose ritonavir is contraindicated (see section 4.3). Concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with darunavir co-administered with low dose ritonavir should be done with caution. If concomitant use of darunavir co-administered with low dose ritonavir with sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended.
For the treatment of pulmonary arterial hypertension Sildenafil Tadalafil	Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and darunavir co-administered with low dose ritonavir may increase plasma concentrations of sildenafil or tadalafil. (CYP3A inhibition)	A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with darunavir and low dose ritonavir has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope). Therefore, co-administration of darunavir with low dose ritonavir and sildenafil when used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3). Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with darunavir and low dose ritonavir is not recommended.
PROTON PUMP INHIBITORS		
Omeprazole 20 mg once daily	[#]darunavir AUC ↔ [#]darunavir C_{min} ↔ [#]darunavir C_{max} ↔	Darunavir co-administered with low dose ritonavir can be co-administered with proton pump inhibitors without dose adjustments.
SEDATIVES/HYPNOTICS		
Buspirone Clorazepate Diazepam Estazolam Flurazepam Midazolam (parenteral) Zoldipem Midazolam (oral) Triazolam	Not studied. Sedative/hypnotics are extensively metabolised by CYP3A. Co-administration with darunavir/ritonavir may cause a large increase in the concentration of these medicines. If parenteral midazolam is co-administered with darunavir co-administered with low dose ritonavir it may cause a large increase in the concentration of this benzodiazepine. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.	Clinical monitoring is recommended when co-administering darunavir with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. If parenteral midazolam is co-administered with darunavir with a low dose ritonavir, it should be done in an intensive care unit (ICU) or similar setting, which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.

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		Darunavir with low dose ritonavir 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 have been performed at lower than recommended doses of darunavir or with a different dosing regimen (see section 4.2 Posology).

[†] The efficacy and safety of the use of darunavir with 100 mg ritonavir and any other HIV PI (e.g. (fos)amprenavir and tipranavir) has not been established in HIV patients. According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended.

[‡] Study was conducted with tenofovir disoproxil fumarate 300 mg once daily.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

There are no adequate and well controlled studies on pregnancy outcome with darunavir in pregnant women. Studies in animals do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Darunavir co-administered with low dose ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk.

Breast-feeding

It is not known whether darunavir is excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk and at high levels (1,000 mg/kg/day) resulted in toxicity. Because of both the potential for HIV transmission and the potential for adverse reactions in breast-fed infants, mothers should be instructed not to breast-feed under any circumstances if they are receiving Darunavir Krka d.d..

Fertility

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

4.7 Effects on ability to drive and use machines

Darunavir in combination with ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing darunavir co-administered with low dose ritonavir and should be borne in mind when considering a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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During the clinical development program (N=2,613 treatment-experienced subjects who initiated therapy with darunavir/ritonavir 600/100 mg twice daily), 51.3% of subjects experienced at least one adverse reaction. The total mean treatment duration for subjects was 95.3 weeks. The most frequent adverse reactions reported in clinical trials and as spontaneous reports are diarrhoea, nausea, rash, headache and vomiting. The most frequent serious reactions are acute renal failure, myocardial infarction, immune reconstitution inflammatory syndrome, thrombocytopenia, osteonecrosis, diarrhoea, hepatitis and pyrexia.

In the 96 week analysis, the safety profile of darunavir/ritonavir 800/100 mg once daily in treatment-naïve subjects was similar to that seen with darunavir/ritonavir 600/100 mg twice daily in treatment-experienced subjects except for nausea which was observed more frequently in treatment-naïve subjects. This was driven by mild intensity nausea. No new safety findings were identified in the 192 week analysis of the treatment-naïve subjects in which the mean treatment duration of darunavir/ritonavir 800/100 mg once daily was 162.5 weeks.

Tabulated list of adverse reactions

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

Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing

MedDRA system organ class Frequency category	Adverse reaction
Infections and infestations	
uncommon	herpes simplex
Blood and lymphatic system disorders	
uncommon	thrombocytopenia, neutropenia, anaemia, leukopenia
rare	increased eosinophil count
Immune system disorders	
uncommon	immune reconstitution inflammatory syndrome, (drug) hypersensitivity
Endocrine disorders	
uncommon	hypothyroidism, increased blood thyroid stimulating hormone
Metabolism and nutrition disorders	
common	diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia
uncommon	gout, anorexia, decreased appetite, decreased weight, increased weight, hyperglycaemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase
Psychiatric disorders	
common	insomnia
uncommon	depression, disorientation, anxiety, sleep disorder, abnormal dreams, nightmare, decreased libido
rare	confusional state, altered mood, restlessness
Nervous system disorders	
common	headache, peripheral neuropathy, dizziness
uncommon	lethargy, paraesthesia, hypoaesthesia, dysgeusia,

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	disturbance in attention, memory impairment, somnolence
rare	syncope, convulsion, ageusia, sleep phase rhythm disturbance
Eye disorders	
uncommon	conjunctival hyperaemia, dry eye
rare	visual disturbance
Ear and labyrinth disorders	
uncommon	vertigo
Cardiac disorders	
uncommon	myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia
rare	acute myocardial infarction, sinus bradycardia, palpitations
Vascular disorders	
uncommon	hypertension, flushing
Respiratory, thoracic and mediastinal disorders	
uncommon	dyspnoea, cough, epistaxis, throat irritation
rare	rhinorrhoea
Gastrointestinal disorders	
very common	diarrhoea
common	vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence
uncommon	pancreatitis, gastritis, gastrooesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia
rare	stomatitis, haematemesis, cheilitis, dry lip, coated tongue
Hepatobiliary disorders	
common	increased alanine aminotransferase
uncommon	hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-glutamyltransferase
Skin and subcutaneous tissue disorders	
common	rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus
uncommon	angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation
rare	DRESS, Stevens-Johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma
not known	toxic epidermal necrolysis, acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	
uncommon	myalgia, osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphokinase
rare	musculoskeletal stiffness, arthritis, joint stiffness

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Renal and urinary disorders	
uncommon	acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria
rare	decreased creatinine renal clearance
Reproductive system and breast disorders	
uncommon	erectile dysfunction, gynaecomastia
General disorders and administration site conditions	
common	asthenia, fatigue
uncommon	pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain
rare	chills, abnormal feeling, xerosis

Description of selected adverse reactions

Rash
In clinical trials, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In cases of severe skin reaction see the warning in section 4.4.

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

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

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

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

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

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

Paediatric population
The safety assessment in paediatric patients is based on the 48-week analysis of safety data from three Phase II trials. The following patient populations were evaluated (see section 5.1):

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- 80 ART-experienced HIV-1 infected paediatric patients aged from 6 to 17 years and weighing at least 20 kg who received darunavir tablets with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 21 ART-experienced HIV-1 infected paediatric patients aged from 3 to < 6 years and weighing 10 kg to < 20 kg (16 participants from 15 kg to < 20 kg) who received darunavir oral suspension with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 12 ART-naïve HIV-1 infected paediatric patients aged from 12 to 17 years and weighing at least 40 kg who received darunavir tablets with low dose ritonavir once daily in combination with other antiretroviral agents (see section 5.1).

Overall, the safety profile in these paediatric patients was similar to that observed in the adult population.

Other special populations
Patients co-infected with hepatitis B and/or hepatitis C virus
Among 1,968 treatment-experienced patients receiving darunavir co-administered with ritonavir 600/100 mg twice daily, 236 patients were co-infected with hepatitis B or C. Co-infected patients were more likely to have baseline and treatment emergent hepatic transaminase elevations than those without chronic viral hepatitis (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Human experience of acute overdose with darunavir co-administered with low dose ritonavir is limited. Single doses up to 3,200 mg of darunavir as oral solution alone and up to 1,600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Antiviral activity *in vitro*

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and

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human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/ml). Darunavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM.

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

Resistance

In vitro selection of darunavir-resistant virus from wild type HIV-1 was lengthy (> 3 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23-50-fold) harboured 2 to 4 amino acid substitutions in the protease gene. The decreased susceptibility to darunavir of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations.

The clinical trial data from ART-experienced patients (*TITAN* trial and the pooled analysis of the *POWER* 1, 2 and 3 and *DUET* 1 and 2 trials) showed that virologic response to darunavir co-administered with low dose ritonavir was decreased when 3 or more darunavir RAMs (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) were present at baseline or when these mutations developed during treatment.

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

Viruses isolated from patients on darunavir/ritonavir 600/100 mg twice daily experiencing virologic failure by rebound that were susceptible to tipranavir at baseline remained susceptible to tipranavir after treatment in the vast majority of cases.

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

The table below shows the development of HIV-1 protease mutations and loss of susceptibility to PIs in virologic failures at endpoint in the *ARTEMIS*, *ODIN* and *TITAN* trials.

	ARTEMIS Week 192	ODIN Week 48		TITAN Week 48
	Darunavir/ritonavir 800/100 mg once daily N=343	darunavir/ritonavir 800/100 mg once daily N=294	darunavir/ritonavir 600/100 mg twice daily N=296	darunavir/ritonavir 600/100 mg twice daily N=298
Total number of virologic failures[a], n (%)	55 (16.0%)	65 (22.1%)	54 (18.2%)	31 (10.4%)
Rebounders	39 (11.4%)	11 (3.7%)	11 (3.7%)	16 (5.4%)
Never suppressed subjects	16 (4.7%)	54 (18.4%)	43 (14.5%)	15 (5.0%)
Number of subjects with virologic failure and paired baseline/endpoint genotypes, developing mutations[b] at endpoint, n/N				
Primary (major) PI mutations	0/43	1/60	0/42	6/28
PI RAMs	4/43	7/60	4/42	10/28
Number of subjects with virologic failure and paired baseline/endpoint phenotypes, showing loss of susceptibility to PIs at endpoint compared to baseline, n/N				
PI				
darunavir	0/39	1/58	0/41	3/26

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amprenavir	0/39	1/58	0/40	0/22
atazanavir	0/39	2/56	0/40	0/22
indinavir	0/39	2/57	0/40	1/24
lopinavir	0/39	1/58	0/40	0/23
saquinavir	0/39	0/56	0/40	0/22
tipranavir	0/39	0/58	0/41	1/25

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

Cross-resistance
Darunavir FC was less than 10 for 90% of 3,309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to most PIs remain susceptible to darunavir.

In the virologic failures of the *ARTEMIS* trial no cross-resistance with other PIs was observed.

Clinical results
Adult patients
For clinical trial results in ART-naïve adult patients, refer to the Summary of Product Characteristics for Darunavir Krka d.d. 400 mg and 800 mg tablets.

Efficacy of darunavir 600 mg twice daily co-administered with 100 mg ritonavir twice daily in ART-experienced patients
The evidence of efficacy of darunavir co-administered with ritonavir (600/100 mg twice daily) in ART-experienced patients is based on the 96 weeks analysis of the Phase III trial *TITAN* in ART-experienced lopinavir naïve patients, on the 48 week analysis of the Phase III trial *ODIN* in ART-experienced patients with no DRV-RAMs, and on the analyses of 96 weeks data from the Phase IIb trials *POWER* 1 and 2 in ART-experienced patients with high level of PI resistance.

TITAN is a randomised, controlled, open-label Phase III trial comparing darunavir co-administered with ritonavir (600/100 mg twice daily) versus lopinavir/ritonavir (400/100 mg twice daily) in ART-experienced, lopinavir naïve HIV-1 infected adult patients. Both arms used an Optimised Background Regimen (OBR) consisting of at least 2 antiretrovirals (NRTIs with or without NNRTIs).

The table below shows the efficacy data of the 48 week analysis from the *TITAN* trial.

TITAN			
Outcomes	Darunavir/ritonavir 600/100 mg twice daily + OBR N=298	Lopinavir/ritonavir 400/100 mg twice daily + OBR N=297	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[a]	70.8% (211)	60.3% (179)	10.5% (2.9; 18.1)[b]
median CD4+ cell count change from baseline (x 10^6/L)[c]	88	81	

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

At 48 weeks non-inferiority in virologic response to the darunavir/ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 400 and < 50 copies/ml, was demonstrated (at the pre-defined 12% non-inferiority margin) for both ITT and OP populations. These results were confirmed in the analysis of data at 96 weeks of treatment in the *TITAN* trial, with 60.4% of patients in the darunavir/ritonavir arm having HIV-1 RNA < 50 copies/ml at week 96 compared to 55.2% in the lopinavir/ritonavir arm [difference: 5.2%, 95% CI (-2.8; 13.1)].

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ODIN is a Phase III, randomised, open-label trial comparing darunavir/ritonavir 800/100 mg once daily versus darunavir/ritonavir 600/100 mg twice daily in ART-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a screening HIV-1 RNA > 1,000 copies/ml. Efficacy analysis is based on 48 weeks of treatment (see table below). Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs.

ODIN			
Outcomes	Darunavir/ritonavir 800/100 mg once daily + OBR N=294	darunavir/ritonavir 600/100 mg twice daily + OBR N=296	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[a]	72.1% (212)	70.9% (210)	1.2% (-6.1; 8.5)[b]
With Baseline HIV-1 RNA (copies/ml) < 100,000 ≥ 100,000	77.6% (198/255) 35.9% (14/39)	73.2% (194/265) 51.6% (16/31)	4.4% (-3.0; 11.9) -15.7% (-39.2; 7.7)
With Baseline CD4+ cell count (x 10^6/L) ≥ 100 < 100	75.1% (184/245) 57.1% (28/49)	72.5% (187/258) 60.5% (23/38)	2.6% (-5.1; 10.3) -3.4% (-24.5; 17.8)
With HIV-1 clade Type B Type AE Type C Other[c]	 70.4% (126/179) 90.5% (38/42) 72.7% (32/44) 55.2% (16/29)	 64.3% (128/199) 91.2% (31/34) 78.8% (26/33) 83.3% (25/30)	 6.1% (-3.4; 15.6) -0.7% (-14.0; 12.6) -6.1% (-2.6; 13.7) -28.2% (-51.0; -5.3)
mean CD4+ cell count change from baseline (x 10^6/L)[e]	108	112	-5[d] (-25; 16)

[a] Imputations according to the TLOVR algorithm
[b] Based on a normal approximation of the difference in % response
[c] Clades A1, D, F1, G, K, CRF02_AG, CRF12_BF, and CRF06_CPX
[d] Difference in means
[e] Last Observation Carried Forward imputation

At 48 weeks, virologic response, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/ml, with darunavir/ritonavir 800/100 mg once daily treatment was demonstrated to be non-inferior (at the pre-defined 12% non-inferiority margin) compared to darunavir/ritonavir 600/100 mg twice daily for both ITT and OP populations.

Darunavir/ritonavir 800/100 mg once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10^6/L (see section 4.2 and 4.4). Limited data is available in patients with HIV-1 clades other than B.

POWER 1 *and* ***POWER 2*** are randomised, controlled trials comparing darunavir co-administered with ritonavir (600/100 mg twice daily) with a control group receiving an investigator-selected PI(s) regimen in HIV-1 infected patients who had previously failed more than 1 PI containing regimen. An OBR consisting of at least 2 NRTIs with or without enfuvirtide (ENF) was used in both trials.

The table below shows the efficacy data of the 48-week and 96-week analyses from the pooled *POWER* 1 and *POWER* 2 trials.

POWER 1 and POWER 2 pooled data		
	Week 48	Week 96

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

[a] Imputations according to the TLOVR algorithm
[b] Last Observation Carried Forward imputation
[c] 95% confidence intervals.

Analyses of data through 96 weeks of treatment in the *POWER* trials demonstrated sustained antiretroviral efficacy and immunologic benefit.

Out of the 59 patients who responded with complete viral suppression (< 50 copies/ml) at week 48, 47 patients (80% of the responders at week 48) remained responders at week 96.

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

Proportion (%) of patients with response (HIV-1 RNA < 50 copies/ml at week 24) to darunavir co-administered with ritonavir (600/100 mg twice daily) by baseline genotype, and baseline darunavir FC and by use of enfuvirtide (ENF): As treated analysis of the POWER and DUET trials.

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

[a] Number of mutations from the list of mutations associated with a diminished response to darunavir/ritonavir (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V)
[b] fold change in EC$_{50}$
[c] "Patients with no/non-naïve use of ENF" are patients who did not use ENF or who used ENF but not for the first time
[d] "Patients with naïve use of ENF" are patients who used ENF for the first time

Paediatric patients
For clinical trial results in ART-naïve paediatric patients aged 12 to 17 years, refer to the Summary of Product Characteristics for Darunavir Krka d.d. 400 mg and 800 mg tablets.

ART-experienced paediatric patients from the age of 6 to < 18 years and weighing at least 20 kg
DELPHI is an open-label, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with low dose ritonavir in 80 ART-experienced HIV-1 infected paediatric patients aged 6 to 17 years and weighing at least 20 kg. These patients received darunavir/ritonavir twice daily in combination with other antiretroviral agents (see section 4.2 for dosage recommendations per body weight). Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 $\log_{10}$ versus baseline.
In the study, patients who were at risk of discontinuing therapy due to intolerance of ritonavir oral

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solution (e.g. taste aversion) were allowed to switch to the capsule formulation. Of the 44 patients taking ritonavir oral solution, 27 switched to the 100 mg capsule formulation and exceeded the weight-based ritonavir dose without changes in observed safety.

DELPHI	
Outcomes at week 48	Darunavir/ritonavir N=80
HIV-1 RNA < 50 copies/ml[a]	47.5% (38)
CD4+ cell count mean change from baseline[b]	147

[a] Imputations according to the TLOVR algorithm.
[b] Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0.

According to the TLOVR non-virologic failure censored algorithm 24 (30.0%) patients experienced virological failure, of which 17 (21.3%) patients were rebounders and 7 (8.8%) patients were non-responders.

ART-experienced paediatric patients from the age of 3 to < 6 years
The pharmacokinetics, safety, tolerability and efficacy of darunavir/ritonavir twice daily in combination with other antiretroviral agents in 21 ART-experienced HIV-1 infected paediatric patients aged 3 to < 6 years and weighing 10 kg to < 20 kg was evaluated in an open-label, Phase II trial, ***ARIEL***. Patients received a weight-based twice daily treatment regimen, patients weighing 10 kg to < 15 kg received darunavir/ritonavir 25/3 mg/kg twice daily, and patients weighing 15 kg to < 20 kg received darunavir/ritonavir 375/50 mg twice daily. At week 48, the virologic response, defined as the percentage of patients with confirmed plasma viral load < 50 HIV-1 RNA copies/ml, was evaluated in 16 paediatric patients 15 kg to < 20 kg and 5 paediatric patients 10 kg to < 15 kg receiving darunavir/ritonavir in combination with other antiretroviral agents (see section 4.2 for dosage recommendations per body weight).

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

[a] Imputations according to the TLOVR algorithm.
[b] NC=F

Limited efficacy data are available in paediatric patients below 15 kg and no recommendation on a posology can be made.

Pregnancy and postpartum
Darunavir/ritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 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 subjects who stayed on the antiretroviral treatment through delivery. There were no new clinically relevant safety findings compared with the known safety profile of darunavir/ritonavir in HIV-1 infected adults (see sections 4.2, 4.4 and 5.2).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of darunavir, co-administered with ritonavir, have been evaluated in healthy adult volunteers and in HIV-1 infected patients. Exposure to darunavir was higher in HIV-1 infected patients than in healthy subjects. The increased exposure to darunavir in HIV-1 infected patients compared to healthy subjects may be explained by the higher concentrations of α_1-acid

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glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG and, therefore, higher plasma concentrations.

Darunavir is primarily metabolised by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

Absorption
Darunavir was rapidly absorbed following oral administration. Maximum plasma concentration of darunavir in the presence of low dose ritonavir is generally achieved within 2.5-4.0 hours.

The absolute oral bioavailability of a single 600 mg dose of darunavir alone was approximately 37% and increased to approximately 82% in the presence of 100 mg twice daily ritonavir. The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily (see section 4.4).

When administered without food, the relative bioavailability of darunavir in the presence of low dose ritonavir is 30% lower as compared to intake with food. Therefore, darunavir tablets should be taken with ritonavir and with food. The type of food does not affect exposure to darunavir.

Distribution
Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma α_1-acid glycoprotein.

Following intravenous administration, the volume of distribution of darunavir alone was 88.1 ± 59.0 l (Mean ± SD) and increased to 131 ± 49.9 l (Mean ± SD) in the presence of 100 mg twice-daily ritonavir.

Biotransformation
In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolised by the hepatic CYP system and almost exclusively by isozyme CYP3A4. A ^{14}C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir with ritonavir dose was due to the parent active substance. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 10-fold less than the activity of darunavir against wild type HIV.

Elimination
After a 400/100 mg ^{14}C-darunavir with ritonavir dose, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir could be retrieved in faeces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in faeces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir.
The intravenous clearance of darunavir alone (150 mg) and in the presence of low dose ritonavir was 32.8 l/h and 5.9 l/h, respectively.

Special populations

Paediatric population
The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 74 treatment-experienced paediatric patients, aged 6 to 17 years and weighing at least 20 kg, showed that the administered weight-based doses of darunavir/ritonavir resulted in darunavir exposure comparable to that in adults receiving darunavir/ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 14 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 15 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in

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adults receiving darunavir/ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 12 ART-naïve paediatric patients, aged 12 to < 18 years and weighing at least 40 kg, showed that darunavir/ritonavir 800/100 mg once daily results in darunavir exposure that was comparable to that achieved in adults receiving darunavir/ritonavir 800/100 mg once daily. Therefore the same once daily dosage may be used in treatment-experienced adolescents aged 12 to < 18 years and weighing at least 40 kg without darunavir resistance associated mutations (DRV-RAMs)* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/L (see section 4.2).
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 10 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 14 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving darunavir/ritonavir 800/100 mg once daily (see section 4.2). In addition, pharmacokinetic modeling and simulation of darunavir exposures in paediatric patients across the ages of 3 to < 18 years confirmed the darunavir exposures as observed in the clinical studies and allowed the identification of weight-based darunavir/ritonavir once daily dosing regimens for paediatric patients weighing at least 15 kg that are either ART-naïve or treatment-experienced paediatric patients without DRV-RAMs* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/L (see section 4.2).
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

Elderly
Population pharmacokinetic analysis in HIV infected patients showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV infected patients (n=12, age ≥ 65) (see section 4.4). However, only limited data were available in patients above the age of 65 year.

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

Renal impairment
Results from a mass balance study with ^{14}C-darunavir with ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine unchanged.
Although darunavir has not been studied in patients with renal impairment, population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected patients with moderate renal impairment (CrCl between 30-60 ml/min, n=20) (see sections 4.2 and 4.4).

Hepatic impairment
Darunavir is primarily metabolised and eliminated by the liver. In a multiple dose study with darunavir co-administered with ritonavir (600/100 mg) twice daily, it was demonstrated that the total plasma concentrations of darunavir in subjects with mild (Child-Pugh Class A, n=8) and moderate (Child-Pugh Class B, n=8) hepatic impairment were comparable with those in healthy subjects. However, unbound darunavir concentrations were approximately 55% (Child-Pugh Class A) and 100% (Child-Pugh Class B) higher, respectively. The clinical relevance of this increase is unknown therefore, darunavir should be used with caution. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see sections 4.2, 4.3 and 4.4).

Pregnancy and postpartum
The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 600/100 mg twice daily and darunavir/ritonavir 800/100 mg once daily as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum. However, for unbound (i.e. active) darunavir, the pharmacokinetic parameters were less reduced during pregnancy compared to postpartum, due to an increase in the unbound fraction of darunavir during pregnancy compared to postpartum.

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Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 600/100 mg twice daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum			
Pharmacokinetics of total darunavir (mean ± SD)	**Second trimester of pregnancy (n=12)[a]**	**Third trimester of pregnancy (n=12)**	**Postpartum (6-12 weeks) (n=12)**
C_{max}, ng/ml	4,668 ± 1,097	5,328 ± 1,631	6,659 ± 2,364
AUC_{12h}, ng.h/ml	39,370 ± 9,597	45,880 ± 17,360	56,890 ± 26,340
C_{min}, ng/ml	1,922 ± 825	2,661 ± 1,269	2,851 ± 2,216

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

Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 800/100 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum			
Pharmacokinetics of total darunavir (mean ± SD)	**Second trimester of pregnancy (n=17)**	**Third Trimester of pregnancy (n=15)**	**Postpartum (6-12 weeks) (n=16)**
C_{max}, ng/ml	4,964 ± 1,505	5,132 ± 1,198	7,310 ± 1,704
AUC_{24h}, ng.h/ml	62,289 ± 16,234	61,112 ± 13,790	92,116 ± 29,241
C_{min}, ng/ml	1,248 ± 542	1,075 ± 594	1,473 ± 1,141

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

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

5.3 Preclinical safety data

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

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

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

In a study conducted in rats, the number of corpora lutea and implantations were decreased in the presence of maternal toxicity. Otherwise, there were no effects on mating or fertility with darunavir treatment up to 1,000 mg/kg/day and exposure levels below (AUC-0.5 fold) of that in human at the clinically recommended dose. Up to same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. The

Medicinal Product no longer authorised

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

Tablet core:

Cellulose, microcrystalline
Crospovidone
Hydroxypropylcellulose
Silica, colloidal anhydrous
Silicified microcrystalline cellulose (Cellulose, microcrystalline; Silica, colloidal anhydrous)
Magnesium stearate (E470b)

Film coating:

Poly(vinyl alcohol)

Medicinal Product no longer authorised

Macrogol
Titanium dioxide (E171)
Talc (E553b)
Iron oxide, yellow (E172)
Iron oxide, red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Shelf life after first opening: 3 months.

6.4 Special precautions for storage

Keep the bottle tightly closed in order to protect from moisture.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Bottle (HDPE), child resistant tamper evident PP closure with a desiccant:
- 30 tablets: 1 bottle of 30 film-coated tablets,
- 60 tablets : 2 bottles of 30 film-coated tablets,
- 90 tablets: 3 bottles of 30 film-coated tablets,
- 180 tablets: 6 bottles of 30 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

30 film-coated tablets: EU/1/17/1248/005
60 film-coated tablets: EU/1/17/1248/006
90 film-coated tablets: EU/1/17/1248/007
180 film-coated tablets: EU/1/17/1248/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 January 2018

10. DATE OF REVISION OF THE TEXT

Medicinal Product no longer authorised

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Medicinal Product no longer authorised

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Medicinal Product no longer authorised

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

KRKA d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

TAD Pharma GmbH
Heinz-Lohmann-Straβe 5
27472 Cuxhaven
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Medicinal Product no longer authorised

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal Product no longer authorised

A. LABELLING

Medicinal Product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX

1. NAME OF THE MEDICINAL PRODUCT

Darunavir Krka d.d. 400 mg film-coated tablets

darunavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 400 mg darunavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets
60 film-coated tablets
90 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf life after first opening: 3 months.

Date of opening:_____

Medicinal Product no longer authorised

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1248/001 30 film-coated tablets
EU/1/17/1248/002 60 film-coated tablets
EU/1/17/1248/003 90 film-coated tablets
EU/1/17/1248/004 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Darunavir Krka d.d. 400 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

Medicinal Product no longer authorised

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL for bottle

1. NAME OF THE MEDICINAL PRODUCT

Darunavir Krka d.d. 400 mg film-coated tablets

darunavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 400 mg darunavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf life after first opening: 3 months.

Date of opening:_____

9. SPECIAL STORAGE CONDITIONS

Medicinal Product no longer authorised

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1248/001 30 film-coated tablets
EU/1/17/1248/002 60 film-coated tablets
EU/1/17/1248/003 90 film-coated tablets
EU/1/17/1248/004 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Medicinal Product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX

1. NAME OF THE MEDICINAL PRODUCT

Darunavir Krka d.d. 600 mg film-coated tablets

darunavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 600 mg darunavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets
60 film-coated tablets
90 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf life after first opening: 3 months.

Date of opening:_____

Medicinal Product no longer authorised

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1248/005 30 film-coated tablets
EU/1/17/1248/006 60 film-coated tablets
EU/1/17/1248/007 90 film-coated tablets
EU/1/17/1248/008 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Darunavir Krka d.d. 600 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

Medicinal Product no longer authorised

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL for bottle

1. NAME OF THE MEDICINAL PRODUCT

Darunavir Krka d.d. 600 mg film-coated tablets

darunavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 600 mg darunavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf life after first opening: 3 months.

Date of opening:_____

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

Medicinal Product no longer authorised

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1248/005 30 film-coated tablets
EU/1/17/1248/006 60 film-coated tablets
EU/1/17/1248/007 90 film-coated tablets
EU/1/17/1248/008 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Medicinal Product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX

1. NAME OF THE MEDICINAL PRODUCT

Darunavir Krka d.d. 800 mg film-coated tablets

darunavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 800 mg darunavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf life after first opening: 3 months.

Date of opening:_____

9. SPECIAL STORAGE CONDITIONS

Medicinal Product no longer authorised

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1248/009 30 film-coated tablets
EU/1/17/1248/010 90 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Darunavir Krka d.d. 800 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

Medicinal Product no longer authorised

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL for bottle

1. NAME OF THE MEDICINAL PRODUCT

Darunavir Krka d.d. 800 mg film-coated tablets

darunavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 800 mg darunavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf life after first opening: 3 months.

Date of opening:_____

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

Medicinal Product no longer authorised

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1248/009 30 film-coated tablets
EU/1/17/1248/010 90 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Medicinal Product no longer authorised

B. PACKAGE LEAFLET

Medicinal Product no longer authorised

Package leaflet: Information for the patient

Darunavir Krka d.d. 400 mg film-coated tablets
Darunavir Krka d.d. 800 mg film-coated tablets
darunavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Darunavir Krka d.d. is and what it is used for

What is Darunavir Krka d.d.?
Darunavir Krka d.d. contains the active substance darunavir. Darunavir Krka d.d. is an antiretroviral medicine used in the treatment of Human Immunodeficiency Virus (HIV) infection. It belongs to a group of medicines called protease inhibitors. Darunavir Krka d.d. works by reducing the amount of HIV in your body. This will improve your immune system and reduces the risk of developing illnesses linked to HIV infection.

What it is used for?
The Darunavir Krka d.d. 400 and 800 milligram tablets are used to treat adults and children (3 years of age and above, at least 40 kilograms body weight) who are infected by HIV and
- who have not used antiretroviral medicines before.
- in certain patients who have used antiretroviral medicines before (your doctor will determine this).

Darunavir Krka d.d. must be taken in combination with a low dose of cobicistat or ritonavir and other anti-HIV medicines. Your doctor will discuss with you which combination of medicines is best for you.

2. What you need to know before you take Darunavir Krka d.d.

Do not take Darunavir Krka d.d.
- if you are allergic to active substance or any of the other ingredients of this medicine (listed in section 6),
- if you have **severe liver problems**. Ask your doctor if you are unsure about the severity of your liver disease. Some additional tests might be necessary.

Do not combine Darunavir Krka d.d. with any of the following medicines
If you are taking any of these, ask your doctor about switching to another medicine.

Medicine	Purpose of the medicine

Medicinal Product no longer authorised

Avanafil	to treat erectile dysfunction
Astemizole or *terfenadine*	to treat allergy symptoms
Triazolam and *oral (*taken by mouth*) midazolam*	to help you sleep and/or relieve anxiety
Cisapride	to treat some stomach conditions
Colchicine (if you have kidney and/or liver problems)	to treat gout or familial Mediterranean fever
Lurasidone, pimozide, quetiapine or sertindole	to treat psychiatric conditions
Ergot alkaloids like ergotamine, dihydroergotamine, ergometrine and methylergonovine	to treat migraine headaches
Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine	to treat certain heart disorders e.g. abnormal heart beat
Lovastatin, simvastatin and lomitapide	to lower cholesterol levels
Rifampicin	to treat some infections such as tuberculosis
The combination product lopinavir/ritonavir	this anti-HIV medicine belongs to the same class as Darunavir Krka d.d.
Elbasvir/grazoprevir	to treat hepatitis C infection
Alfuzosin	to treat enlarged prostate
Sildenafil	to treat high blood pressure in the pulmonary circulation
Dabigatran, ticagrelor	to help stop the clumping of platelets in the treatment of patients with a history of a heart attack
Naloxegol	to treat opioid induced constipation
Dapoxetine	to treat premature ejaculation
Domperidone	to treat nausea and vomiting

Do not combine Darunavir Krka d.d. with products that contain St John's wort *(Hypericum perforatum)*.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Darunavir Krka d.d..

Darunavir Krka d.d. is not a cure for HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

People taking Darunavir Krka d.d. may still develop infections or other illnesses associated with HIV infection. You must keep in regular contact with your doctor.

People taking Darunavir Krka d.d. may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking Darunavir Krka d.d.and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

Tell your doctor about your situation BEFORE and DURING your treatment
Make sure that you check the following points and tell your doctor if any of these apply to you.
- Tell your doctor if you have had **problems with your liver** before, including hepatitis B or C infection. Your doctor may evaluate how severe your liver disease is before deciding if you can take Darunavir Krka d.d..
- Tell your doctor if you have **diabetes**. Darunavir Krka d.d. might increase sugar levels in the blood.

Medicinal Product no longer authorised

- Tell your doctor immediately if you notice any **symptoms of infection** (for example enlarged lymph nodes and fever). In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.
- In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.
- Tell your doctor if you have **haemophilia**. Darunavir Krka d.d. might increase the risk of bleeding.
- Tell your doctor if you are **allergic to sulphonamides** (e.g. used to treat certain infections).
- Tell your doctor if you notice any **musculoskeletal problems**. Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Elderly
Darunavir Krka d.d. has only been used in limited numbers of patients 65 years or older. If you belong to this age group, please discuss with your doctor if you can use Darunavir Krka d.d..

Children and adolescents
The Darunavir Krka d.d. 400 or 800 milligram tablet is not for use in children younger than 3 years of age or weighing less than 40 kilograms.

Other medicines and Darunavir Krka d.d.
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

There are some medicines that **you must not combine** with Darunavir Krka d.d.. These are mentioned above under the heading 'Do not combine Darunavir Krka d.d. with any of the following medicines:'

In most cases, Darunavir Krka d.d. can be combined with anti-HIV medicines belonging to another class [e.g. NRTIs (nucleoside reverse transcriptase inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors), CCR5 antagonists and FIs (fusion inhibitors)]. Darunavir Krka d.d. with cobicistat or ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. In some cases dosage of other medicines might need to be changed. Therefore always tell your doctor if you take other anti-HIV medicines and follow your doctor's instruction carefully on which medicines can be combined.

The effects of Darunavir Krka d.d. might be reduced if you take any of the following products. Tell your doctor if you take:
- *Phenobarbital, phenytoin* (to prevent seizures)
- *Dexamethasone* (corticosteroid)
- *Efavirenz* (HIV infection)
- *Rifapentine, rifabutin* (medicines to treat some infections such as tuberculosis)
- *Saquinavir* (HIV infection).

The effects of other medicines might be influenced if you take Darunavir Krka d.d.. Tell your doctor if

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you take:
- *Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nicardipine*, *propafenone*, *timolol, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Apixaban, edoxaban, rivaroxaban, warfarin, clopidogrel* (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. Darunavir Krka d.d. might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.
- *Ethinylestradiol/drospirenone*. Darunavir Krka d.d. might increase the risk for elevated potassium levels by drospirenone.
- *Atorvastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Clarithromycin* (antibiotic)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased. Your doctor might want to do some additional tests.
- *Corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone*. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the skin, eyes, joints and muscles and other inflammatory conditions. These medicines are generally taken orally, inhaled, injected or applied to the skin. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone* (medicines to treat opioid dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria)
- *Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine* (to treat cancer)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension)
- *Glecaprevir/pibrentasvir* (to treat hepatitis C infection)
- *Fentanyl, oxycodone, tramadol* (to treat pain)
- *Fesoterodine*, *solifenacin* (to treat urologic disorders).

The dosage of other medicines might need to be changed since either their own or Darunavir Krka d.d.'s therapeutic effect or side effects may be influenced when combined.
Tell your doctor if you take:
- *Alfentanil* (injectable strong and short-acting painkiller that is used for surgical procedures)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Itraconazole, isavuconazole, fluconazole, posaconazole, clotrimazole* (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- *Rifabutin* (against bacterial infections)
- *Sildenafil, vardenafil, tadalafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Maraviroc* (to treat HIV infection)
- *Methadone* (to treat opiate dependence)
- *Carbamazepine, clonazepam* (to prevent seizures or to treat certain types of nerve pain)
- *Colchicine* (to treat gout or familial Mediterranean fever)
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam when used as injection, zoldipem* (sedative agents)

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– *Perphenazine, risperidone, thioridazine* (to treat psychiatric conditions)
– *Metformin* (to treat type 2 diabetes).

This is **not** a complete list of medicines. Tell your healthcare provider about ***all*** medicines that you are taking.

Darunavir Krka d.d. with food and drink
See section 3 'How to take Darunavir Krka d.d..'

Pregnancy and breast-feeding
Tell your doctor immediately if you are pregnant, planning to become pregnant or if you are breast-feeding. Pregnant or breast-feeding mothers should not take Darunavir Krka d.d. with ritonavir unless specifically directed by the doctor. Pregnant or breast feeding mothers should not take darunavir with cobicistat.

It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of your baby becoming infected with HIV through your breast milk and because of the unknown effects of the medicine on your baby.

Driving and using machines
Do not operate machines or drive if you feel dizzy after taking Darunavir Krka d.d..

3. How to take Darunavir Krka d.d.

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.
Even if you feel better, do not stop taking Darunavir Krka d.d. and cobicistat or ritonavir without talking to your doctor.

After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

Darunavir Krka d.d. 400 and 800 milligram tablets are only to be used to construct the once daily 800 milligram regimen.

This product is only available as film coated tablets and is thus not suitable for patients who are unable to swallow intact tablets, for example young children. For use in these patients, more suitable formulations containing darunavir should be checked for their availability.

Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this)
The usual dose of Darunavir Krka d.d. is 800 milligram (2 tablets containing 400 milligram of Darunavir Krka d.d. or 1 tablet containing 800 milligram of Darunavir Krka d.d.) once daily.
You must take Darunavir Krka d.d. every day and always in combination with 150 milligram of cobicistat or 100 milligram of ritonavir and with food. Darunavir Krka d.d. cannot work properly without cobicistat or ritonavir and food. You must eat a meal or a snack within 30 minutes prior to taking your Darunavir Krka d.d. and cobicistat or ritonavir. The type of food is not important. Even if you feel better, do not stop taking Darunavir Krka d.d. and cobicistat or ritonavir without talking to your doctor.

Instructions for adults
– Take two 400 milligram tablets at the same time or one 800 miligram tablet, once a day, every day.
– Take Darunavir Krka d.d. always together with 150 milligram of cobicistat or100 milligram of ritonavir.
– Take Darunavir Krka d.d. with food.

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– Swallow the tablets with a drink such as water or milk.
– Take your other HIV medicines used in combination with Darunavir Krka d.d. and cobicistat or ritonavir as recommended by your doctor.

Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)
Maybe you will require a different dose of Darunavir Krka d.d. which cannot be administered with these 400 or 800 milligram tablets. Other strengths of Darunavir Krka d.d. are available.
The dose is either:
– 800 milligram Darunavir Krka d.d. (2 tablets containing 400 milligram of Darunavir Krka d.d. or 1 tablet containing 800 milligram of Darunavir Krka d.d.) together with 150 milligram cobicistat or 100 milligram ritonavir once daily.
OR
– 600 milligram Darunavir Krka d.d. (1 tablet containing 600 milligram of Darunavir Krka d.d.) together with 100 milligram ritonavir twice daily.

Please discuss with your doctor which dose is right for you.

Dose for children 3 years of age and above with ritonavir, and 12 years of age and above with cobicistat, weighing more than 40 kilograms who have not taken antiretroviral medicines before (your child's doctor will determine this)
– The usual dose of Darunavir Krka d.d. is 800 milligram (2 tablets containing 400 milligram of Darunavir Krka d.d. or 1 tablet containing 800 milligram of Darunavir Krka d.d.) together with 100 milligram ritonavir or 150 milligram of cobicistat once daily.

Dose for children 3 years of age and above with ritonavir, and 12 years of age and above with cobicistat, weighing more than 40 kilograms who have taken antiretroviral medicines before (your child's doctor will determine this)
The dose is either:
– 800 milligram Darunavir Krka d.d. (2 tablets containing 400 milligram of Darunavir Krka d.d. or 1 tablet containing 800 milligram of Darunavir Krka d.d.) together with 100 milligram ritonavir or 150 milligram of cobicistat once daily.
OR
– 600 milligram Darunavir Krka d.d. (1 tablet containing 600 milligram of Darunavir Krka d.d.) together with 100 milligram ritonavir twice daily.

Please discuss with your doctor which dose is right for you.

Instructions for children 3 years of age and above with ritonavir, and 12 years of age and above with cobicistat, weighing more than 40 kilograms
– Take 800 milligram Darunavir Krka d.d. (2 tablets containing 400 milligram of Darunavir Krka d.d. or 1 tablet containing 800 milligram of Darunavir Krka d.d.) at the same time, once a day, every day.
– Take Darunavir Krka d.d. always together with 100 milligram of ritonavir or 150 milligram of cobicistat.
– Take Darunavir Krka d.d. with food.
– Swallow the tablets with a drink such as water or milk.
– Take your other HIV medicines used in combination with Darunavir Krka d.d. and ritonavir or cobicistat as recommended by your doctor.

If you take more Darunavir Krka d.d. than you should
Contact your doctor, pharmacist or nurse immediately.

If you forget to take Darunavir Krka d.d.
If you notice **within 12 hours**, you must take the tablets immediately. Always take with cobicistat or ritonavir and food. If you notice **after 12 hours**, then skip the intake and take the next doses as usual. Do not take a double dose to make up for a forgotten dose.

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If you vomit after taking Darunavir Krka d.d. and cobicistat or ritonavir
If you vomit **within 4 hours** of taking the medicine, another dose of Darunavir Krka d.d. and cobicistat or ritonavir should be taken with food as soon as possible. If you vomit **more than 4 hours** after taking the medicine, then you do not need to take another dose of Darunavir Krka d.d. and cobicistat or ritonavir until the next regularly scheduled time.

Contact your doctor **if you are uncertain** about what to do if you miss a dose or vomit.

Do not stop taking Darunavir Krka d.d. without talking to your doctor first
Anti-HIV medicines may make you feel better. Even when you feel better, do not stop taking Darunavir Krka d.d.. Talk to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor if you develop any of the following side effects
Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start Darunavir Krka d.d.. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or pain and discomfort on your right side below your ribs.

Skin rash (more often when used in combination with raltegravir), itching. The rash is usually mild to moderate. A skin rash might also be a symptom of a rare severe situation. It is important to talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether Darunavir Krka d.d. must be stopped.

Other severe side effects were diabetes (common) and inflammation of the pancreas (uncommon).

Very common side effects (may affect more than 1 in 10 people)
- diarrhoea.

Common side effects (may affect up to 1 in 10 people)
- vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

Uncommon side effects (may affect up to 1 in 100 people)
- chest pain, changes in electrocardiogram, rapid heart beating
- decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory, problems with your balance
- difficulty breathing, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching
- kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of

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urine, sometimes at night
- urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails
- muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis
- slowing down of the thyroid gland function. This can be seen in a blood test.
- high blood pressure, flushing
- red or dry eyes
- fever, swelling of lower limbs due to fluids, malaise, irritability, pain
- symptoms of infection, herpes simplex
- erectile dysfunction, enlargement of breasts
- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive

Rare side effects (may affect up to 1 in 1,000 people)
- a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung]
- heart attack, slow heart beating, palpitations
- visual disturbance
- chills, feeling abnormal
- a feeling of confusion or disorientation, altered mood, restlessness
- fainting, epileptic fits, changes or loss of taste
- mouth sores, vomiting blood, inflamation of the lips, dry lips, coated tongue
- running nose
- skin lesions, dry skin
- stiffness of muscles or joints, joint pain with or without inflammation
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.

Some side effects are typical for anti-HIV medicines in the same family as Darunavir Krka d.d.. These are:
- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Darunavir Krka d.d.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

Keep the bottle tightly closed in order to protect from moisture.
Shelf life after first opening: 3 months.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

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What Darunavir Krka d.d. contains

- The active substance is darunavir. Each film-coated tablet contains 400 mg or 800 mg darunavir.
- The other ingredients are cellulose, microcrystalline; crospovidone, hydroxypropylcellulose; silica, colloidal anhydrous; silicified microcrystalline cellulose (cellulose, microcrystalline; silica, colloidal anhydrous) and magnesium stearate (E470b) in the tablet core and poly(vinyl alcohol), macrogol, titanium dioxide (E171), talc (E553b), yellow iron oxide (E172) – only for 400 mg film-coated tablets and red iron oxide (E172) in film coating.

What Darunavir Krka d.d. looks like and contents of the pack

Darunavir Krka d.d. 400 mg film-coated tablets (tablets):
Yellowish brown, oval, biconvex film-coated tablets (tablets), engraved with a mark S1 on one side.
Tablet dimension: 17 x 8.5 mm.
Darunavir Krka d.d. 800 mg film-coated tablets (tablets):
Brownish red, oval, biconvex film-coated tablets (tablets), engraved with a mark S3 on one side.
Tablet dimension: 20 x 10 mm.

Darunavir Krka d.d. 400 mg film-coated tablets are available in bottles containing 30 film-coated tablets (1 bottle of 30 film-coated tablets), 60 film-coated tablets (2 bottles of 30 film-coated tablets), 90 film-coated tablets (3 bottles of 30 film-coated tablets) and 180 film-coated tablets (6 bottles of 30 film-coated tablets) in a box.
Darunavir Krka d.d. 800 mg film-coated tablets are available in bottles containing 30 film-coated tablets (1 bottle of 30 film-coated tablets) and 90 film-coated tablets (3 bottles of 30 film-coated tablets) in a box.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

Manufacturer
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
TAD Pharma GmbH, Heinz-Lohmann-Straße 5, 27472 Cuxhaven, Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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Package leaflet: Information for the patient

Darunavir Krka d.d. 600 mg film-coated tablets
darunavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Darunavir Krka d.d. is and what it is used for

What is Darunavir Krka d.d.?
Darunavir Krka d.d. contains the active substance darunavir. Darunavir Krka d.d. is an antiretroviral medicine used in the treatment of Human Immunodeficiency Virus (HIV) infection. It belongs to a group of medicines called protease inhibitors. Darunavir Krka d.d. works by reducing the amount of HIV in your body. This will improve your immune system and reduces the risk of developing illnesses linked to HIV infection.

What it is used for?
Darunavir Krka d.d. is used to treat adults and children of 3 years of age and above, and at least 15 kilogram body weight who are infected by HIV and who have already used other antiretroviral medicines.

Darunavir Krka d.d. must be taken in combination with a low dose of ritonavir and other anti-HIV medicines. Your doctor will discuss with you which combination of medicines is best for you.

2. What you need to know before you take Darunavir Krka d.d.

Do not take Darunavir Krka d.d.
- if you are allergic to active substance or any of the other ingredients of this medicine (listed in section 6)
- if you have **severe liver problems**. Ask your doctor if you are unsure about the severity of your liver disease. Some additional tests might be necessary.

Do not combine Darunavir Krka d.d. with any of the following medicines
If you are taking any of these, ask your doctor about switching to another medicine.

Medicine	**Purpose of the medicine**
Avanafil	to treat erectile dysfunction
Astemizole or *terfenadine*	to treat allergy symptoms
Triazolam and *oral* (taken by mouth) *midazolam*	to help you sleep and/or relieve anxiety

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Cisapride	to treat some stomach conditions
Colchicine (if you have kidney and/or liver problems)	to treat gout or familial Mediterranean fever
Lurasidone, pimozide, quetiapine or sertindole	to treat psychiatric conditions
Ergot alkaloids like ergotamine, dihydroergotamine, ergometrine and methylergonovine	to treat migraine headaches
Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine	to treat certain heart disorders e.g. abnormal heart beat
Lovastatin, simvastatin and lomitapide	to lower cholesterol levels
Rifampicin	to treat some infections such as tuberculosis
The combination product lopinavir/ritonavir	this anti-HIV medicine belongs to the same class as Darunavir Krka d.d.
Elbasvir/grazoprevir	to treat hepatitis C infection
Alfuzosin	to treat enlarged prostate
Sildenafil	to treat high blood pressure in the pulmonary circulation
Dabigatran, ticagrelor	to help stop the clumping of platelets in the treatment of patients with a history of a heart attack
Naloxegol	to treat opioid induced constipation
Dapoxetine	to treat premature ejaculation
Domperidone	to treat nausea and vomiting

Do not combine Darunavir Krka d.d. with products that contain St John's wort *(Hypericum perforatum)*.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Darunavir Krka d.d..

Darunavir Krka d.d. is not a cure for HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

People taking Darunavir Krka d.d. may still develop infections or other illnesses associated with HIV infection. You must keep in regular contact with your doctor.

People taking Darunavir Krka d.d. may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking Darunavir Krka d.d. and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

Tell your doctor about your situation BEFORE and DURING your treatment
Make sure that you check the following points and tell your doctor if any of these apply to you.
- Tell your doctor if you have had **problems with your liver** before, including hepatitis B or C infection. Your doctor may evaluate how severe your liver disease is before deciding if you can take Darunavir Krka d.d..
- Tell your doctor if you have **diabetes**. Darunavir Krka d.d.might increase sugar levels in the blood.
- Tell your doctor immediately if you notice any **symptoms of infection** (for example enlarged lymph nodes and fever). In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may

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have been present with no obvious symptoms.
- In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.
- Tell your doctor if you have **haemophilia**. Darunavir Krka d.d. might increase the risk of bleeding.
- Tell your doctor if you are **allergic to sulphonamides** (e.g. used to treat certain infections).
- Tell your doctor if you notice any **musculoskeletal problems**. Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Elderly
Darunavir Krka d.d. has only been used in limited numbers of patients 65 years or older. If you belong to this age group, please discuss with your doctor if you can use Darunavir Krka d.d..

Children and adolescents
Darunavir Krka d.d. is not for use in children younger than 3 years of age or weighing less than 15 kilograms.

Other medicines and Darunavir Krka d.d.
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

There are some medicines that **you must not combine** with Darunavir Krka d.d.. These are mentioned above under the heading 'Do not combine Darunavir Krka d.d. with any of the following medicines:'

In most cases, Darunavir Krka d.d. can be combined with anti-HIV medicines belonging to another class [e.g. NRTIs (nucleoside reverse transcriptase inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors), CCR5 antagonists and FIs (fusion inhibitors)]. Darunavir Krka d.d. with ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. In some cases dosage of other medicines might need to be changed. Therefore always tell your doctor if you take other anti-HIV medicines and follow your doctor's instruction carefully on which medicines can be combined.

The effects of Darunavir Krka d.d. might be reduced if you take any of the following products. Tell your doctor if you take:
- *Phenobarbital, phenytoin* (to prevent seizures)
- *Dexamethasone* (corticosteroid)
- *Efavirenz* (HIV infection)
- *Rifapentine, rifabutin* (medicines to treat some infections such as tuberculosis)
- *Saquinavir* (HIV infection).

The effects of other medicines might be influenced if you take Darunavir Krka d.d.. Tell your doctor if you take:
- *Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nicardipine*, *propafenone*, *timolol, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Apixaban, edoxaban, rivaroxaban, warfarin, clopidogrel* (to reduce clotting of the blood) as

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their therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. Darunavir Krka d.d. might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.
- *Ethinylestradiol/drospirenone*. Darunavir Krka d.d. might increase the risk for elevated potassium levels by drospirenone.
- *Atorvastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Clarithromycin* (antibiotic)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased. Your doctor might want to do some additional tests.
- *Corticosteroids including bethametasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone*. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the skin, eyes, joints and muscles and other inflammatory conditions. These medicines are generally taken orally, inhaled, injected or applied to the skin. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone* (medicines to treat opioid dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria)
- *Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine* (to treat cancer)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension)
- *Glecaprevir/pibrentasvir* (to treat hepatitis C infection)
- *Fentanyl, oxycodone, tramadol* (to treat pain)
- *Fesoterodine, solifenacin* (to treat urologic disorders).

The dosage of other medicines might need to be changed since either their own or Darunavir Krka d.d. d.d.'s therapeutic effect or side effects may be influenced when combined.
Tell your doctor if you take:
- *Alfentanil* (injectable strong and short-acting painkiller that is used for surgical procedures)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Itraconazole, isavuconazole, fluconazole, posaconazole, clotrimazole* (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- *Rifabutin* (against bacterial infections)
- *Sildenafil, vardenafil, tadalafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Maraviroc* (to treat HIV infection)
- *Methadone* (to treat opiate dependence)
- *Carbamazepine, clonazepam* (to prevent seizures or to treat certain types of nerve pain)
- *Colchicine* (to treat gout or familial Mediterranean fever)
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam when used as injection, zoldipem* (sedative agents)
- *Perphenazine, risperidone, thioridazine* (to treat psychiatric conditions).

This is **not** a complete list of medicines. Tell your healthcare provider about ***all*** medicines that you are taking.

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Darunavir Krka d.d. with food and drink
See section 3 'How to take Darunavir Krka d.d..'

Pregnancy and breast-feeding
Tell your doctor immediately if you are pregnant, planning to become pregnant or if you are breast-feeding. Pregnant or breast-feeding mothers should not take Darunavir Krka d.d. with ritonavir unless specifically directed by the doctor. Pregnant or breast feeding mothers should not take darunavir with cobicistat.

It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of your baby becoming infected with HIV through your breast milk and because of the unknown effects of the medicine on your baby.

Driving and using machines
Do not operate machines or drive if you feel dizzy after taking Darunavir Krka d.d..

3. How to take Darunavir Krka d.d.

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.
Even if you feel better, do not stop taking Darunavir Krka d.d. and ritonavir without talking to your doctor.

After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

Darunavir Krka d.d. 600 mg film coated tablets must not be chewed or crushed. This strength is not suitable for dosages below 600 mg. It is not possible to administer all paediatric dosages with this product. Other tablet strengths and formulations of darunavir are available.

Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this)
You will require a different dose of Darunavir Krka d.d. which cannot be administered with these 600 milligram tablets. Other strengths of Darunavir Krka d.d. are available.

Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)
The dose is either:
- 600 milligram Darunavir Krka d.d. (1 tablet containing 600 milligram of Darunavir Krka d.d.) together with 100 milligram ritonavir twice daily.

OR
- 800 milligram Darunavir Krka d.d. (2 tablets containing 400 milligram of Darunavir Krka d.d. or 1 tablet containing 800 milligram of Darunavir Krka d.d.) together with 100 milligram ritonavir once daily. Darunavir Krka d.d. 400 milligram and 800 milligram tablets are only to be used to construct the once daily 800 milligram regimen.

Please discuss with your doctor which dose is right for you.

Instructions for adults
- Take Darunavir Krka d.d. always together with ritonavir. Darunavir Krka d.d. cannot work properly without ritonavir.
- In the morning, take one 600 milligram Darunavir Krka d.d. tablet together with 100 milligram ritonavir.
- In the evening, take one 600 milligram Darunavir Krka d.d. tablet together with 100 milligram ritonavir.
- Take Darunavir Krka d.d. with food. Darunavir Krka d.d. cannot work properly without food. The type of food is not important.

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– Swallow the tablets with a drink such as water or milk.

Dose for children of 3 years of age and above, weighing at least 15 kilograms who have not taken antiretroviral medicines before (your child's doctor will determine this)
The doctor will work out the right once daily dose based on the weight of the child (see table below). This dose must not exceed the recommended adult dose, which is 800 milligram Darunavir Krka d.d. together with 100 milligram ritonavir once a day.
The doctor will inform you on how much Darunavir Krka d.d. tablets the child must take.

Weight	Darunavir dose is	One ritonavir[a] dose is
between 15 and 30 kilograms	600 milligram	100 milligram
between 30 and 40 kilograms	675 milligram	100 milligram
more than 40 kilograms	800 milligram	100 milligram

[a] ritonavir oral solution: 80 milligram per millilitre

Dose for children of 3 years of age and above, weighing at least 15 kilograms who have taken antiretroviral medicines before (your child's doctor will determine this)
The doctor will work out the right dose based on the weight of the child (see table below). The doctor will determine if once daily dosing or twice daily dosing is appropriate for the child. This dose must not exceed the recommended adult dose, which is 600 milligram Darunavir Krka d.d. together with 100 miligran of ritonavir two times per day or 800 milligram Darunavir Krka d.d. together with 100 miligran of ritonavir once a day. The doctor will inform you on how many Darunavir Krka d.d. tablets and how much ritonavir (capsules, tablets or solution) the child must take. Tablets of lower strengths are available to construct the appropriate dosing regimen.
Your doctor will determine whether Darunavir Krka d.d. tablets is right for the child.

Twice daily dosing

Weight	One dose is
between 15 and 30 kilograms	375 milligram darunavir + 50 milligram ritonavir twice a day
between 30 and 40 kilograms	450 milligram darunavir + 60 milligram ritonavir twice a day
more than 40 kilograms*	600 milligram darunavir + 100 milligram ritonavir twice a day

* For children aged 12 or more and weighing at least 40 kilograms, your child's doctor will determine if Darunavir Krka d.d. 800 milligram once daily dosing may be used. This cannot be administered with these 600 milligram tablets. Other strengths of Darunavir Krka d.d. are available.

Once daily dosing

Weight	Darunavir dose is	One ritonavir[a] dose is
between 15 and 30 kilograms	600 milligram	100 milligram
between 30 and 40 kilograms	675 milligram	100 milligram
more than 40 kilograms	800 milligram	100 milligram

[a] ritonavir oral solution: 80 milligram per millilitre

Instructions for children
– The child must take Darunavir Krka d.d. always together with ritonavir. Darunavir Krka d.d. cannot work properly without ritonavir.
– The child must take the appropriate doses of Darunavir Krka d.d. and ritonavir two times per day or once a day. If prescribed Darunavir Krka d.d. twice daily the child must take one dose in the morning, and one dose in the evening. Your child's doctor will determine the appropriate dosing regimen for your child.
– The child must take Darunavir Krka d.d. with food. Darunavir Krka d.d. cannot work properly without food. The type of food is not important.
– The child must swallow the tablets with a drink such as water or milk.

If you take more Darunavir Krka d.d. than you should

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Contact your doctor, pharmacist or nurse immediately.

If you forget to take Darunavir Krka d.d.
If you notice **within 6 hours**, you must take your missed dose immediately. Always take with ritonavir and food. If you notice **after 6 hours**, then skip the intake and take the next doses as usual. Do not take a double dose to make up for a forgotten dose.

If you vomit after taking Darunavir Krka d.d. and ritonavir
If you vomit **within 4 hours** of taking the medicine, another dose of Darunavir Krka d.d. and ritonavir should be taken with food as soon as possible. If you vomit **more than 4 hours** after taking the medicine, then you do not need to take another dose of Darunavir Krka d.d. and ritonavir until the next regularly scheduled time.

Contact your doctor **if you are uncertain** about what to do if you miss a dose or vomit.

Do not stop taking Darunavir Krka d.d. without talking to your doctor first
Anti-HIV medicine may make you feel better. Even when you feel better, do not stop taking Darunavir Krka d.d.. Talk to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor if you develop any of the following side effects
Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start Darunavir Krka d.d.. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or pain and discomfort on your right side below your ribs.

Skin rash (more often when used in combination with raltegravir), itching. The rash is usually mild to moderate. A skin rash might also be a symptom of a rare severe situation. It is therefore important to talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether Darunavir Krka d.d. must be stopped.

Other severe side effects were diabetes (common) and inflammation of the pancreas (uncommon).

Very common side effects (may affect more than 1 in 10 people)
- diarrhoea.

Common side effects (may affect up to 1 in 10 people)
- vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

Uncommon side effects (may affect up to 1 in 100 people)
- chest pain, changes in electrocardiogram, rapid heart beating
- decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory,

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problems with your balance
- difficulty breathing, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching
- kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of urine, sometimes at night
- urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails
- muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis
- slowing down of the thyroid gland function. This can be seen in a blood test.
- high blood pressure, flushing
- red or dry eyes
- fever, swelling of lower limbs due to fluids, malaise, irritability, pain
- symptoms of infection, herpes simplex
- erectile dysfunction, enlargement of breasts
- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive

Rare side effects (may affect up to 1 in 1,000 people)
- a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung]
- heart attack, slow heart beating, palpitations
- visual disturbance
- chills, feeling abnormal
- a feeling of confusion or disorientation, altered mood, restlessness
- fainting, epileptic fits, changes or loss of taste
- mouth sores, vomiting blood, inflamation of the lips, dry lips, coated tongue
- running nose
- skin lesions, dry skin
- stiffness of muscles or joints, joint pain with or without inflammation
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.

Some side effects are typical for anti-HIV medicines in the same family as Darunavir Krka d.d.. These are:
- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Darunavir Krka d.d.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

Keep the bottle tightly closed in order to protect from moisture.
Shelf life after first opening: 3 months.

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Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Darunavir Krka d.d. contains

- The active substance is darunavir. Each film-coated tablet contains 600 mg darunavir.
- The other ingredients are cellulose, microcrystalline; crospovidone, hydroxypropylcellulose; silica, colloidal anhydrous; silicified microcrystalline cellulose (cellulose, microcrystalline; silica, colloidal anhydrous) and magnesium stearate (E470b) in the tablet core and poly(vinyl alcohol), macrogol, titanium dioxide (E171), talc (E553b), yellow iron oxide (E172) and red iron oxide (E172) in film coating.

What Darunavir Krka d.d. looks like and contents of the pack

Film-coated tablets (tablets) are orangish brown, oval, biconvex, engraved with a mark S2 on one side. Tablet dimension: 19.5 x 10 mm.

Darunavir Krka d.d. is available in bottles containing 30 film-coated tablets (1 bottle of 30 film-coated tablets), 60 film-coated tablets (2 bottles of 30 film-coated tablets), 90 film-coated tablets (3 bottles of 30 film-coated tablets) and 180 film-coated tablets (6 bottles of 30 film-coated tablets) in a boxes.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

Manufacturer

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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