SUMMARY OF PRODUCT CHARACTERISTICS

1. NAAM VAN HET GENEESMIDDELNAME OF THE MEDICINAL PRODUCT

Darunavir Zentiva 400 mg, filmomhulde tabletten
Darunavir Zentiva 800 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Darunavir Zentiva 400 mg film-coated tablets:
Each film-coated tablet contains 400 mg of darunavir.
Excipient with known effect:
Each tablet contains 0.258 mg sunset yellow FCF (E110).

Darunavir Zentiva 800 mg film-coated tablets:
Each film-coated tablet contains 800 mg of darunavir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Darunavir Zentiva 400 mg film-coated tablets:
Light orange oval shaped film-coated tablet, debossed with '400' on one side and plain on the other side, with dimensions of approximately 17.1 mm x 8.6 mm.

Darunavir Zentiva 800 mg film-coated tablets:
Dark red oval shaped film-coated tablets, debossed with '800' on one side and plain on the other side, with dimensions of approximately 20.2 mm x 10.1 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Darunavir Zentiva, 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 Zentiva, co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of 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 Zentiva 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 Zentiva in such ART-experienced patients, genotypic testing should guide the use of Darunavir Zentiva (see sections 4.2, 4.3, 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 Zentiva 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 Zentiva 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 Zentiva. 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.

Darunavir is also available as an oral suspension for use in patients who are unable to swallow tablets (please refer to the Summary of Product Characteristics for oral suspension containing darunavir).

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 Zentiva 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 Zentiva 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 75 mg, 150 mg, Darunavir Zentiva 600 mg tablets or 100 mg/ml oral suspension containing darunavir.

* 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 Zentiva 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 Zentiva 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 Zentiva 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 Zentiva 400 mg/800 mg tablets can be used to construct the once daily

800 mg regimen. The dose of cobicistat to be used with Darunavir Zentiva in children less than 12 years of age has not been established.

- 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 100 mg/ml oral suspension containing darunavir, darunavir 75 mg, 150 mg or Darunavir Zentiva 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 Zentiva 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 Zentiva 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 medicinal product, another dose of Darunavir Zentiva with cobicistat or ritonavir should be taken with food as soon as possible. If a patient vomits more than 4 hours after taking the medicinal product, the patient does not need to take another dose of Darunavir Zentiva with cobicistat or ritonavir until the next regularly scheduled time.

Special populations
Elderly
Limited information is available in this population, and therefore, Darunavir Zentiva 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 Zentiva 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 Zentiva 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 Zentiva 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 Zentiva 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).

Darunavir Zentiva 400 mg and 800 mg tablets are not suitable for this patient population. Other formulations are available, see the Summary of Product Characteristics for darunavir 75 mg, 150 mg and DarunavirZentiva 600 mg tablets and 100 mg/ml oral suspension containing darunavir.

Pregnancy and postpartum
No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. Darunavir Zentiva/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 Zentiva/ritonavir may be considered as an alternative.

Method of administration
Patients should be instructed to take Darunavir Zentiva 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).
- Strong CYP3A inducers such as 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
- 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)
- ticagrelor (see section 4.5).

4.4 Special warnings and precautions for use

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

Darunavir 400 mg or 800 mg 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
DarunavirZentiva/ 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 Cmin 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 Zentiva/cobicistat should not be initiated during pregnancy, and women who become pregnant during therapy with Darunavir Zentiva/cobicistat should be switched to an alternative regimen (see sections 4.2 and 4.6). Darunavir Zentiva 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).

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).

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 strong CYP3A inducers such as 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 75 mg, 150 mg and Darunavir Zentiva 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).

Excipients
Darunavir Zentiva 400 mg tablets contain sunset yellow FCF (E110) which may cause allergic reactions.

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)
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 similar to the recommendations 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 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 product examples by therapeutic area	**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 didanosine C_{max} ↓ 16% darunavir AUC ↔ darunavir C_{min} ↔ darunavir C_{max} ↔	Boosted darunavir 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 boosted darunavir given with food.
Tenofovir disoproxil 245 mg once daily	tenofovir AUC ↑ 22% tenofovir C_{min} ↑ 37%	Monitoring of renal function may be indicated when boosted

	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)	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 (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). 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 co-administered with low dose ritonavir and etravirine

	darunavir AUC ↑ 15% darunavir C_{min} ↔ darunavir C_{max} ↔	**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: 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. 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	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

	400/100 mg in combination with indinavir 800 mg twice daily.	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/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 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. Co-administration of boosted darunavir and amiodarone, bepridil, dronedarone, ivabradine, quinidine, or ranolazine is contraindicated (see section 4.3).
Amiodarone Bepridil Dronedarone Ivabradine Quinidine Ranolazine		
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 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 boosted darunavir. For patients with renal impairment the Summary of Product Characteristics for clarithromycin should be consulted for the recommended dose.
ANTICOAGULANT/PLATELET AGGREGATION INHIBITOR		
Apixaban Rivaroxaban	Not studied. Co-administration of boosted darunavir with these anticoagulants may increase concentrations of the anticoagulant. (CYP3A and/or P-gp inhibition)	The use of boosted darunavir with a direct oral anticoagulant (DOAC) that is metabolised by CYP3A4 and transported by P-gp is not recommended as this may lead to an increased bleeding risk.
Dabigatran etexilate Edoxaban	dabigatran etexilate (150 mg): <u>darunavir/ritonavir 800/100 mg single dose:</u> dabigatran AUC ↑ 72% dabigatran C_{max} ↑ 64% <u>darunavir/ritonavir 800/100 mg once daily:</u> dabigatran AUC ↑ 18% dabigatran C_{max} ↑ 22% <u>darunavir/cobicistat 800/150 mg single dose:</u> dabigatran AUC ↑ 164% dabigatran C_{max} ↑ 164%	Darunavir/ritonavir: Clinical monitoring and/or dose reduction of the DOAC should be considered when a DOAC transported by P-gp but not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co-administered with darunavir/rtv. Darunavir/cobicistat: Clinical monitoring and dose reduction is required when a DOAC transported by P-gp but

	<u>darunavir/cobicistat 800/150 mg once daily:</u> dabigatran AUC ↑ 88% dabigatran Cmax ↑ 99%	not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co-administered with darunavir/cobi.
Ticagrelor	Based on theoretical considerations, co-administration of boosted darunavir with ticagrelor may increase concentrations of ticagrelor (CYP3A and/or P-glycoprotein inhibition).	Concomitant administration of boosted darunavir with ticagrelor is contraindicated (see section 4.3).
Clopidogrel	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.	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 medicinal products. The use of these medicinal products 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	Clinical monitoring is recommended when co-

	may increase concentrations of clonazepam. (CYP3A inhibition)	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} ↔ 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	Not studied. Boosted darunavir may increase antifungal plasma concentrations and posaconazole,	Caution is warranted and clinical monitoring is recommended. When co-administration is

Posaconazole Clotrimazole	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)	required the daily dose of itraconazole should not exceed 200 mg.
ANTIGOUT MEDICINAL PRODUCTS		
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%	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

	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 once every other day).	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 rifabutin is not recommended.
ANTINEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine	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.
Everolimus Irinotecan		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 medicinal products are concomitantly administered with boosted darunavir.
CORTICOSTEROIDS		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, fluticasone, budesonide, 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 boosted darunavir, resulting in reduced serum cortisol concentrations.	Concomitant use of boosted darunavir and corticosteroids (all routes of administration) that are metabolised by CYP3A may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. 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.	Systemic dexamethasone should be used with caution when combined with boosted darunavir.

	(CYP3A induction)	
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 atorvastatin AUC ↑ 290% Ω atorvastatin Cmax ↑ 319% Ω atorvastatin Cmin ND Ω Ω with darunavir/cobicistat 800/150 mg	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 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 Cmax ↑ 277%§ rosuvastatin Cmin 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.

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 co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalaemia. Alternative or additional contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with boosted darunavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.
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] with darunavir/ritonavir	
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-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) Zolpidem	Not studied. Sedative/hypnotics are extensively metabolised by CYP3A. Co-administration with boosted darunavir may cause a large increase in the concentration of these medicinal products.	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).

[†] 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.

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 of the offspring.

Because of the potential for adverse reactions in breast-fed infants, women should be instructed not to breast-feed if they are receiving darunavir.

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed.

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) 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 rare	thrombocytopenia, neutropenia, anaemia, leukopenia 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 uncommon	diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia gout, anorexia, decreased appetite, decreased weight, increased weight, hyperglycaemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase

MedDRA system organ class **Frequency category**	**Adverse reaction**
Psychiatric disorders	
common	insomnia
uncommon	depression, disorientation, anxiety, sleep disorder, abnormal dreams, nightmare, decreased libido
rare	confusional state, altered mood, restlessness
Nervous system disorders	
common	headache, peripheral neuropathy, dizziness
uncommon	lethargy, paraesthesia, hypoaesthesia, dysgeusia, disturbance in attention, memory impairment, somnolence
rare	syncope, convulsion, ageusia, sleep phase rhythm disturbance
Eye disorders	
uncommon	conjunctival hyperaemia, dry eye
rare	visual disturbance
Ear and labyrinth disorders	
uncommon	vertigo
Cardiac disorders	
uncommon	myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia
rare	acute myocardial infarction, sinus bradycardia, palpitations
Vascular disorders	
uncommon	hypertension, flushing
Respiratory, thoracic and mediastinal disorders	
uncommon	dyspnoea, cough, epistaxis, throat irritation
rare	rhinorrhoea
Gastrointestinal disorders	
very common	diarrhoea
common	vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence
uncommon	pancreatitis, gastritis, gastrooesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia
rare	stomatitis, haematemesis, cheilitis, dry lip, coated tongue
Hepatobiliary disorders	
common	increased alanine aminotransferase

MedDRA system organ class **Frequency category**	**Adverse reaction**
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, crystal nephropathy[§]
Reproductive system and breast disorders	
uncommon	erectile dysfunction, gynaecomastia
General disorders and administration site conditions	
common	asthenia, fatigue
uncommon	pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain
rare	chills, abnormal feeling, xerosis

[§] adverse reaction identified in the post-marketing setting. Per the guideline on Summary of Product Characteristics (Revision 2, September 2009), the frequency of this adverse reaction in the post-marketing setting was determined using the "Rule of 3".

Adverse reactions observed with darunavir/cobicistat in adult patients

MedDRA system organ class **Frequency category**	**Adverse reaction**
Immune system disorders	
common	(drug) hypersensitivity

MedDRA system organ class **Frequency category**	**Adverse reaction**
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 common uncommon	diarrhoea, nausea vomiting, abdominal pain, abdominal distension, dyspepsia, flatulence, pancreatic enzymes increased pancreatitis acute
Hepatobiliary disorders	
common uncommon	hepatic enzyme increased hepatitis*, cytolytic hepatitis*
Skin and subcutaneous tissue disorders	
very common common rare not known	rash (including macular, maculopapular, papular, erythematous, pruritic rash, generalised rash, and allergic dermatitis) angioedema, pruritus, urticaria drug reaction with eosinophilia and systemic symptoms*, Stevens-Johnson syndrome* toxic epidermal necrolysis*, acute generalised exanthematous pustulosis*
Musculoskeletal and connective tissue disorders	
common uncommon	myalgia, osteonecrosis*
Renal and urinary disorders	
rare	crystal nephropathy*§
Reproductive system and breast disorders	
uncommon	gynaecomastia*
General disorders and administration site conditions	
common uncommon	fatigue 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.

§ adverse reaction identified in the post-marketing setting. Per the guideline on Summary of Product Characteristics (Revision 2, September 2009), the frequency of this adverse reaction in the post-marketing setting was determined using the "Rule of 3".

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.

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 x 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.

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
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-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]
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)	77.6% (198/255)	73.2% (194/265)	4.4% (-3.0; 11.9)
< 100 000	35.9% (14/39)	51.6% (16/31)	-15.7% (-39.2; 7.7)
≥ 100 000			
With Baseline CD4+ cell count (x 10^6/l)	75.1% (184/245)	72.5% (187/258)	2.6% (-5.1; 10.3)
≥ 100	57.1% (28/49)	60.5% (23/38)	-3.4% (-24.5; 17.8)
< 100			
With HIV-1 clade			
Type B	70.4% (126/179)	64.3% (128/199)	6.1% (-3.4; 15.6)
Type AE	90.5% (38/42)	91.2% (31/34)	-0.7% (-14.0; 12.6)
Type C	72.7% (32/44)	78.8% (26/33)	-6.1% (-2.6; 13.7)
Other[c]	55.2% (16/29)	83.3% (25/30)	-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.

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 75 mg, 150 mg or <Invented name> 600 mg tablets and 100 mg/ml oral suspension containing darunavir.

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 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
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)
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)**
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 Cmax, AUC24h and Cmin were 49%, 56% and 92% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir Cmax, AUC24h and Cmin values were 37%, 50% and 89% lower, respectively, as compared with postpartum.

The unbound fraction was also substantially reduced, including around 90% reductions of Cmin 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 Cmin 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 darunavir alone, in mice, rats and dogs and in combination with ritonavir in rats and dogs.

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

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

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

Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, darunavir with low dose ritonavir should not be used in paediatric patients below 3 years of age.

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1 000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumours in rodents are considered to be of limited

relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

After 2 years administration of darunavir at exposures at or below the human exposure, kidney changes were observed in mice (nephrosis) and rats (chronic progressive nephropathy).

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose, microcrystalline (E460)
Crospovidone (type A) (E1202)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)

Tablet film-coat
Poly (vinyl alcohol) (E1203)
Titanium dioxide (E171)
Macrogol (3350) (E1521)
Talc (E553b)
Only for Darunavir Zentiva 400 mg: Sunset yellow FCF (E110)
Only for Darunavir Zentiva 800 mg: Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Darunavir Zentiva 400 mg film-coated tablets
White, High Density Polyethylene (HDPE) plastic bottle containing 60 tablets, stoppered with a white, polypropylene (PP), child resistant closure.
Darunavir Zentiva 800 mg film-coated tablets
White, High Density Polyethylene (HDPE) plastic bottle containing 30 tablets, stoppered with a white, polypropylene (PP), child resistant closure.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Zentiva k.s., U Kabelovny 130, 102 37 Praha 10 – Dolní Měcholupy, Czech Republic

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

400 mg: RVG 118331
800 mg: RVG 118333

9. DATUM VAN HERZIENING VAN DE TEKST

Datum van eerste verlening van de vergunning: 12 april 2017
Datum van laatste verlenging: 15 mei 2021

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft de rubrieken 1, 4.3, 4.4, 4.5, 4.6, 4.8 en 7: 24 mei 2023.