NEW ZEALAND DATA SHEET

DARUNAVIR MYLAN

1. Product Name

Darunavir Mylan, 300 mg, 400 mg & 600 mg, film coated tablets.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 300 mg, 400 mg or 600 mg of darunavir.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Darunavir Mylan 300 mg – White to Off white, oval shaped, biconvex film coated tablets debossed with 'M' on one side of the tablet and 'DV3' on other side.
Dimensions: (16.50 x 8.20) + 0.3 mm approximately.

Darunavir Mylan 400 mg – White to Off white, oval shaped, biconvex film coated tablets debossed with 'M' on one side of the tablet and 'DV4' on other side.
Dimensions: (19.15 x 9.60) + 0.3 mm approximately.

Darunavir Mylan 600 mg – White to Off white, oval shaped, biconvex film coated tablets debossed with 'M' on one side of the tablet and 'DV5' on other side.
Dimensions: (21.20 x 10.60) + 0.3 mm approximately.

4. Clinical Particulars

4.1 Therapeutic indications

Adult Patients

Darunavir Mylan (with low dose ritonavir as a pharmacokinetic enhancer) is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adult patients.

Paediatric patients

Darunavir Mylan (with low dose ritonavir as a pharmacokinetic enhancer) is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in treatment-experienced paediatric patients aged ≥ 6 years old and weighing at least 40 kg.

4.2 Dose and method of administration

Dose

Antiretroviral treatment-naïve patients

The recommended dosage of darunavir is 800 mg once daily (q.d.) taken with ritonavir 100 mg q.d. and with food.

Antiretroviral treatment-experienced patients

For antiretroviral treatment experienced patients, genotypic testing is recommended. However, when genotypic testing is not feasible, the darunavir/rtv once daily dosing regimen is recommended in HIV protease inhibitor naïve patients and the twice daily dosing regimen (see below) is recommended in protease inhibitor experienced patients.

When genotypic testing results are available, the recommended dosing is:

Antiretroviral treatment-experienced patients	
with no darunavir resistance associated mutations (DRV-RAMs)*	**with at least one darunavir resistance associated mutation (DRV-RAM)***
800 mg darunavir once daily (q.d.) taken with 100 mg ritonavir and with food	600 mg darunavir twice daily (b.i.d.) taken with 100 mg ritonavir and with food

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

The type of food does not affect the exposure to darunavir. Ritonavir (100 mg) is used as a pharmacokinetic enhancer of darunavir (see sections 4.5 and 5.2).

Special populations

Paediatric

Antiretroviral treatment-experienced paediatric patients (6 to < 18 years of age)

The recommended dose of darunavir/rtv for paediatric patients (6 to < 18 years of age and weighing at least 40 kg) is 600 mg darunavir/100 mg ritonavir b.i.d. and should not exceed the recommended adult dose (600/100 mg b.i.d.). Darunavir tablets should be taken with ritonavir twice daily and with food. The type of food does not affect exposure to darunavir.

Antiretroviral treatment-experienced children less than 6 years of age and antiretroviral treatment-naïve paediatric patients

The safety and efficacy of darunavir/rtv in antiretroviral treatment-experienced children aged 3 to less than 6 years and in antiretroviral treatment-naïve paediatric patients have not been established.

Darunavir/rtv should not be used in children below 3 years of age (see section 4.4).

Pregnancy and postpartum

No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. Caution should be used in patients with concomitant medications which may further decrease darunavir exposure (see sections 5.2 and 4.6).

Treatment with darunavir/cobicistat during pregnancy results in low darunavir exposure (see section 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 section 4.6). darunavir/ritonavir may be considered as an alternative.

Hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however darunavir should be used with caution in these patients due to increased darunavir exposure and adverse events. No pharmacokinetic data are available in

patients with severe hepatic impairment. Therefore, darunavir should not be used in patients with severe hepatic impairment (see section 4.4).

Renal impairment

No dose adjustment is required in patients with renal impairment (see section 4.4).

Method of administration

Darunavir must always be given with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The prescribing information of ritonavir must therefore be consulted prior to initiation of therapy with darunavir/rtv.

Do not halve tablets. Dose equivalence when tablets are divided has not been established.

After therapy with darunavir has been initiated, patients should be advised not to alter the dosage or discontinue therapy without consulting their physician.

For combination use with cobicistat and darunavir please refer to the cobicistat data sheet.

4.3 Contraindications

Hypersensitivity to darunavir or to any of the excipients.

Darunavir and ritonavir are both inhibitors of the CYP3A isoform. Darunavir/rtv should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These medicinal products include alfuzosin, antiarrhythmic drugs (e.g. amiodarone, bepridil, flecainide, systemic lidocaine, quinidine), apixaban, astemizole, cisapride, colchicine (in patients with renal and/or hepatic impairment), dapoxetine, dronedarone, elbasvir/grazoprevir, the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine and methylergonovine), ivabradine, lomitapide, lovastatin, lurasidone, midazolam (oral), naloxegol, pimozide, ranolazine, sildenafil (when used for treatment of pulmonary arterial hypertension), simvastatin, terfenadine and triazolam (see section 4.5).

Patients taking darunavir should not use products containing rifampicin or St. John's Wort because co-administration may result in reduced plasma concentrations of darunavir. This may result in loss of therapeutic effect and development of resistance.

Due to the need for co-administration of darunavir with low dose ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications and precautions.

In addition, carbamazepine, phenobarbital and phenytoin are also contraindicated for use with darunavir/cobicistat (see section 4.5). For further information on combination use with darunavir and cobicistat please refer to the cobicistat data sheet.

4.4 Special warnings and precautions for use

Darunavir must be co-administered with ritonavir and food to exert its therapeutic effect (see section 4.2). Failure to correctly administer darunavir with ritonavir and food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired therapeutic effect.

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 b.i.d. 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 b.i.d.

Increasing the dose of ritonavir did not significantly affect darunavir concentrations. It is not recommended to alter the dose of ritonavir.

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV. Appropriate precautions should continue to be employed.

Hepatotoxicity

Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with darunavir/rtv. During the clinical development program (N = 3063), hepatitis has been reported in 0.5% of patients receiving combination therapy with darunavir/rtv. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse events.

Post-marketing cases of liver injury, including some fatalities, have been reported. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection, and/or developing immune reconstitution syndrome. A causal relationship with darunavir/rtv therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with darunavir/rtv 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/rtv 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 on darunavir/rtv, interruption or discontinuation of treatment must be considered.

Severe skin reactions

During the 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. Stevens-Johnson Syndrome has been rarely (< 0.1%) reported; and during post-marketing experience toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and acute generalised exanthematous pustulosis have been reported very rarely (< 0.01%). Discontinue darunavir immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash (all grades, regardless of causality) occurred in 10.3% of patients treated with darunavir (see section 4.8). Rash was mostly mild-to-moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in patients using darunavir/rtv was 0.5%.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing darunavir/rtv + raltegravir compared to subjects receiving darunavir/rtv without raltegravir or raltegravir without darunavir/rtv. However, rash that was considered drug related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

Darunavir contains a sulfonamide moiety. Darunavir should be used with caution in patients with a known sulfonamide allergy. In clinical studies with darunavir/rtv, the incidence and severity of rash was similar in patients with or without a history of sulfonamide allergy.

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 HIV PIs. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with HIV 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.

Diabetes mellitus / hyperglycaemia

New onset diabetes mellitus, hyperglycaemia, or exacerbation of existing diabetes mellitus has been reported in patients receiving antiretroviral therapy, including HIV PIs. In some of these patients the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

Fat redistribution & metabolic disorders

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and HIV PIs and lipoatrophy and NRTIs has been hypothesized. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Immune reconstitution inflammatory syndrome

In HIV infected patients with severe immune deficiency at the time of institution 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 *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders such as Graves' disease have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment (see section 4.8).

Interactions with medicinal products

See section 4.3 and section 4.5.

Darunavir, ritonavir and cobicistat are metabolized by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir, ritonavir and cobicistat resulting in lower plasma concentrations of darunavir, ritonavir and cobicistat.

Darunavir boosted with cobicistat is more sensitive to CYP3A induction than darunavir boosted with ritonavir. (see **section 4.3** and **section 4.5**) Co-administration with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir, ritonavir and cobicistat and may result in increased plasma concentrations of darunavir, ritonavir and cobicistat (see **section 4.5**).

Co-administration of darunavir/cobicistat or darunavir/rtv 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 **section 4.5**).

Elderly

As limited information is available on the use of darunavir/rtv 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 section 5.2).

Use in children

Darunavir/rtv should not be used in children below 3 years of age in view of toxicity observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1,000 mg/kg) up to days 23 to 26 of age (see section 4.6).

The safety and efficacy of darunavir/rtv in antiretroviral treatment-experienced children aged 3 to less than 6 years and in antiretroviral treatment naïve paediatric patients have not been established.

Patients with co-existing conditions

Patients with hepatic impairment

The safety and efficacy of darunavir have not been established in patients with severe hepatic impairment. Therefore, darunavir should not be used in patients with severe hepatic impairment. Due to an increase in unbound darunavir plasma concentrations, darunavir should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2 and 5.2).

Patients with renal impairment

There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease. Since the renal clearance of darunavir is limited, a decrease in total body clearance is not expected 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 (see sections 4.2 and 5.2).

4.5 Interaction with other medicines and other forms of interaction

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as a pharmacokinetic enhancer. Darunavir may therefore have different recommendations for concomitant medications depending on whether darunavir is boosted with ritonavir or cobicistat.

Darunavir should not be used in combination with other antiretrovirals that also require pharmacokinetic boosting with ritonavir or cobicistat.

Darunavir, when used in combination with ritonavir, is an inhibitor of CYP3A and CYP2D6 and P-gp. Co-administration with medicinal products primarily metabolized by CYP3A, CYP2D6, or transported by P-gp may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect and adverse events (see Tables 1 and 2). Co-administration of darunavir/cobicistat or darunavir/rt with drugs that have active metabolite(s) formed by CYPA3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect.

Darunavir, ritonavir and cobicistat are metabolised by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir, ritonavir and cobicistat resulting in lower plasma concentrations of darunavir, ritonavir and cobicistat.

Darunavir boosted with cobicistat is more sensitive to CYP3A induction than darunavir boosted with ritonavir. Co-administration with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir, ritonavir and cobicistat and may result in increased plasma concentrations of darunavir, ritonavir and cobicistat.

For further information on combination use with cobicistat and darunavir please refer to the cobicistat data sheet.

Drugs that are contraindicated and not recommended for concomitant administration with darunavir/rtv are included in Table 1. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

The below list of examples of drug-drug interactions in Tables 1 and 2 are not comprehensive and therefore the data sheet 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.

Table 1. Drugs that should not be concomitantly administered with darunavir/rtv or darunavir/cobicistat

Drug class: drug name	Clinical comment
Alpha blocker: alfuzosin	Exposure to alfuzosin may be increased when co-administered with darunavir/rtv or darunavir/cobicistat. Concomitant use of darunavir/rtv or darunavir/cobicistat with alfuzosin is contraindicated.
Anti-anginal: ranolazine, ivabradine	Exposure to ranolazine may be increased (CYP3A inhibition) when co-administered with darunavir/rtv or darunavir/cobicistat. Concomitant use of darunavir/rtv or darunavir/cobicistat with ranolazine is contraindicated. Concomitant use of darunavir/rtv or darunavir/cobicistat with ivabradine is contraindicated.
Anticoagulants: Direct Oral Anticoagulants (DOACs), apixaban, dabigatran, edoxaban, rivaroxaban	DOACs are primarily metabolized by CYP3A4 and/or transported by P-gp. Co-administration with darunavir/rtv or darunavir/cobicistat may result in increased plasma concentrations of the DOAC, which may lead to an increased bleeding risk. Co-administration of a DOAC affected by both P-gp and CYP3A4, including rivaroxaban, is not recommended with darunavir/rtv or darunavir/cobicistat. Co-administration of apixaban with darunavir/rtv or darunavir/cobicistat is contraindicated. Clinical monitoring and/or dose adjustment is recommended when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran and edoxaban, is co-administered with darunavir/rtv or darunavir/cobicistat.
Antiarrhythmics: amiodarone, bepridil, disopyramide, dronedarone, flecainide, mexiletine, propafenone, lidocaine (systemic), quinidine	Concentrations of these antiarrhythmics may be increased when co-administered with darunavir/rtv or darunavir/cobicistat. Concomitant use of these antiarrhythmics and darunavir/rtv or darunavir/cobicistat is contraindicated.
Antihistamines: astemizole, terfenadine	Exposure to these antihistamines may be increased when co-administered with darunavir/rtv or darunavir/cobicistat. Concomitant use of darunavir/rtv or darunavir/cobicistat with astemizole and terfenadine is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac

Drug class: drug name	Clinical comment
	arrhythmias.
Antimycobacterials: rifampicin, rifapentine	Co-administration of darunavir/rtv or darunavir/cobicistat with rifampicin and rifapentine may decrease darunavir concentrations (induction of CYP3A), which may result in loss of therapeutic effect of darunavir. Co-administration of darunavir/rtv or darunavir/cobicistat with rifampicin is contraindicated. Co-administration of darunavir/rtv or darunavir/cobicistat with rifapentine is not recommended.
Antiplatelets: clopidogrel	Co-administration of darunavir/cobicistat or darunavir/rtv with clopidogrel is expected to decrease clopidogrel active metabolite plasma concentration, which may reduce the antiplatelet activity of clopidogrel. Co-administration of darunavir/cobicistat or darunavir/rtv with clopidogrel is not recommended.
Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	Exposure to the ergot alkaloids may be increased when co-administered with darunavir/rtv or darunavir/cobicistat. Concomitant use of darunavir/rtv or darunavir/cobicistat with ergot alkaloids is contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Gastrointestinal motility agent: cisapride	Exposure to cisapride may be increased when co-administered with darunavir/rtv or darunavir/cobicistat. Concomitant use of darunavir/rtv or darunavir/cobicistat with cisapride is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Gout agents: colchicine	Concomitant use of colchicine and darunavir/rtv or darunavir/cobicistat may increase the exposure to colchicine. The following dose adjustments are recommended for colchicine. For the treatment of gout-flares in patients on darunavir/rtv or darunavir/cobicistat, the recommended dose of colchicine is 0.6 mg, followed by 0.3 mg 1 hour later. Treatment course to be repeated no earlier than 3 days. For the prophylaxis of gout-flares in patients on darunavir/rtv or darunavir/cobicistat, the recommended dose of colchicine is 0.3 mg q.d. or q.o.d. For the treatment of familial Mediterranean fever in patients on darunavir/rtv or darunavir/cobicistat, the maximum dose of colchicine is 0.6 mg q.d. (may be given as 0.3 mg b.i.d.). Co-administration of darunavir/rtv or darunavir/cobicistat with colchicine in patients with renal or hepatic impairment is contraindicated.
Herbal products: St. John's wort (*Hypericum perforatum*)	Darunavir/rtv or darunavir/cobicistat should not be used concomitantly with products containing St. John's wort (Hypericum perforatum) because co-administration may cause significant decreases in darunavir or cobicistat plasma concentrations (induction of CYP3A). This may result in loss of therapeutic effect to darunavir. Co-administration of darunavir/rtv or darunavir/cobicistat with products containing St John's wort (Hypericum perforatum) is contraindicated.

Drug class: drug name	Clinical comment
Antipsychotic/Neuroleptic: pimozide, lurasidone	Concomitant use of pimozide and darunavir/rtv or darunavir/cobicistat may increase the exposure to pimozide (inhibition of CYP3A and CYP2D6). Concomitant use of darunavir/rtv or darunavir/cobicistat with pimozide is contraindicated due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias. Concomitant use of lurasidone and darunavir/rtv or darunavir/cobicistat may increase the exposure to lurasidone (inhibition of CYP3A4). Concomitant use of darunavir/rtv or darunavir/cobicistat with lurasidone is contraindicated.
Sedative/Hypnotics: midazolam, triazolam	Contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. Co-administration of darunavir/rtv or darunavir/cobicistat with oral midazolam or triazolam is contraindicated.
HIV-Protease inhibitor: lopinavir/ritonavir	Results of interaction trials with darunavir with or without ritonavir and lopinavir/ritonavir (1200 mg darunavir b.i.d. with or without 100 mg ritonavir b.i.d. and lopinavir/ritonavir 400/100 mg b.i.d. or 533/133.3 mg b.i.d.) demonstrated a decrease in the exposure (AUC) of darunavir by 40%. This may significantly affect the therapeutic effect of darunavir in HIV-1 infected patients. The appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer darunavir/rtv with lopinavir/ritonavir.
HIV-Protease inhibitor: saquinavir	An interaction trial between darunavir (400 mg b.i.d.), saquinavir (1000 mg b.i.d.), and low-dose ritonavir (100 mg b.i.d.) demonstrated that darunavir exposure was decreased by 26% when co-administered with saquinavir and ritonavir; saquinavir exposure was not affected when administered concomitantly with darunavir/ritonavir. It is not recommended to co-administer saquinavir and darunavir, with or without low-dose ritonavir.
Anticonvulsants: phenobarbital, phenytoin, carbamazepine	Phenobarbital and phenytoin are inducers of CYP450 enzymes. Darunavir/rtv should not be used in combination with these medicines, as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to darunavir. Co-administration of phenobarbital and phenytoin with darunavir/cobicistat may decrease cobicistat plasma concentrations and that of darunavir, which may result in loss of therapeutic effect and development of resistance. Co-administration of these drugs with darunavir/cobicistat is contraindicated. Co-administration of carbamazepine with darunavir/cobicistat may decrease cobicistat plasma concentrations and that of darunavir, which may result in loss of therapeutic effect and development of resistance. Co-administration of carbamazepine with darunavir/cobicistat is contraindicated. No dose adjustment for darunavir/rtv is recommended with co-administration of carbamazepine and darunavir/rtv, however the carbamazepine dose may need to be reduced by 25% to 50% (For further information, see Table 2).
HMG-CoA reductase	HMG-CoA reductase inhibitors, such as lovastatin and

Drug class: drug name	Clinical comment
inhibitors: atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin	simvastatin, which are highly dependent on CYP3A metabolism, are expected to have markedly increased plasma concentrations when co-administered with darunavir/rtv or darunavir/cobicistat. Increased concentrations of HMGCoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of darunavir/rtv or darunavir/cobicistat with lovastatin or simvastatin is contraindicated. For information regarding atorvastatin, pitavastatin, pravastatin, rosuvastatin see Table 2.
Other lipid modifying agents: lomitapide	Darunavir/rtv or darunavir/cobicistat is expected to increase the exposure of lomitapide when co-administered. Co-administration is contraindicated.
PDE-5 inhibitors for pulmonary arterial hypertension: sildenafil, tadalafil	A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope) when co-administered with darunavir/rtv or darunavir/cobicistat. Therefore, co-administration of darunavir/rtv or darunavir/cobicistat with sildenafil when used for pulmonary arterial hypertension is contraindicated. For information regarding tadalafil, see Table 2.
Hepatitis C Virus (HCV) direct-acting antivirals (NS3- 4A inhibitors): boceprevir, elbasvir/grazoprevir, glecaprevir/pibrentasvir	In an interaction trial between darunavir/rtv (600/100 mg b.i.d. from day 10 to 31) and boceprevir (800 mg three times daily from day 25 to 31), darunavir AUC_{last} (Geometric means ratio 0.56 (90% CI: 0.51, 0.61)) was reduced by 44% and boceprevir AUC_h (Geometric means ratio 0.68 (90% CI: 0.65, 0.72)) was reduced by 32%. It is not recommended to co-administer darunavir/rtv or darunavir/cobicistat with boceprevir. Concomitant use of elbasvir/grazoprevir and darunavir/rtv or darunavir/cobicistat may increase the exposure to grazoprevir (inhibition of OATP1B and CYP3A). Concomitant use of darunavir/rtv or darunavir/cobicistat with elbasvir/grazoprevir is contraindicated. Concomitant use of glecaprevir/pibrentasvir and darunavir/rtv or darunavir/cobicistat may increase the exposure to glecaprevir and pibrentasvir (inhibition of P-gp, BCRP and/or OATP1B1/3). Co-administration of darunavir/rtv or darunavir/cobicistat with glecaprevir/pibrentasvir is not recommended.
Opioid antagonist: naloxegol	Co-administration of darunavir/rtv or darunavir/cobicistat with naloxegol is contraindicated.
Treatment of premature ejaculation: dapoxetine	Co-administration of darunavir/rtv or darunavir/cobicistat with dapoxetine is contraindicated.

Table 2. Established and other potentially significant drug interactions: Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interactions

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
HIV-Antiviral agents: Integrase strand transfer inhibitors		
dolutegravir		Darunavir/rtv (600/100 mg b.i.d.) did not have a clinically relevant effect on dolutegravir exposure. Using cross-study comparisons to historical pharmacokinetic data, dolutegravir had no clinically significant effect on the pharmacokinetics of darunavir. Darunavir/rtv or darunavir/cobicistat co-administered with dolutegravir can be used without dose adjustment.
elvitegravir		When darunavir/ritonavir (600/100 mg b.i.d) is used in combination with elvitegravir, the dose of elvitegravir should be 150 mg daily. The pharmacokinetics and dosing recommendations for other doses of darunavir or with elvitegravir/cobicistat have not been established. Therefore, co-administration of darunavir/ritonavir in doses other than 600/100 mg b.i.d and elvitegravir is not recommended. Co-administration of darunavir/ritonavir and elvitegravir in the presence of cobicistat is not recommended.
raltegravir		Some clinical studies suggest raltegravir may cause a modest decrease in darunavir plasma concentrations. At present the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically relevant. Darunavir co-administered with low dose ritonavir or darunavir/cobicistat and raltegravir can be used without dose adjustments.
HIV-Antiviral agents: Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
delavirdine	↑ darunavir ↑ delavirdine	Co-administration of darunavir/ritonavir or darunavir/cobicistat and delavirdine may increase darunavir and delavirdine concentrations (inhibition of CYP3A). The appropriate doses of darunavir/ritonavir or darunavir/cobicistat and delavirdine have not been established. The combination of darunavir/ritonavir or darunavir/cobicistat and delavirdine is not recommended.
efavirenz	↓ darunavir ↑ efavirenz	An interaction trial between darunavir (300 mg twice daily [b.i.d.]), low-dose ritonavir (100 mg b.i.d.), and efavirenz (600 mg once daily [q.d.]) has been performed. In the presence of efavirenz a decrease of 13% for darunavir exposure was observed. Exposure to efavirenz increased by 21% when administered in combination with darunavir and ritonavir. Since this difference is not

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
		considered to be clinically relevant, the combination of darunavir/rtv and efavirenz can be used without dose adjustments. Co-administration of darunavir/cobicistat with efavirenz may decrease darunavir and/or cobicistat concentrations which may result in loss of therapeutic effect and development of resistance. Co-administration with darunavir/cobicistat with efavirenz is not recommended.
etravirine	↔ darunavir ↓ etravirine	A pharmacokinetic interaction study between darunavir/rtv and etravirine in healthy subjects indicated that etravirine has no significant effect on the pharmacokinetics of darunavir. In this study, when 100 mg b.i.d. of etravirine was co-administered with 600/100 mg b.i.d. darunavir/rtv a 37 % decrease in etravirine plasma levels was observed. However, when 200 mg b.i.d. etravirine was co-administered, exposure was increased by 80% compared with etravirine alone. Based on the results of this study, a dose adjustment for darunavir is not considered necessary when co-administered with 200 mg etravirine and 100 mg rtv. Co-administration with darunavir/cobicistat with etravirine may decrease darunavir and/or cobicistat concentrations which may result in loss of therapeutic effect and development of resistance. Co-administration with darunavir/cobicistat is not recommended.
nevirapine	↔ darunavir ↑ nevirapine	The results of an interaction trial with darunavir (400 mg b.i.d.), low-dose ritonavir (100 mg b.i.d.), and nevirapine (200 mg b.i.d.) demonstrated that darunavir exposure was not affected when administered concomitantly with nevirapine. Exposure to nevirapine increased by 27% (compared to historical controls) when administered in combination with darunavir and ritonavir. Since this difference is not considered to be clinically relevant, the combination of darunavir/rtv and nevirapine can be used without dose adjustments. Co-administration of darunavir/cobicistat with nevirapine may decrease darunavir and/or cobicistat concentrations which may result in loss of therapeutic effect and development of resistance. Nevirapine concentrations may be increased when co-administered with darunavir/cobicistat. Co-administration of darunavir/cobicistat with nevirapine is not recommended.

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
rilpivirine	↑ rilpivirine ↔ darunavir	In an interaction trial between darunavir/rtv (800/100 mg q.d.) and rilpivirine (150 mg q.d.), no clinically relevant effect on darunavir exposure was observed. Exposure to rilpivirine increased by 130% (2.3-fold) when administered in combination with darunavir/rtv. Since the difference is not considered to be clinically relevant, the combination of darunavir/rtv or darunavir/cobicistat and rilpivirine can be used without dose adjustment.
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine	↔ didanosine	Darunavir/rtv (600/100 mg b.i.d) did not significantly affect didanosine exposure. The combination of darunavir co-administered with 100 mg ritonavir or darunavir/cobicistat and didanosine can be used without dose adjustments. It is recommended that didanosine be administered on an empty stomach. Didanosine should be administered one hour before or two hours after darunavir/rtv or darunavir/cobicistat (which are administered with food).
tenofovir disoproxil fumarate	↔ darunavir ↑ tenofovir	The results of an interaction trial between darunavir (300 mg b.i.d.), low-dose ritonavir (100 mg b.i.d.), and tenofovir disoproxil fumarate (300 mg q.d.) demonstrated that darunavir exposure was not significantly affected when administered concomitantly with tenofovir disoproxil fumarate. Exposure to tenofovir disoproxil fumarate increased by 22% when administered in combination with darunavir and ritonavir. This finding is not considered to be clinically relevant. There was no change in the urinary excretion of tenofovir disoproxil fumarate or darunavir during co-administration. The combination of darunavir/rtv or darunavir/cobicistat and tenofovir disoproxil fumarate can be used without dose adjustments.
HIV-Antiviral agents: Protease Inhibitors (HIV PIs)		
ritonavir	↑ darunavir	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 b.i.d. Therefore, darunavir should only be used in combination with low-dose ritonavir as a pharmacokinetic enhancer (see sections 4.4 and 5).

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
atazanavir	↔ darunavir ↔ atazanavir	An interaction trial between darunavir (400 mg b.i.d.), low-dose ritonavir (100 mg b.i.d.), and atazanavir (300 mg q.d.) demonstrated that exposure to darunavir and atazanavir was not significantly affected when co-administered. Atazanavir can be co-administered with darunavir/rtv.
indinavir	↑ darunavir ↑ indinavir	An interaction trial between darunavir (400 mg b.i.d.), low-dose ritonavir (100 mg b.i.d.), and indinavir (800 mg b.i.d.) demonstrated that darunavir exposure was increased by 24% when co-administered with indinavir and ritonavir; indinavir exposure was increased by 23% when administered concomitantly with darunavir/ritonavir. When used in combination with darunavir/rtv, dose adjustment of indinavir from 800 mg b.i.d. to 600 mg b.i.d. may be warranted in case of intolerance.
emtricitabine / tenofovir alafenamide	↔ tenofovir alafenamide ↑ tenofovir	Tenofovir exposure is increased when darunavir /rtv is used in combination with emtricitabine/tenofovir alafenamide. The recommended dose of emtricitabine/tenofovir alafenamide when used in combination with darunavir /rtv is 200/10 mg daily.
HIV-Antiviral agents: CCR5 antagonist		
maraviroc	↑ maraviroc ↔ darunavir	When used in combination with darunavir/rtv or darunavir/cobicistat, the dose of maraviroc should be 150 mg twice daily. An interaction trial between darunavir/rtv (600/100 mg b.i.d.) and maraviroc (150 mg b.i.d.) demonstrated that in the presence of darunavir/rtv the exposure of maraviroc was increased by 305%. There was no apparent effect of maraviroc on darunavir/ritonavir exposure.
Other agents		
Analgesics: fentanyl, oxycodone, tramadol	↑ fentanyl ↑ oxycodone ↑ tramadol	Co-administration of darunavir/rtv with fentanyl, oxycodone or tramadol may increase concentrations of the analgesic. Clinical monitoring is recommended when co-administering darunavir/rtv with these analgesics.
Antiarrhythmic: digoxin	↑ digoxin	An interaction trial with darunavir/rtv (600/100 mg b.i.d.) and a single dose of digoxin (0.4 mg) showed an increase of digoxin AUC_{last} of 77% (ratio of Least Square Means (LSM) was 1.77 with a 90% CI of 0.90 to 3.50). The pharmacokinetics of digoxin were significantly influenced by darunavir/rtv. Therefore, it is recommended that the lowest possible dose of

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
		digoxin should initially be prescribed in case digoxin is given to patients on darunavir/rtv or darunavir/cobicistat therapy. Given that digoxin has a narrow therapeutic index, the digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject.
Anticoagulant: warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations may be affected when co-administered with darunavir/rtv or darunavir/cobicistat. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with darunavir/rtv or darunavir/cobicistat.
Anticonvulsant: carbamazepine	↑ carbamazepine ↔ darunavir	An interaction trial between darunavir/rtv (600/100 mg b.i.d.) and carbamazepine (200 mg b.i.d.) showed that the exposure to darunavir, co-administered with ritonavir, was unaffected by carbamazepine. Ritonavir exposure (AUC_{12h}) was decreased by 49%. For carbamazepine, AUC_{12h} was increased by 45%. No dose adjustment for darunavir/rtv is recommended. If there is a need to combine darunavir/rtv 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/rtv. Co-administration of carbamazepine with darunavir/cobicistat may decrease cobicistat plasma concentrations and that of darunavir, which may result in loss of therapeutic effect and development of resistance. Coadministration of carbamazepine with darunavir/cobicistat is contraindicated see Table 1).
clonazepam	↑ clonazepam	Co-administration of darunavir/rtv with clonazepam may increase concentrations of clonazepam. Clinical monitoring is recommended when co-administering darunavir/rtv with clonazepam
oxcarbazepine	↑ oxcarbazepine	Co-administration of darunavir/cobicistat with oxcarbazepine may decrease darunavir and/or cobicistat concentrations, which may result in loss of therapeutic effect and development of resistance. Co-administration of darunavir/cobicistat with oxcarbazepine is not recommended. Alternative anticonvulsants

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
		should be considered.
Anti-infective: clarithromycin	↑ clarithromycin	An interaction trial between darunavir (400 mg b.i.d.), low-dose ritonavir (100 mg b.i.d.), and clarithromycin (500 mg b.i.d.) demonstrated an increase in exposure to clarithromycin by 57%, while exposure to darunavir was not affected. Darunavir/rtv or darunavir/cobicistat and clarithromycin can be used without dose adjustment in patients with normal renal function. For patients with renal impairment, a dose reduction of clarithromycin should be considered.
Anti-emetics: domperidone	↑ domperidone	Use with caution: monitor for domperidone adverse reactions.
Antifungals: clotrimazole, fluconazole, isavuconazole, itraconazole, ketoconazole, posaconoazole, voriconazole	↑ clotrimazole, ↑ fluconazole, ↑ isavuconazole ↑ ketoconazole ↑ posaconazole ↑ darunavir ↑ itraconazole (not studied) ↓ voriconazole (not studied)	Clotrimazole, fluconazole, ketoconazole, posaconazole itraconazole, and voriconazole are moderate to potent inhibitors of CYP3A and/or some are substrates of CYP3A. Concomitant systemic use of these antifungals and darunavir/rtv or darunavir/cobicistat may increase plasma concentrations of darunavir or cobicistat. Simultaneously, plasma concentrations of some of these antifungals may be increased by darunavir/rtv or darunavir/cobicistat. This was confirmed in an interaction trial where the concomitant administration of ketoconazole (200 mg b.i.d.) with darunavir (400 mg b.i.d.) and ritonavir (100 mg b.i.d.) increased exposure of ketoconazole and darunavir by 212% and 42%, respectively. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Clinical monitoring is recommended when co-administering darunavir/rtv or darunavir/cobicistat with posaconazole or isavuconazole. Plasma concentrations of voriconazole may be decreased in the presence of darunavir/rtv and the effect in the presence of darunavir/cobicistat is unknown. Voriconazole should not be administered to patients receiving darunavir/rtv or darunavir/cobicistat unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Antimalarials: artemether/ lumefantrine	↓ artemether ↑ lumefantrine ↔ darunavir	An interaction trial between darunavir/rtv (600/100 mg b.i.d.) and artemether/lumefantrine (80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours) showed an increase in exposure to lumefantrine by 2.75-fold, while exposure to darunavir was not

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
	↓ dihydroartemisinin	affected. The exposure to artemether and its active metabolite, dihydroartemisinin, decreased by 16% and 18%, respectively. The combination of darunavir/rtv or darunavir/cobicistat and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution due to the potential risk of prolonged QT interval.
Antimycobacterial: rifabutin	↑ rifabutin ↓ darunavir	Rifabutin is a substrate of CYP450 enzymes. In an interaction trial, an increase of systemic exposure to darunavir by 57% was observed, when darunavir/rtv (600/100 mg b.i.d.) was administered with rifabutin (150 mg once every other day [q.o.d.]). Based on the safety profile of darunavir/rtv, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for darunavir/rtv. The interaction trial showed a comparable systemic exposure for rifabutin between treatment at 300 mg q.d. alone and at 150 mg q.o.d. in combination with darunavir/rtv (600/100 mg b.i.d.) with an increase in exposure to the active metabolite 25-O-desacetylrifabutin. A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg q.o.d.) and increased monitoring for rifabutin-related adverse events is warranted in patients receiving the combination. Co-administration of darunavir/cobicistat with rifabutin is not recommended. If combination of rifabutin and darunavir/cobicistat is required, the recommended dose of rifabutin is 150 mg every other day. Clinical monitoring is recommended when co-administering darunavir/cobicistat with rifabutin.
Antineoplastics: dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine	↑ dasatinib ↑ everolimus ↑ irinotecan ↑ nilotinib ↑ vinblastine ↑ vincristine	The plasma concentrations of these antineoplastics are expected to increase with co-administration of darunavir/rtv or darunavir/cobicistat (inhibition of CYP3A), resulting in the potential for adverse events usually associated with these agents. Caution should be exercised when combining one of these antineoplastic agents with darunavir/rtv or darunavir/cobicistat. Concomitant use of everolimus or irinotecan and darunavir/rtv or darunavir/cobicistat is not recommended.
Antiplatelets: prasugrel	↔ prasugrel active metabolite	Darunavir/cobicistat or darunavir/rtv is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
		of prasugrel.
Antipsychotics/ neuroleptics: perphenazine, risperidone, thioridazine, quetiapine	↑ perphenazine ↑ risperidone ↑ thioridazine ↑quetiapine	Concomitant use of perphenazine and darunavir/rtv or darunavir/cobicistat may increase concentrations of the neuroleptic (inhibition of CYP3A4 or CYP2D6). Clinical monitoring is recommended when co-administering darunavir/rtv or darunavir/cobicistat with perphenazine and a lower dose of the neuroleptic should be considered. Concomitant use of risperidone or thioridazine and darunavir/rtv or darunavir/cobicistat may increase the exposure to these antipsychotics (inhibition CYP2D6 and/or P-gp). Decrease of risperidone or thioridazine dose may be needed when co-administered with darunavir/rtv or darunavir/cobicistat. Concomitant use of quetiapine and darunavir/rtv or darunavir/cobicistat may increase the exposure to quetiapine (inhibition of CYP3A). The quetiapine dose should be substantially reduced when co-administered with darunavir. For details, refer to the quetiapine data sheet.
Beta agonists: salmeterol	↑ salmeterol	Concomitant use of salmeterol and darunavir/rtv or darunavir/cobicistat is not recommended. The combination may result in increased risk of cardiovascular adverse events with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Beta-Blockers: carvedilol, metaprolol, timolol	↑carvedilol ↑metaprolol ↑timolol	Co-administration of darunavir/rtv or darunavir/cobicistat and beta-blockers may increase concentrations of the beta-blocker (inhibition of CYP2D6). Clinical monitoring is recommended when co-administering darunavir/rtv or darunavir/cobicistat with beta-blockers and a lower dose of the beta- blocker should be considered.
Calcium Channel Blockers: amlodipine, diltiazem, felodipine, nicardipine, nifedipine verapamil	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g. felodipine, nifedipine, nicardipine, amlopidine, diltiazem and verapamil) may increase when darunavir/rtv or darunavir/cobicistat are co-administered (inhibition of CYP2D6 and/or CYP3A). Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: systemic/inhaled/nasal:	↑ betamethasone	Concomitant use of systemic or inhaled/nasal corticosteroids primarily metabolized by

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone	↑ budesonide ↑ fluticasone ↑ mometasone ↑ prednisone ↑ triamcinolone	CYP3A (betamethasone, budesonide, fluticasone, mometasone, prednisone or triamcinolone) and darunavir/rtv or darunavir/cobicistat may increase plasma concentrations of these corticosteroids. Concomitant use may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when co-administering darunavir/rtv or darunavir/cobicistat with corticosteroids. Alternatives should be considered, particularly for long term use.
Systemic dexamethasone	↓ darunavir	Systemic dexamethasone induces CYP3A and can thereby decrease darunavir plasma concentrations. This may result in loss of therapeutic effect to darunavir. Therefore, this combination should be used with caution.
Endothelin receptor antagonist: bosentan	↑ bosentan	Concomitant use of bosentan and darunavir/rtv or darunavir/cobicistat may increase plasma concentrations of bosentan. In patients who have been receiving darunavir/rtv or darunavir/cobicistat for at least 10 days, start bosentan at 62.5 mg q.d. or q.o.d. based upon individual tolerability. For patients on bosentan and initiating darunavir/rtv or darunavir/cobicistat, discontinue the use of bosentan at least 36 hours prior to initiation of darunavir/rtv or darunavir/cobicistat. After at least 10 days following the initiation of darunavir/rtv or darunavir/cobicistat, resume bosentan at 62.5 mg q.d. or q.o.d. based upon individual tolerability.
Eugeroics: armodafinil, modafinil	↓ darunavir ↓ cobicistat	Co-administration of darunavir/cobicistat with armodafinil or modafinil may decrease darunavir and/or cobicistat concentrations, which may result in loss of therapeutic effect and development of resistance. Co-administration of darunavir/cobicistat and armodafinil or modafinil is not recommended.
Gout therapy: colchicine	↑ colchicine	Concomitant use of colchicine and darunavir/rtv or darunavir/cobicistat may increase the exposure to colchicine. The following dose adjustments are recommended for colchicine. For the treatment of gout-flares in patients on darunavir/rtv or darunavir/cobicistat, the recommended dose of colchicine is 0.6 mg, followed by 0.3 mg 1 hour later. Treatment course to be repeated no earlier than 3 days. For the prophylaxis of

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
		gout-flares in patients on darunavir/rtv or darunavir/cobicistat, the recommended dose of colchicine is 0.3 mg q.d. or q.o.d. For the treatment of familial Mediterranean fever in patients on darunavir/rtv or darunavir/cobicistat, the maximum dose of colchicine is 0.6 mg q.d. (may be given as 0.3 mg b.i.d.). Co-administration of darunavir/rtv or darunavir/cobicistat with colchicine in patients with renal or hepatic impairment is contraindicated.
Oestrogen-based contraceptive: ethinyl oestradiol and norethindrone	↓ ethinyl oestradiol and norethindrone	The results of an interaction trial between darunavir/rtv (600/100 mg b.i.d.) and ethinyl oestradiol and norethindrone demonstrated that at steady-state systemic exposures to ethinyl oestradiol and norethindrone are decreased by 44% and 14%, respectively. The effect of darunavir/cobicistat on norethindrone exposure is not known.
ethinyl oestradiol and drospirenone	↓ ethinyl oestradiol and norethindrone	The results of an interaction trial between darunavir/cobicistat (800/150 mg q.d.) and ethinyl oestradiol and drospirenone demonstrated that single dose systemic exposures to ethinyl oestradiol and drospirenone are decreased by 30% and increased by 58%, respectively. The effect of darunavir/rtv on drospirenone exposure is not known. When darunavir/rtv or darunavir/cobicistat is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential of hyperkalaemia. No data are available to make recommendations on the use of darunavir/rtv or darunavir/cobicistat with other hormonal contraceptives. Therefore, additional or alternative (non-hormonal) methods of contraception are recommended.
HMG-CoA reductase inhibitors: atorvastatin, pitavastatin, pravastatin, rosuvastatin	↑ HMG-CoA reductase inhibitors	An interaction trial between darunavir (300 mg b.i.d.), low-dose ritonavir (100 mg b.i.d.), and atorvastatin (10 mg q.d.) demonstrated that exposure to atorvastatin was only 15% lower when co-administered with darunavir and ritonavir than when atorvastatin (40 mg q.d.) was administered alone. The results of an interaction trial with darunavir/cobicistat (800/150 mg g.d.) and atorvastatin (10 mg g.d.) showed a 3.9-fold increase in exposure to atorvastatin. When administration of atorvastatin and darunavir/rtv or darunavir/cobicistat is desired, it is

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
		recommended to start with an atorvastatin dose of 10 mg q.d. A gradual dose increase of atorvastatin may be tailored to the clinical response. An interaction study evaluating darunavir/rtv (800/100 mg q.d.) in combination with pitavastatin (4 mg q.d.) resulted in a decrease in pitavastatin exposure, which is not considered clinically relevant. The effect of darunavir/cobicistat is not known. Darunavir/rtv and pitavastatin can be co-administered without dose adjustment. Clinical monitoring is recommended when co-administering darunavir/cobicistat with pitavastatin and a lower dose of pitavastatin should be considered. An interaction trial between darunavir/ritonavir (600/100mg b.i.d.) and pravastatin (40mg, single dose) demonstrated that darunavir/ritonavir did not increase exposure to a single dose of pravastatin in most subjects but up to 5-fold in a limited subset of subjects. When administration of pravastatin and darunavir co-administered with low dose ritonavir or cobicistat is required, it is recommended to start with the lowest possible dose of pravastatin and titrate it up to the desired clinical effect while monitoring for safety. An interaction study evaluating darunavir/rtv (600/100 mg b.i.d.) in combination with rosuvastatin (10 mg q.d.) resulted in an increase in rosuvastatin exposure. The results of an interaction trial with darunavir/cobicistat (800/150 mg q.d.) and rosuvastatin (10 mg q.d.) showed a 1.9-fold increase in exposure to rosuvastatin. When administration of rosuvastatin and darunavir/rtv or darunavir/cobicistat is desired, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.
Acid reducing agents Proton Pump Inhibitors: esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	↔ darunavir	Co-administration of omeprazole (20 mg q.d.) or ranitidine (150 mg b.i.d.) and darunavir (400 mg b.i.d.) in the presence of low-dose ritonavir (100 mg b.i.d.) did not affect the exposure to darunavir. Based on these results, darunavir/rtv or darunavir/cobicistat can be co-administered with H2-receptor antagonists and proton pump inhibitors without dose

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
		adjustments.
Antacids: e.g. aluminium/ magnesium hydroxide, calcium carbonate	↔ darunavir	No interaction is expected between antacids and darunavir/rtv or darunavir/cobicistat. Darunavir/rtv or darunavir/cobicistat and antacids can be used concomitantly without dose adjustments.
H2-Receptor Antagonists: cimetidine, famotidine, nizatidine, ranitidine	↔ darunavir	Co-administration of ranitidine (150 mg b.i.d.) and darunavir/rtv (400/100 mg b.i.d.) did not affect the exposure to darunavir. Darunavir/rtv or darunavir/cobicistat can be co-administered with H2-receptor antagonists without dose adjustments.
Immunosuppressants: cyclosporine, everolimus, tacrolimus, sirolimus	↑ immuno-suppressants	Exposure to these immunosuppressants may be increased when co-administered with darunavir/rtv or darunavir/cobicistat. Therapeutic concentration monitoring of the immunosuppressive agent is recommended when co-administered with darunavir/rtv or darunavir/cobicistat. Concomitant use of everolimus and darunavir/rtv or darunavir/cobicistat is not recommended.
Narcotic analgesic/treatment of opioid dependence: methadone, buprenorphine/ naloxone	↔ methadone ↔ buprenorphine /naloxone	An interaction trial investigating the effect of darunavir/rtv (600/100 mg b.i.d.) on a stable methadone maintenance therapy showed an AUC decrease of 16% for R-methadone. Based on pharmacokinetic and clinical findings, no adjustment of methadone dosage is required when initiating co-administration of darunavir/rtv or darunavir/cobicistat. However, clinical monitoring is recommended as maintenance therapy may need to be adjusted in some patients. The results of an interaction trial with darunavir/rtv and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when administered with darunavir/rtv. Exposure of the active metabolite, norbuprenorphine, increased by 46%. No dose adjustment for buprenorphine was required. Careful clinical monitoring is recommended if darunavir/rtv or darunavir/cobicistat and buprenorphine are co-administered.
PDE-5 inhibitors for treatment of erectile dysfunction: avanafil,	↑ PDE-5 inhibitors	Treatment of erectile dysfunction: In an interaction trial, a comparable systemic exposure to sildenafil was observed for a single dose of 100 mg sildenafil alone and a

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
sildenafil, tadalafil, vardenafil		single dose of 25 mg sildenafil co-administered with darunavir (400 mg b.i.d.) and low-dose ritonavir (100 mg b.i.d.). Concomitant use of PDE-5 inhibitors with darunavir/rtv or darunavir/cobicistat should be done with caution. If concomitant use of darunavir/rtv or darunavir/cobicistat 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 dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours, is recommended. Co-administration of darunavir/rtv or darunavir/cobicistat and avanafil is not recommended.
PDE-5 inhibitors for pulmonary arterial hypertension: sildenafil, tadalafil		Treatment of pulmonary arterial hypertension: co-administration of darunavir/rtv or darunavir/cobicistat with sildenafil when used for pulmonary arterial hypertension is contraindicated (see Table 1). For the treatment of pulmonary arterial hypertension with tadalafil co-administered with darunavir/rtv or darunavir/cobicistat, a dose adjustment for tadalafil is warranted. In patients who have been receiving darunavir/rtv or darunavir/cobicistat for at least 1 week, start tadalafil at 20 mg q.d., and increase to 40 mg q.d. based upon individual tolerability. For patients on tadalafil and initiating darunavir/rtv or darunavir/cobicistat, discontinue the use of tadalafil at least 24 hours prior to initiating darunavir/rtv or darunavir/cobicistat and avoid the use of tadalafil during the initiation of darunavir/rtv or darunavir/cobicistat. After at least 1 week following the initiation of darunavir/rtv or darunavir/cobicistat, resume tadalafil at 20 mg q.d. and increase to 40 mg q.d. based upon individual tolerability.
Antidepressants: paroxetine, sertraline, amitriptyline, desipramine, imipramine, nortriptyline, trazodone	↔ darunavir ↓ sertraline ↓ paroxetine ↑ amitriptyline ↑ desipramine ↑ imipramine ↑ nortriptyline	An interaction trial between paroxetine (20 mg q.d.) or sertraline (50 mg q.d.) and darunavir (400 mg b.i.d.) and low- dose ritonavir (100 mg b.i.d.) demonstrated that exposure to darunavir was not affected by the co-administration of sertraline or paroxetine. Exposure to sertraline or paroxetine decreased by 49% and 39%, respectively, when co-administered with darunavir and ritonavir. The effect of darunavir/cobicistat on the exposure to sertraline or paroxetine is not known. If sertraline or paroxetine is co-administered with darunavir/rtv, the recommended approach is a careful dose

Drug class: drug name	Effect on concentration of darunavir or drug	Clinical comment
	↑ trazodone	titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with darunavir/rtv should be monitored for an antidepressant response. Clinical monitoring is recommended when co-administering darunavir/cobicistat with these antidepressants and a dose adjustment of the antidepressant may be needed. Concomitant use of darunavir/rtv or darunavir/cobicistat and the antidepressants amitriptyline, desipramine, imipramine, nortriptyline and trazodone may increase concentrations of the antidepressant (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when co-administering darunavir/rtv or darunavir/cobicistat with these antidepressants and a dose adjustment of the antidepressant may be needed.
Platelet aggregation inhibitors: ticagrelor	↑ ticagrelor	Co-administration of darunavir/rtv with ticagrelor may increase concentrations of ticagrelor. Co-administration of darunavir/rtv and ticagrelor is not recommended.
Sedatives/Hypnotics: buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zoldipem	↔ darunavir ↑ sedative/hypnotic	Co-administration of darunavir/rtv or darunavir/cobicistat with these sedatives/hypnotics may increase concentrations of the sedative/hypnotic (inhibition of CYP3A). Clinical monitoring is recommended when co-administering darunavir/rtv or darunavir/cobicistat with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. Co-administration of parenteral midazolam should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral midazolam should be considered, especially if more than a single dose of midazolam is administered. Co-administration of darunavir/rtv or darunavir/cobicistat with oral midazolam or triazolam is contraindicated (see Table 1).
Urinary antispasmodics: fesoterodine, solifenacin	↑ urinary antispasmodics	Use with caution: monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary.

Other NRTIs:

Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no drug interactions are expected for these drugs and darunavir/rtv or darunavir/cobicistat.

Other HIV protease inhibitors:

The concomitant administration of darunavir/rtv and HIV PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir has not been studied. Therefore, such concomitant administration is not recommended.

Effects of laboratory tests

None known.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B2.

There are no adequate and well controlled studies on pregnancy outcome with darunavir in pregnant women. Darunavir/ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk.

To monitor maternal-fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry has been established (http://www.apregistry.com). This is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products (ARVs). Prevalence of birth defects with first trimester exposure to any ARV was 2.8 (230 babies with birth defects out of 8277 live births as of data cut-off date of 31 July 2016). This rate is similar to 2nd and 3rd trimester exposure to the darunavir and other ARVs, as compared to overall prevalence of birth defects.

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 during the second and third trimesters, and postpartum. The pharmacokinetic data demonstrate that exposure to darunavir and ritonavir as part of an antiretroviral regimen was lower during pregnancy compared with postpartum (6 to 12 weeks). 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. Darunavir/ritonavir was well tolerated during pregnancy and postpartum. There were no new clinically relevant safety findings compared with the known safety profile of darunavir/ritonavir in HIV-1 infected adults (see sections 5.2 and 5.3).

Darunavir/cobicistat (800/150 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 7 pregnant women during the second and third trimesters, and postpartum (6 to 12 weeks). The pharmacokinetic data demonstrate that exposure to darunavir and cobicistat was substantially lower during pregnancy compared with postpartum (see section 5.2). Virologic response was sustained throughout the study period in 5 out of 6 women who completed the study; the subject with virologic failure was not compliant with study medication.

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 section 4.2). Darunavir/ritonavir may be considered as an alternative.

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

Breast-feeding

It is not known whether darunavir is excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk. Because of both the potential for HIV transmission and the potential for serious adverse events in breast-feeding infants, mothers should be instructed not to breastfeed if they are receiving darunavir (see section 5.3).

Fertility

For pre-clinical fertility data refer to section 5.3

4.7 Effects on ability to drive and use machines

No trials on the effects of darunavir in combination with ritonavir on the ability to drive or use machines have been performed. However, dizziness has been reported in some patients during treatment with regimens containing darunavir/rtv 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

The overall safety profile of darunavir is based on all available clinical trial and post-marketing data, and is consistent with the data presented below. Adverse drug reactions to darunavir/rtv identified in the safety assessment of the clinical trials in adults.

Please refer to the ritonavir data sheet for ritonavir-associated adverse reactions.

For combination use with cobicistat and darunavir please refer to the cobicistat data sheet.

Adverse drug reactions to darunavir/rtv (800/100 mg once daily) identified in antiretroviral treatment naïve patients:

The safety assessment is based on all safety data from the Phase III trial ARTEMIS comparing darunavir/rtv 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day in antiretroviral naïve HIV-1 infected adult patients. The total patient years exposure in the darunavir/rtv arm and the lopinavir/rtv arm was 626.6 and 608.1, respectively.

The majority of the ADRs reported during treatment with darunavir/rtv were mild in severity.

The most frequent (≥ 5%) ADRs of moderate to severe (grade 2 to 4) intensity were diarrhoea and headache and abdominal pain.

The most frequent (> 1%) ADRs of severe (grade 3 or 4) intensity were related to laboratory abnormalities. All other grade 3 or 4 ADRs were reported in less than 1% of the patients.

2.3% of the patients in the darunavir/rtv arm discontinued treatment due to ADRs.

Adverse Drug Reactions to darunavir/rtv 800/100 mg once daily of at least moderate intensity (grade 2 to 4) in antiretroviral treatment naïve HIV-1 infected adult patients are presented in the table below*:

System Organ Class Adverse Drug Reaction	**darunavir/rtv 800/100 mg once daily + TDF/FTC#** N = 343	**lopinavir/rtv 800/200 mg per day + TDF/FTC#** N = 346
Nervous system disorders		
Headache	5.8%	4.6%
Gastrointestinal disorders		
Abdominal pain	5.2%	5.8%
Acute pancreatitis	0.3%	0.3%
Diarrhoea	7.6%	14.7%
Dyspepsia	0.3%	0%
Flatulence	0.9%	0.9%

System Organ Class Adverse Drug Reaction	darunavir/rtv 800/100 mg once daily + TDF/FTC# N = 343	lopinavir/rtv 800/200 mg per day + TDF/FTC# N = 346
Nausea	2.6%	3.5%
Vomiting	1.5%	3.2%
Skin and subcutaneous tissue disorders		
Angioedema†	0.3%	0%
Lipodystrophy (lipohypertrophy, lipodystrophy,and lipoatrophy)	0.3%	0.6%
Pruritus	0.9%	0.6%
Rash	1.7%	4.0%
Stevens-Johnson Syndrome	0.3%	0%
Urticaria†	0.9%	0.3%
Musculoskeletal and connective tissue disorders		
Myalgia	0.6%	1.2%
Metabolism and nutrition disorders		
Anorexia	1.5%	0.9%
Diabetes mellitus	0.6%	0.6%
General disorders and administration site Conditions		
Asthenia	0.9%	0%
Fatigue	0.3%	2.6%
Immune system disorders		
(Drug) Hypersensitivity†	0.6%	1.4%
Immune reconstitution inflammatory syndrome	0.3%	0.3%
Hepatobiliary disorders		
Hepatitis acute, cytolytic hepatitis, hepatotoxicity	0.3%	0.6%
Psychiatric disorders		
Abnormal dreams	0.3%	0.3%

* Excluding laboratory abnormalities reported as ADRs
# Tenofovir disoproxil fumarate/emtricitabine
† Adverse drug reactions identified from post-marketing experience

Laboratory abnormalities, grade 2 to 4, considered ADRs, in antiretroviral treatment naïve HIV-1 infected adult patients are shown in the table below*:

Laboratory parameter	Limit	darunavir/rtv 800/100 mg once daily + TDF/FTC# N = 343	lopinavir/rtv 800/200 mg per day + TDF/FTC# N = 346
ALT			
Grade 2	> 2.5 to ≤ 5.0 x ULN	7.3%	6.1%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.9%	2.6%
Grade 4	> 10.0 x ULN	0.9%	2.9%
AST			
Grade 2	> 2.5 to ≤ 5.0 x ULN	6.1%	6.1%
Grade 3	> 5.0 to ≤ 10.0 x ULN	4.1%	1.8%
Grade 4	> 10.0 x ULN	1.2%	2.3%
ALP			

Laboratory parameter	Limit	darunavir/rtv 800/100 mg once daily + TDF/FTC[#] N = 343	lopinavir/rtv 800/200 mg per day + TDF/FTC[#] N = 346
Grade 2	> 2.5 to ≤ 5.0 x ULN	1.5%	1.2%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0%	0.3%
Grade 4	> 10.0 x ULN	0%	0%
Triglycerides			
Grade 2	500-750 mg/dl	2.6%	7.9%
Grade 3	751-1200 mg/dl	1.2%	4.7%
Grade 4	> 1200 mg/dl	0.6%	0.9%
Total cholesterol*			
Grade 2	240-300 mg/dl	16.4%	23.0%
Grade 3	> 300 mg/dl	1.2%	4.7%
LDL cholesterol*			
Grade 2	160-190 mg/dl	13.5%	9.6%
Grade 3	≥ 191 mg/dl	4.7%	5.0%
Elevated glucose levels			
Grade 2	126-250 mg/dl	7.3%	7.6%
Grade 3	251-500 mg/dl	0.9%	0%
Grade 4	> 500 mg/dl	0%	0%
Pancreatic lipase			
Grade 2	> 1.5 to ≤ 3.0 x ULN	1.8%	1.2%
Grade 3	> 3.0 to ≤ 5.0 x ULN	0.6%	0.6%
Grade 4	> 5.0 x ULN	0%	0.6%
Pancreatic amylase			
Grade 2	> 1.5 to ≤ 2.0 x ULN	4.7%	1.7%
Grade 3	> 2.0 to ≤ 5.0 x ULN	2.6%	2.9%
Grade 4	> 5.0 x ULN	0%	0.6%

* Grade 4 data not applicable in Division of AIDS grading scale
[#] Tenofovir disoproxil fumarate/emtricitabine

Adverse drug reactions to darunavir/rtv (600/100 mg twice daily) identified in antiretroviral treatment experienced adult patients – TITAN study

The safety assessment is based on all safety data from the Phase III trial TITAN comparing darunavir/rtv 600/100 mg b.i.d. versus lopinavir/ritonavir 400/100 mg b.i.d. in antiretroviral treatment experienced HIV-1 infected adult patients. The total patient years of exposure in the darunavir/rtv arm and the lopinavir/rtv arm was 462.5 and 436.1, respectively.

The majority of the ADRs reported during treatment with darunavir/rtv were mild in severity. The most frequent (≥ 5%) ADRs of moderate to severe (grade 2 to 4) intensity were diarrhoea, hypertriglyceridaemia, hypercholesterolaemia, nausea, abdominal pain, vomiting, lipodystrophy, hepatic enzymes increased and rash. The most frequent (> 1%) severe (grade 3 or 4) ADRs were lipodystrophy or related to laboratory abnormalities. All other grade 3 or 4 ADRs were reported in less than 1% of the patients. 4.7% of the patients discontinued treatment due to ADRs.

Adverse Drug Reactions to darunavir/rtv 600/100 mg b.i.d. of at least moderate intensity (grade 2 to 4) in antiretroviral treatment experienced HIV-1 infected adult patients in the TITAN trial are mentioned in the table below*:

System Organ Class Adverse Drug Reaction	darunavir/rtv 600/100 mg b.i.d. + OBR[#] N = 298	lopinavir/rtv 400/100 mg b.i.d. + OBR[#] N = 297

System Organ Class Adverse Drug Reaction	darunavir/rtv 600/100 mg b.i.d. + OBR[#] N = 298	lopinavir/rtv 400/100 mg b.i.d. + OBR[#] N = 297
Nervous system disorders		
Headache	2.7%	3.0%
Gastrointestinal disorders		
Abdominal distension	2.0%	0.3%
Abdominal pain	5.7%	2.7%
Acute pancreatitis	0.3%	0.3%
Diarrhoea	14.4%	19.9%
Dyspepsia	2.0%	1.0%
Flatulence	0.3%	1.0%
Nausea	7.0%	6.4%
Vomiting	5.4%	2.7%
Skin and subcutaneous tissue disorders		
Lipodystrophy (lipohypertrophy, lipodystrophy,and lipoatrophy)	5.4%	4.4%
Pruritus	1.0%	1.0%
Rash	5.0%	2.0%
Urticaria[†]	0.3%	0%
Musculoskeletal and connective tissue disorders		
Myalgia	1.0%	0.7%
Metabolism and nutrition disorders		
Anorexia	1.7%	2.0%
Diabetes mellitus	1.7%	0.3%
General disorders and administration site conditions		
Asthenia	3.4%	1.0%
Fatigue	2.0%	1.3%
Immune system disorders		
Immune reconstitution syndrome	0.3%	0%
Reproductive system and breast disorders		
Gynaecomastia	0.3%	0.3%
Psychiatric disorders		
Abnormal dreams	0.7%	0%

* Excluding laboratory abnormalities reported as ADRs
[#] Optimised Background Regimen
[†] Adverse drug reactions identified from post-marketing experience

Laboratory abnormalities, grade 2 to 4, considered ADRs, in antiretroviral treatment experienced HIV-1 infected adult patients in the TITAN trial are shown in the table below*:

Laboratory parameter	Limit	darunavir/rtv 600/100 mg b.i.d. + OBR[#] N = 298	lopinavir/rtv 400/100 mg b.i.d. + OBR[#] N = 297
ALT			
Grade 2	> 2.5 to ≤ 5.0 x ULN	6.9%	4.8%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.4%	2.4%
Grade 4	> 10.0 x ULN	1.0%	1.7%
AST			
Grade 2	> 2.5 to ≤ 5.0 x ULN	5.5%	6.2%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.4%	1.7%

Laboratory parameter	Limit	darunavir/rtv 600/100 mg b.i.d. + OBR# N = 298	lopinavir/rtv 400/100 mg b.i.d. + OBR# N = 297
Grade 4	> 10.0 x ULN	0.7%	1.7%
ALP			
Grade 2	> 2.5 to ≤ 5.0 x ULN	0.3%	0%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0.3%	0.3%
Grade 4	> 10.0 x ULN	0%	0%
Triglycerides			
Grade 2	500-750 mg/dl	10.4%	11.4%
Grade 3	751-1200 mg/dl	6.9%	9.7%
Grade 4	> 1200 mg/dl	3.1%	6.2%
Total cholesterol*			
Grade 2	240-300 mg/dl	24.9%	23.2%
Grade 3	> 300 mg/dl	9.7%	13.5%
LDL cholesterol*			
Grade 2	160-190 mg/dl	114.4%	13.5%
Grade 3	≥ 191 mg/dl	7.7%	9.3%
Elevated glucose levels			
Grade 2	126-250 mg/dl	10.0%	11.4%
Grade 3	251-500 mg/dl	1.4%	0.3%
Grade 4	> 500 mg/dl	0.3%	0%
Pancreatic lipase			
Grade 2	> 1.5 to ≤ 3.0 x ULN	2.8%	3.5%
Grade 3	> 3.0 to ≤ 5.0 x ULN	2.1%	0.3%
Grade 4	> 5.0 x ULN	0.3%	0%
Pancreatic amylase			
Grade 2	> 1.5 to ≤ 2.0 x ULN	6.2%	7.3%
Grade 3	> 2.0 to ≤ 5.0 x ULN	6.6%	2.8%
Grade 4	> 5.0 x ULN	0%	0%

* Grade 4 data not applicable in Division of AIDS grading scale
# Optimised Background Regimen

Adverse Drug Reactions to darunavir/rtv (600/100 mg twice daily) identified in adults in the pooled trials POWER 1, 2 and 3

In the pooled POWER trials, the total patient years of exposure was 812.4 in patients who immediately started treatment on darunavir/rtv 600/100 mg b.i.d. (see section 5.1).

The majority of the ADRs reported during treatment with darunavir/rtv were mild in severity. The most frequent (≥ 5%) moderate to severe (grade 2 to 4) ADRs were diarrhoea, headache, abdominal pain, nausea and vomiting. The most frequent grade 3 or 4 ADRs were increased hepatic and pancreatic enzymes, hypertriglyceridaemia, diarrhoea, hypercholesterolaemia, headache, abdominal pain and vomiting. All other grade 3 or 4 ADRs were reported in less than 1% of the patients.

2.1% of the patients discontinued treatment due to ADRs.

Adverse Drug Reactions to darunavir/rtv 600/100 mg b.i.d. of at least moderate intensity (grade 2 to 4) in antiretroviral treatment experienced HIV-1 infected adult patients in the pooled trials POWER 1, 2 and 3, are mentioned in the table below[1]:

System Organ Class Adverse Drug Reaction	darunavir/rtv 600/100 mg b.i.d. + OBR[2] (n=467)

System Organ Class Adverse Drug Reaction	**darunavir/rtv 600/100 mg b.i.d. + OBR[2]** (n=467)
Nervous system disorders	
Headache	8.8%
Gastrointestinal disorders	
Abdominal distension	1.9%
Abdominal pain	6.4%
Acute pancreatitis	0.4%
Diarrhoea	13.7%
Dyspepsia	1.5%
Flatulence	1.5%
Nausea	6.2%
Vomiting	5.6%
Skin and subcutaneous tissue disorders	
Lipodystrophy (lipohypertrophy, lipodystrophy, and lipoatrophy)	3.0%
Pruritus	2.6%
Rash	3.4%
Urticaria†	0.6%
Musculoskeletal and connective tissue disorders	
Myalgia	3.2%
Osteonecrosis†	0.6%
Metabolism and nutrition disorders	
Anorexia	2.4%
Diabetes mellitus	1.3%
General disorders and administration site conditions	
Asthenia	3.6%
Fatigue	3.9%
Immune system disorders	
(Drug) hypersensitivity†	0.6%
Immune reconstitution syndrome	0.2%
Hepatobiliary disorders	
Hepatitis acute, cytolytic hepatitis, hepatotoxicity	0.4%
Reproductive system and breast disorders	
Gynaecomastia	0.9%
Psychiatric disorders	
Abnormal dreams	0.4%

[1] Excluding laboratory abnormalities reported as ADRs.
[2] Optimised Background Regimen.
† Adverse drug reactions identified from post-marketing experience.

Laboratory abnormalities, considered ADRs, in antiretroviral treatment experienced HIV-1 infected adult patients in the pooled trials POWER 1, 2 and 3 are shown in the table below:

Laboratory parameter Preferred Term	**Limit**	**darunavir/rtv 600/100 mg b.i.d. + OBR[1]** N = 467
ALT		
Grade 2	> 2.5 to ≤ 5.0 x ULN	6.1%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.4%
Grade 4	> 10.0 x ULN	0.9%
AST		

Laboratory parameter Preferred Term	**Limit**	**darunavir/rtv** **600/100 mg b.i.d. + OBR**[1] N = 467
Grade 2	> 2.5 to ≤ 5.0 x ULN	6.9%
Grade 3	> 5.0 to ≤ 10.0 x ULN	3.0%
Grade 4	> 10.0 x ULN	0.6%
ALP		
Grade 2	> 2.5 to ≤ 5.0 x ULN	3.9%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0.9%
Grade 4	> 10.0 x ULN	0%
Triglycerides		
Grade 2	500 – 750 mg/dl	9.3%
Grade 3	751 – 1200 mg/dl	8.2%
Grade 4	> 1200 mg/dl	3.9%
Total cholesterol[2]		
Grade 2	240 – 300 mg/dl	17.7%
Grade 3	> 300 mg/dl	7.1%
LDL cholesterol[2]		
Grade 2	160 – 190 mg/dl	13.2%
Grade 3	≥ 191 mg/dl	9.1%
Elevated glucose levels		
Grade 2	126 – 250 mg/dl	15.4%
Grade 3	251 – 500 mg/dl	1.7%
Grade 4	> 500 mg/dl	0.2%
Pancreatic lipase		
Grade 2	> 1.5 to ≤ 3.0 x ULN	5.2%
Grade 3	> 3.0 to ≤ 5.0 x ULN	2.6%
Grade 4	> 5.0 x ULN	0.9%
Pancreatic amylase		
Grade 2	> 1.5 to ≤ 2.0 x ULN	7.4%
Grade 3	> 2.0 to ≤ 5.0 x ULN	7.8%
Grade 4	> 5.0 x ULN	1.1%

[1] Optimised Background Regimen.
[2] Grade 4 data not applicable in Division of AIDS grading scale.

Additional adverse drug reactions to darunavir/rtv identified in adult patients in other clinical studies

System Organ Class	**Adverse Drug Reaction**	**Incidence***
Musculoskeletal and connective tissue disorders	Osteonecrosis[+]	0.4%

* Incidence of at least grade 2 ADRs, calculated on pooled data of phase IIb and III trials (N=3,063)

[+] Adverse drug reactions identified from post-marketing experience.

Adverse drug reactions to darunavir/rtv identified in paediatric patients

The safety assessment in children and adolescents is based on the safety data from the Phase II trial DELPHI in which 80 antiretroviral treatment-experienced HIV-1 infected paediatric patients aged from 6 to < 18 years and weighing at least 20 kg received darunavir/rtv in combination with other antiretroviral agents (see section 5.1). Frequency, type and severity of adverse drug reactions in children and adolescents were comparable to those observed in adults.

Post-marketing experience

Adverse drug reactions identified during post-marketing experience

System Organ Class	Adverse Drug Reaction	Incidence
Skin and subcutaneous tissue disorders	DRESS	Very rare
	Toxic Epidermal Necrolysis	Very rare
	Acute generalised exanthematous pustulosis	Very rare

Rarely, events of rhabdomyolysis (associated with co-administration with HMG-CoA reductase inhibitors and darunavir) have been reported.

Effects of combination antiretroviral therapy

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has also been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (immune reactivation syndrome). Autoimmune disorders such as Graves' disease have also been reported in the context of immune reactivation syndrome (see section 4.4).

There have been reports of increased spontaneous bleeding in haemophilia patients receiving HIV PIs.

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

Special Populations

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

In patients co-infected with hepatitis B or C virus receiving darunavir/rtv, the incidence of adverse events and clinical chemistry abnormalities was not higher than in patients receiving darunavir/rtv who were not co-infected, except for increased hepatic enzymes. The pharmacokinetic exposure in co-infected patients was comparable to that in patients without co-infection. Increased AST/ALT monitoring should be considered in patients with hepatitis co-infection, especially during the first months of darunavir/rtv therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Symptoms

Human experience of acute overdose with darunavir/rtv is limited. Single doses up to 3200 mg of the oral solution of darunavir alone and up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

Management

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.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitor,

ATC code: J05AE10.

Mechanism of action

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

Darunavir binds to HIV-1 protease with a K_D of 4.5 x 10^{-12} M.

Darunavir was not a significant inhibitor of any of 13 tested human cellular proteases.

Pharmacodynamic effects

Antiviral activity in vitro

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages and laboratory strains of HIV-2 in acutely infected T-cell lines, with median EC_{50} values ranging from 1.2 to 8.5 nanoM (0.7 to 5.0 nanog/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 nanoM.

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

The EC_{50} value of darunavir increased by a median factor of 5.4 in the presence of 50% human serum *in vitro*.

Darunavir showed synergistic antiviral activity when studied in combination with the HIV protease inhibitors ritonavir, nelfinavir, or amprenavir and additive antiviral activity when studied in combination with the HIV protease inhibitors indinavir, saquinavir, lopinavir, atazanavir, or tipranavir, the nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs) zidovudine, lamivudine, zalcitabine, didanosine, stavudine, abacavir, emtricitabine, or tenofovir, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine, or efavirenz and the fusion inhibitor enfuvirtide. No antagonism was observed between darunavir and any of those antiretrovirals.

Resistance in vitro

In vitro selection of darunavir-resistant virus from wildtype HIV-1 was lengthy (> 3 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 400 nanoM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23 to 50-fold) harboured 2 to 4 amino acid substitutions in the protease gene.

In vitro selection of darunavir-resistant HIV-1 (range: 53 to 641-fold change in EC_{50} values [FC]) from 9 HIV-1 strains harbouring multiple HIV PI Resistance-Associated Mutations (RAMs) resulted in the overall emergence of 22 mutations in the protease, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V and I84V were present in more than 50% of the 9 darunavir-resistant isolates.

In 1113 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir and in 886 baseline isolates from the patients enrolled in the POWER 1 (TMC114 – C213) and POWER 2 (TMC114 – C202) trials and in the POWER 3 (TMC114 – C215 + TMC 114 – C208) analysis, only the subgroups with > 10 HIV PI RAMs showed a median FC for darunavir > 10.

Cross-resistance in vitro

Cross-resistance has been observed among HIV protease inhibitors. Darunavir has a < 10-fold decreased susceptibility against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir, showing that viruses resistant to most HIV PIs remain susceptible to darunavir.

Seven of the 9 darunavir-resistant viruses selected from HIV PI-resistant viruses had phenotypic data for tipranavir. Six of those showed a fold change in EC_{50} value < 3 for tipranavir, indicative of limited cross-resistance between these 2 HIV protease inhibitors.

Cross-resistance between darunavir and N(t)RTIs, NNRTIs or fusion inhibitors, is unlikely because the viral targets for those inhibitors are different.

Selection of viral resistance during darunavir/rtv therapy in vivo

In the 48 week analysis of the ODIN trial the number of virologic failures was comparable in the darunavir/rtv 800/100 mg q.d. group and the darunavir/rtv 600/100 mg b.i.d. group (22.1% vs. 18.2%, respectively). In the virologic failures in the darunavir/rtv 800/100 mg q.d. group 7 subjects (12%) with developing HIV PI RAMs were identified, compared to 4 subjects (10%) in the darunavir/rtv 600/100 mg b.i.d. group. One subject in the darunavir/rtv 800/100 mg q.d. group developed primary (i.e. major) HIV PI mutations, which included 3 DRV RAMs, resulting in decreased susceptibility to darunavir. All the virologic failures from the darunavir/rtv 600/100 mg b.i.d. group retained susceptibility to darunavir. Four (6.7%) and 3 (7.1%) virologic failures developed 1 or 2 NRTI RAMs in the darunavir/rtv 800/100 mg q.d. and the darunavir/rtv 600/100 mg b.i.d. groups, respectively. In 3 and 2 of these virologic failures in the darunavir/rtv 800/100 mg q.d. and the darunavir/rtv 600/100 mg b.i.d. groups, respectively, the development of these NRTI RAMs was associated with a decreased susceptibility to a NRTI included in the treatment regimen.

In the 96 week analysis of the ARTEMIS trial, the number of virologic failures was lower in the group of patients receiving darunavir/rtv 800/100 mg q.d. than in patients receiving lopinavir/ritonavir 800/200 mg per day (11.7% vs. 17.1%, respectively). In the virologic failures of the darunavir/rtv group, 3 patients with developing HIV PI RAMs were identified. In the virologic failures of the lopinavir/rtv group, 5 patients with developing PI RAMs were identified. None of the developing mutations in the darunavir/rtv group or in the lopinavir/rtv group were primary (i.e. major) HIV PI mutations. In 1 virologic failure of the darunavir/rtv group and 4 virologic failures of the lopinavir/rtv group, 1 developing NRTI RAM was identified. The development of the NRTI RAM at position 184 (n = 4) was associated with a decreased susceptibility to FTC included in the background regimen.

In the 96 week analysis of the TITAN trial, the number of virologic failures was lower in the group of subjects receiving darunavir/rtv 600/100 mg b.i.d. than in subjects receiving lopinavir/ritonavir 400/100 mg b.i.d. (13.8% vs. 25.6%, respectively). Fewer virologic failures treated with darunavir/rtv 600/100 mg b.i.d. than with lopinavir/rtv 400/100 mg b.i.d. developed primary (i.e. major) HIV PI mutations (7 vs. 25, respectively) or NRTI RAMs (4 vs. 20, respectively) or lost susceptibility to the PI (3 vs. 17, respectively) or NRTI(s) (4 vs. 20, respectively) used in the treatment regimen.

In a pooled analysis of the POWER and DUET trials, the identified amino acid substitutions that developed on darunavir/rtv 600/100 mg b.i.d. in ≥ 20% of the isolates from patients who experienced virological failure by rebound were V32I, I54L, and L89V. Amino acid substitutions that developed in 10 to 20% of the isolates were V11I, I13V, L33F, I50V, and F53L.

Cross-resistance with other HIV protease inhibitors in vivo

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

Of the viruses isolated from subjects receiving darunavir/rtv 600/100 mg b.i.d. experiencing virologic failures in the TITAN trial, 8% of those susceptible to darunavir at baseline developed decreased susceptibility to darunavir during treatment. In the same group of subjects, 97% to 100% that were susceptible at baseline to amprenavir, atazanavir, indinavir, lopinavir, saquinavir or tipranavir remained susceptible after darunavir/rtv treatment.

Of the viruses isolated from subjects receiving darunavir/rtv 800/100 mg q.d. experiencing virologic failure in the ODIN trial, 98% remained susceptible to darunavir after treatment. In the same group of subjects, 96% to 100% that were susceptible at baseline to amprenavir, atazanavir, indinavir, lopinavir, saquinavir or tipranavir remained susceptible to these HIV protease inhibitors after treatment. In the virologic failures receiving darunavir/rtv 600/100 mg b.i.d. no cross-resistance with other PIs was observed.

Of the viruses isolated from patients experiencing virologic failure by rebound from the darunavir/rtv 600/100 mg b.i.d. group of the POWER and DUET trials, 85% that were susceptible to darunavir at baseline developed decreased susceptibility to darunavir during treatment. In the same group of patients, 71% of viruses that were susceptible to tipranavir at baseline remained susceptible after treatment. In the POWER trials, patients with resistance to tipranavir (FC > 3) at baseline showed a mean change in viral load at Week 24 of –1.38 $\log_{10}$. Cross-resistance with the other HIV PIs could not be studied in the POWER or DUET trials, since most of the baseline viruses were already resistant to these PIs. Patients with no susceptible HIV PI at baseline (excluding tipranavir) showed a mean change in viral load at Week 24 of -1.57 $\log_{10}$.

Baseline genotype or phenotype and virologic outcome

In a pooled analysis of the darunavir/rtv 600/100mg b.i.d. groups of the POWER and DUET trials, the presence at baseline of three or more of the mutations V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V was associated with a decreased virologic response to darunavir/rtv.

In early treatment experienced patients (TITAN) three or more of these mutations were only found in 4% of the patients at baseline.

Response (HIV-1 RNA < 50 copies/mL at Week 24) to darunavir/rtv 600/100 mg b.i.d. by baseline genotype* and by use of enfuvirtide: As-treated analysis of the POWER and DUET trials

Number of mutations at baseline*	All % n/N	No/non-naïve use of enfuvirtide % n/N	Naïve use of enfuvirtide % n/N
All ranges	45% 455/1014	39% 290/741	60% 165/273
0 – 2	54% 359/660	50% 238/477	66% 121/183
3	39% 67/172	29% 35/120	62% 32/52
≥ 4	12%	7%	28%

	20/171	10/135	10/36

* Number of mutations from the list of mutations associated with a diminished response to darunavir/rtv (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V).

Baseline darunavir phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Response rates assessed by baseline darunavir phenotype are shown in the table below. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to darunavir.

Response (HIV-1 RNA < 50 copies/mL at Week 24) to darunavir/rtv 600/100 mg b.i.d. by baseline darunavir phenotype and by use of enfuvirtide: As-treated analysis of the POWER and DUET trials

Baseline darunavir phenotype (fold change ranges)	All % n/N	No/non-naïve use of enfuvirtide % n/N	Naïve use of enfuvirtide % n/N
All ranges	45% 455/1014	39% 290/741	60% 165/273
< 10	55% 364/659	51% 244/477	66% 120/182
10 - 40	29% 59/203	17% 25/147	61% 34/56
> 40	8% 9/118	5% 5/94	17% 4/24

In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to treatment history of the individual patient and the patterns of mutations associated with different agents. When available, genotypic or phenotypic testing can be performed to guide the use of darunavir.

Clinical efficacy and safety

The evidence of efficacy of darunavir/rtv 800/100 mg once daily (q.d.) is based on the analyses of 96 week data from the randomised, controlled, open-label Phase III trial ARTEMIS in antiretroviral treatment naïve HIV-1 infected patients comparing darunavir/rtv 800/100 mg q.d. with lopinavir/rtv 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 q.d. (TDF) and emtricitabine 200 mg q.d. (FTC).

HIV-1 infected patients who were eligible for this trial had plasma HIV-1 RNA > 5000 copies/mL. Randomisation was stratified by screening plasma viral load and screening CD4+ cell count. Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 50 copies/mL.

Demographics and baseline characteristics were balanced between the darunavir/rtv arm and the lopinavir/rtv arm. The 343 patients on darunavir/rtv 800/100 mg q.d. had a median age of 34 years (range 18 to 70), 70% were male, 40% white, 23% black, 23% hispanic, and 13% asian. The mean baseline plasma HIV-1 RNA was 4.86 $\log_{10}$ copies/mL and the median baseline CD4+ cell count was 228 x 10^6 cells/L (range 4 – 750 x 10^6 cells/L).

Below table shows the efficacy data of the 48 week analyses from the ARTEMIS trial.

Efficacy data from the ARTEMIS trial (48 week analysis)

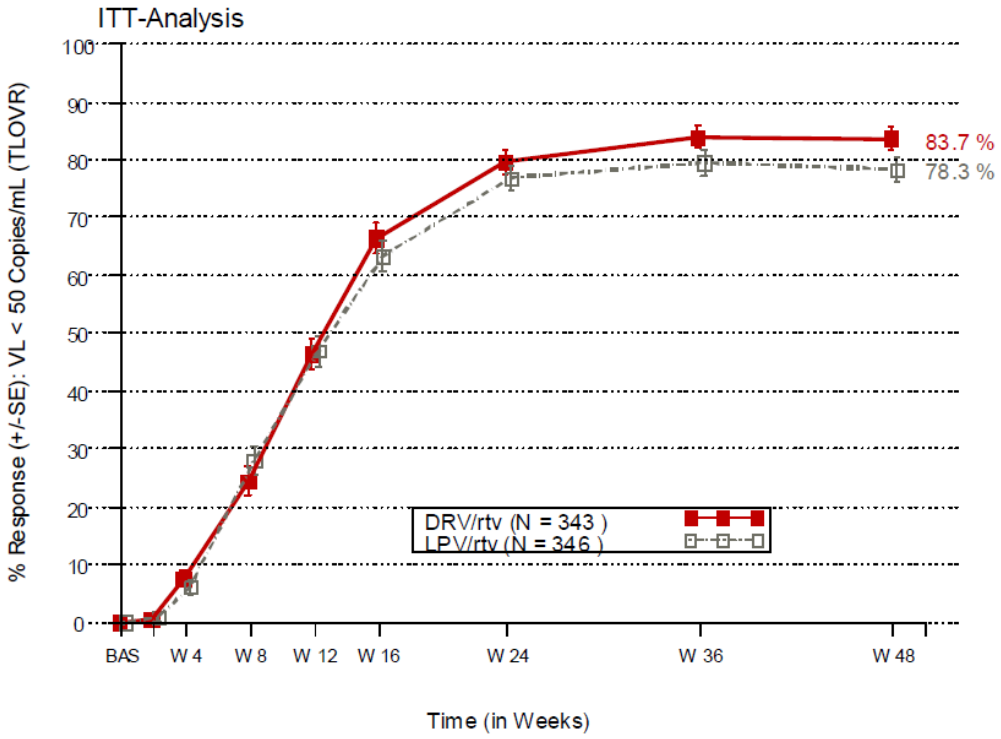
Outcomes	At week 48[a]			At week 96[b]		
	darunavir/rtv 800/100 mg q.d. N = 343	lopinavir/rtv 800/200 mg per day N = 346	Treatment difference (95% CI of difference)	darunavir/rtv 800/100 mg q.d. N = 343	lopinavir/rtv 800/200 mg per day N = 346	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/mL[c]	287 (83.7%)	271 (78.3%)	5.3 (-0.5; 11.2)[d]	271 (79.0%)	245 (70.8%)	8.2 (1.7; 14.7)[d]
HIV-1 RNA < 400 copies/mL[c]	301 (87.8%)	295 (85.3%)	2.5 (-2.6; 7.6)[d]	285 (83.1%)	268 (77.5%)	5.6 (-0.3; 11.6)
mean HIV-1 RNA log change from baseline (log_{10} copies/mL)[e]	-2.77	-2.65	-0.11[f] (-0.30; 0.07)[d]	–2.64	–2.45	-0.20[f] (-0.40; 0.01)[d]
median CD4+ cell count change from baseline (x 10^6/L)[e]	137	141		171	188	

a) Data based on analysis at week 48
b) Data based on analysis 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
f) Difference in means

In the 48 week analysis, the virologic response (HIV-1 RNA < 50 copies/mL) for the darunavir/rtv arm was 83.7% and for the lopinavir/rtv arm 78.3% (Figure 1). Statistical comparisons between the treatment arms at week 48 confirmed non-inferiority of DRV/rtv versus lopinavir/rtv (p-value < 0.001) for both ITT (Intent-To-Treat) & OP (On Protocol) population.

Analyses of data at 96 weeks of treatment in the ARTEMIS trial demonstrated sustained antiretroviral efficacy and immunological benefit. In the 96 week analysis, virologic response (HIV-1 RNA < 50 copies/mL) was 79.0% and 70.8% for the darunavir/rtv arm and lopinavir/ritonavir arm, respectively. Non-inferiority in virologic response was demonstrated (p < 0.001) for both ITT and OP population, furthermore superiority of the darunavir/rtv arm over the lopinavir/rtv arm was demonstrated (p = 0.012 for the ITT population and p = 0.011 for the OP population).

Figure 1. Virologic Response Over Time: Percentage of Subjects with Viral Load < 50 Copies/mL (ITT – TLOVR) – ARTEMIS



The virological response (< 50 copies/mL) at 96 weeks by baseline viral load and baseline CD4+ cell count is presented in below table.

Virologic response (HIV-1 RNA < 50 copies/mL) by baseline viral load

	darunavir/rtv 800/100 mg q.d. N = 343		lopinavir/rtv 800/200 mg per day N = 346		treatment difference
	N	number of responders at week 96 n (%)	N	number of responders at week 96 n (%)	Difference in % response (95% CI of difference in % response)[a]
Baseline plasma viral load (copies/mL)					
< 100.000	226	182 (80.5%)	226	170 (75.2%)	5.3 (-2.3; 13.0)
≥ 100.000	117	89 (76.1%)	120	75 (62.5%)	13.6 (1.9; 25.3)
Baseline CD4+ cell count (x 10^6/L)					
< 200	141	111 (78.7%)	148	96 (64.9%)	13.9 (3.5; 24.2)
≥ 200	202	160 (79.2%)	198	149 (75.3%)	4.0 (-4.3; 12.2)

a) Based on a normal approximation to the difference in % response.

Efficacy of darunavir/rtv (800/100 mg once daily) in treatment-experienced adult patients

The evidence of comparable efficacy of darunavir/rtv 800/100 mg once daily and darunavir/rtv 600/100 mg twice daily in treatment-experienced patients with no darunavir RAMs is based on the 48 week analysis of the Phase III trial ODIN.

ODIN is a randomised, open-label trial comparing darunavir/rtv 800/100 mg once daily to darunavir/rtv 600/100 mg twice daily in treatment-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 viral load of > 1,000 HIV-1 RNA copies/ml. Both arms used an optimised background regimen consisting of ≥ 2 NRTIs selected by the investigator.

Demographics and baseline characteristics were balanced between the darunavir/rtv once daily arm and the darunavir/rtv twice daily arm. The 590 patients in total had a median age of 40 years (range 18-77), 64% were male, 36% white, 26% black, 18% hispanic, and 15% asian. The mean baseline plasma HIV-1 RNA was 4.16 $\log_{10}$ copies/mL and the median baseline CD4+ cell count was 228 x 10^6 cells/l (range 24 – 1306 x 10^6 cells/L).

The table below shows the efficacy data of the 48 week analysis from the ODIN trial:

ODIN			
Outcomes	darunavir/rtv 800/100 mg once daily + OBR N = 294	darunavir/rtv 600/100 mg twice daily + OBR N = 296	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/mL[a]	212 (72.1%)	210 (70.9%)	1.2% (-6.1; 8.5)[b]
mean HIV-1 RNA log change from baseline ($\log_{10}$ copies/mL)[e]	-1.84	-1.80	-0.04[d] (-0.24; 0.16)
mean CD4+ cell count change from baseline (x 10^6/L)[c]	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] Last Observation Carried Forward imputation
[d] Difference in means
[e] NC=F

In the 48 week analysis, the virologic response defined as a confirmed plasma HIV-1 RNA viral load < 50 copies/mL, was 72.1% for the darunavir/rtv once daily arm and 70.9% for the darunavir/rtv twice daily arm. Statistical comparisons between the treatment arms at week 48 confirmed non-inferiority of darunavir/rtv once daily versus darunavir/rtv twice daily for both the ITT and OP population (p-value < 0.001).

Efficacy of darunavir/rtv (600/100 mg twice daily) in treatment experienced lopinavir-naïve adult patients.

The evidence of efficacy of darunavir/rtv 600/100 mg b.i.d. in treatment experienced patients is based on the 96 week analysis of the Phase III trial TITAN in treatment experienced, lopinavir/rtv naïve patients and on the analyses of 96 week data from the Phase IIb trials POWER 1, 2 and 3, in patients with high level of PI resistance.

TITAN is a randomised, controlled, open-label Phase III trial comparing darunavir/rtv 600/100 mg b.i.d. versus lopinavir/rtv 400/100 mg b.i.d. in antiretroviral treatment experienced, lopinavir/rtv naïve HIV-1 infected adult patients. Both arms used an optimised background regimen (OBR) consisting of at least 2 antiretrovirals (NRTIs with or without NNRTIs).

HIV-1 infected patients who were eligible for this trial had plasma HIV-1 RNA > 1000 copies/mL and were on a highly active antiretroviral therapy regimen (HAART) for at least 12 weeks.

Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 400 copies/mL. Analyses included 595 patients in the TITAN trial who had completed 96 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the darunavir/rtv arm and the lopinavir/ritonavir arm. The 298 patients on darunavir/rtv 600/100 mg b.i.d. had a median age of 40 years (range 18 to 68), 77% were male, 54% white, 18% black, 15% hispanic, and 9% asian. The mean baseline plasma HIV-1 RNA was 4.33 $\log_{10}$ copies/ml and the median baseline CD4+ cell count was 235 x 10^6 cells/L (range 3 to 831 x 10^6 cells/L).

Below table shows the efficacy data of the 48 week and 96 week analyses from the TITAN trial.

Efficacy data from the TITAN trial (48 week analysis)

Outcomes	At week 48[a]			At week 96[b]		
	darunavir/rtv 600/100 mg b.i.d. + OBR N = 298	lopinavir/rtv 400/100 mg b.i.d. + OBR N = 297	Treatment difference (95% CI of difference)	darunavir/rtv 600/100 mg b.i.d. + OBR N = 298	lopinavir/rtv 400/100 mg b.i.d. + OBR N = 297	Treatment difference (95% CI of difference)
HIV-1 RNA < 400 copies/mL[c]	228 (76.5%)	199 (67.0%)	9.5% (2.3; 16.7)[d]	199 (66.8%)	175 (58.9%)	7.9% (0.1; 15.6)[d]
HIV-1 RNA < 50 copies/mL[c]	211 (70.8%)	179 (60.3%)	10.5% (-2.9; 18.1)[d]	180 (60.4%)	164 (55.2%)	5.2% (-2.8; 13.1)[d]
mean HIV-1 RNA log change from baseline ($\log_{10}$ copies/mL)[e]	-1.95	-1.72	-0.23[f] (-0.44; 0.02)[d]	–1.71	–1.52	-0.19[f] (-0.40; 0.03)[d]
median CD4+ cell count change from baseline (x 10^6/L)[e]	88	81		81	93	

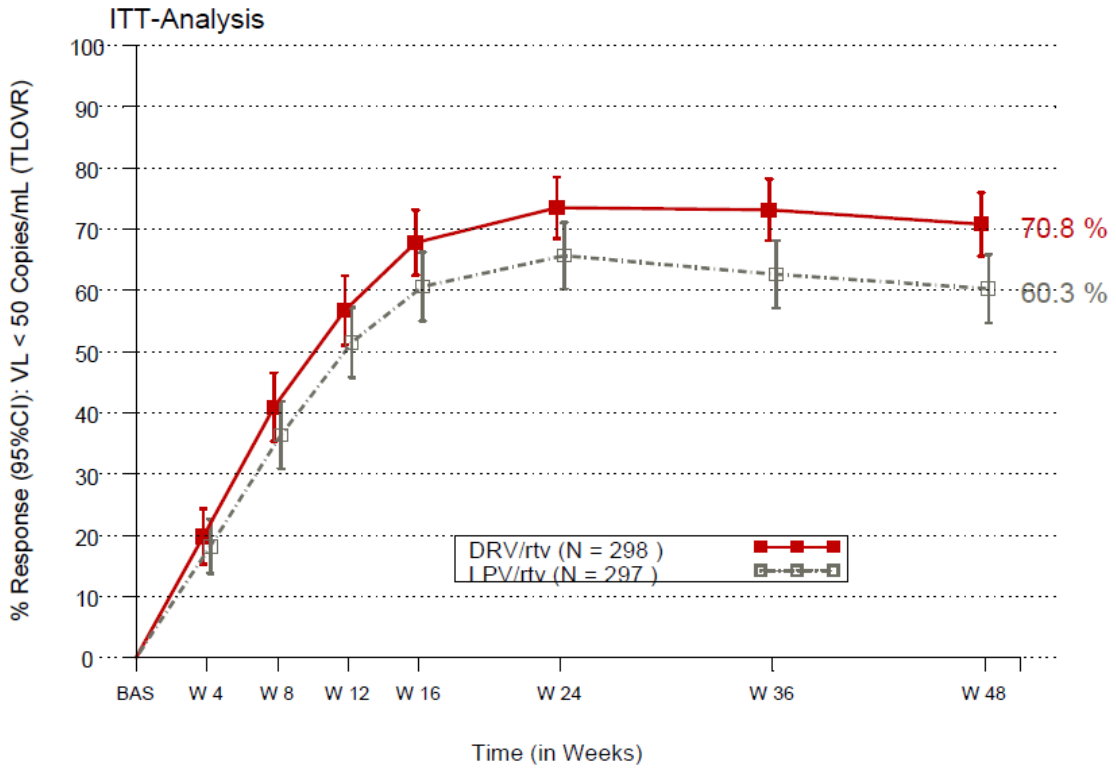
a) Data based on analyses at week 48
b) Data based on analyses at week 96
c) Imputations according to the TLOVR algorithm
d) Based on normal approximation to the difference in % response
e) NC=F
f) Difference in means

In the 48 week analysis, virologic response, defined as the percentage of subjects with plasma HIV-1 RNA level < 400 copies/mL, was 76.5% and 67.0% for the darunavir/rtv arm and lopinavir/rtv arm, respectively. Non-inferiority in virologic response was demonstrated (p < 0.001) for both the ITT (Figure 2) and OP population.

Analyses of data at 96 weeks of treatment in the TITAN trial demonstrated sustained antiretroviral efficacy and immunological benefit. In the 96 week analysis, virologic response, defined as the percentage of subjects with plasma HIV-1 RNA level < 400 copies/mL, was 66.8% and 58.9% for the darunavir/rtv arm and lopinavir/rtv arm, respectively. Non-inferiority in virologic response was demonstrated (p < 0.001) for both ITT and OP population, furthermore superiority of darunavir/rtv

over the lopinavir/rtv arm was demonstrated (p = 0.034 for the ITT population and p = 0.033 for the OP population). 60.4% of patients on darunavir/rtv reached HIV-1 RNA less than 50 copies/mL versus 55.2% in the lopinavir/rtv arm.

Figure 2. Virologic Response Over Time: Percentage of Subjects with Viral Load < 50 Copies/mL (ITT – TLOVR) – TITAN



Efficacy of darunavir/rtv in treatment-experienced adult patients who failed more than one PI-containing regimen

POWER 1 (TMC114 – C213) and POWER 2 (TMC114 – C202) are randomised, controlled Phase 2b trials in patients with a high level of HIV PI resistance, consisting of 2 parts: an initial partially blinded, dose-finding part and a second long term part in which all patients randomised to darunavir/rtv received the recommended dose of 600/100 mg b.i.d.

HIV-1 infected patients who were eligible for these trials had plasma HIV-1 ribonucleic acid (RNA) > 1000 copies/mL, had prior treatment with HIV PI(s), NNRTI(s) and NRTI(s), had at least 1 primary (i.e. major) PI mutation at screening and were on a stable HIV PI-containing regimen at screening for at least 8 weeks. Randomisation was stratified by the number of PI mutations, screening viral load and the use of enfuvirtide.

Demographics and baseline characteristics were balanced between the darunavir/rtv arm and the comparator HIV PI arm. In both trials combined, the 131 patients on darunavir/rtv 600/100 mg b.i.d. had a median age of 43 years (range 27 to 73), 89% were male, 81% white, 10% black and 7% hispanic. The mean baseline plasma HIV-1 RNA was 4.61 $\log_{10}$ copies/mL and the median baseline CD4+ cell count was 153 x 10^6 cells/L (range 3 to 776 x 10^6 cells/L). The median darunavir FC was 4.3. In the darunavir/rtv 600/100 mg b.i.d. arm patients had prior exposure to a mean of 4 HIV PIs, 5 NRTIs and 1 NNRTI versus 4 PIs, 6 NRTIs and 1 NNRTI in the comparator arm. Twenty percent of the patients in the darunavir/rtv arm had prior use of enfuvirtide versus 17% in the comparator arm.

The virologic response, defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 $\log_{10}$ versus baseline, was evaluated in patients receiving darunavir/rtv plus an optimised background regimen (OBR) versus a control arm receiving an investigator-selected PI(s) regimen plus an OBR.

The OBR consisted of at least 2 NRTIs with or without enfuvirtide (ENF). Based on resistance testing and prior medical history, selected PIs in the control arm included: lopinavir/ritonavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%. 23% of the control patients used dual-boosted HIV PIs. Approximately 47% of all patients used enfuvirtide and 35% of the use was in patients who were ENF-naïve.

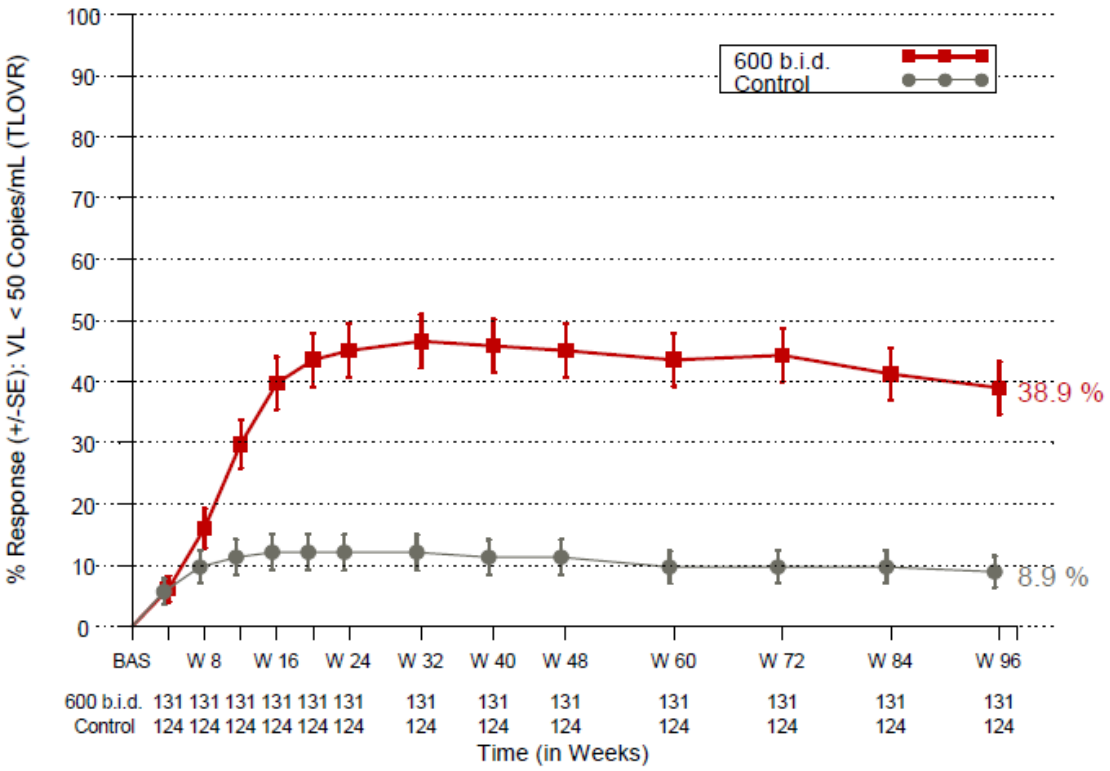
Below table shows the efficacy data of the 48 week and 96 week analyses from the pooled POWER 1 and POWER 2 trials.

Efficacy Outcomes at Weeks 48 and 96 of the Studies POWER 1 and POWER 2 (Pooled Analysis)

	Randomized Studies POWER 1 and POWER 2		
	darunavir/rtv 600 mg b.i.d. + OBR n = 131	Comparator HIV PI + OBR n = 124	Treatment difference (95% CI of difference)
Week 48 time point			
HIV-1 RNA $\log_{10}$ mean change from baseline ($\log_{10}$ copies/mL)[a]	-1.69	-0.37	-1.32 (-1.58; -1.05)
HIV-1 RNA $\geq$ 1 $\log_{10}$ below baseline[d]	81 (61.8%)	20 (16.1%)	45.7% (35.0%; 56.4%)[e]
HIV-1 RNA < 400 copies/mL[d]	72 (55.0%)	18 (14.5%)	40.4% (29.8%; 51.1%)[e]
HIV-1 RNA < 50 copies/mL[d]	59 (45.0%)	14 (11.3%)	33.7% (23.4%; 44.1%)[e]
CD4+ cell count mean change from baseline (x 10^6/L)[c]	103	17	86[b] (57; 114)
Week 96 time point			
HIV-1 RNA $\log_{10}$ mean change from baseline ($\log_{10}$ copies/mL)[a]	-1.58	-0.25	-1.33 (-1.59; -1.07)
HIV-1 RNA $\geq$ 1 $\log_{10}$ below baseline[d]	74 (56.5%)	12 (9.7%)	46.8% (36.9%; 56.8%)[e]
HIV-1 RNA < 400 copies/mL[d]	65 (49.6%)	12 (9.7%)	39.9% (29.9%; 50.0%)[e]
HIV-1 RNA < 50 copies/mL[d]	51 (38.9%)	11 (8.9%)	30.1% (20.3%; 39.8%)[e]
CD4+ cell count mean change from baseline (x 10^6/L)[c]	133	15	118[b] (84; 152)

a) Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0
b) P-values < 0.001, based on the ANOVA model
c) Last Observation Carried Forward imputation
d) Imputations according to the TLOVR algorithm
e) Confidence interval around observed differences of response rates; P-values < 0.001, based on the logistic regression model.

Figure 3. Virologic Response Over Time: Percentage of Subjects with Plasma Viral Load < 50 Copies/mL (ITT – TLOVR) in the pooled POWER 1 and POWER 2 trials



POWER 3

Additional data on the efficacy of darunavir/rtv 600/100 mg b.i.d. have been obtained in treatment-experienced adult subjects participating in the non-randomized trial TMC114 – C215 (POWER 3). At week 48, 334 patients were included in the POWER 3 efficacy analysis who had initiated therapy with darunavir/rtv with the recommended dose of 600/100 mg b.i.d. The OBR consisted of at least two NRTIs with or without enfuvirtide. Entry criteria for the POWER 3 analysis were the same as those for studies POWER 1 and POWER 2.

Baseline characteristics of the subjects included in the POWER 3 analysis were comparable to those subjects in Studies POWER 1 and POWER 2.

The POWER 3 48-week efficacy analysis supported the viral load reduction and CD4+ cell count increases observed in the Studies POWER 1 and POWER 2. Of the 334 subjects at Week 48, 59% had a virologic response defined as a decrease of at least 1.0 $\log_{10}$ in plasma viral load versus baseline and 46% of the subjects reached less than 50 HIV-1 RNA copies/mL.

Analyses of data through 96 weeks of treatment with darunavir/rtv (600/100 mg b.i.d.) in the POWER 3 study supported the sustained antiretroviral efficacy and immunological benefit as demonstrated in the studies POWER 1 and POWER 2. Of the 336 subjects at Week 96 in study POWER 3, 52.2% of patients had a virologic response defined as a decrease of at least 1 $\log_{10}$ in HIV-1 RNA from baseline. 42.1% of the patients reached an HIV-1 RNA level < 50 copies/mL and 50.0% of patients reached less than 400 HIV-1 RNA copies/mL. The mean decrease in HIV-1 RNA level compared to baseline was 1.43 $\log_{10}$ copies/mL and a mean increase in CD4+ cell count of 103 x 10^6 cells/L was observed. Out of the 206 patients who responded with complete viral suppression (< 50 copies/mL) at week 48 in Studies POWER 1, POWER 2 and POWER 3, 177 patients (86% of the responders at week 48) remained responders at week 96.

Description of the clinical study in paediatric patients

DELPHI is an open-label, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir/rtv in 80 antiretroviral treatment-experienced HIV-1 infected paediatric patients aged 6 to < 18 years and weighing at least 20 kg. At week 24, the virologic response rate was evaluated in paediatric patients receiving darunavir/rtv in combination with other antiretroviral agents (see section 4.2). Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 $\log_{10}$ versus baseline. The mean baseline plasma HIV-1 RNA was 4.64 $\log_{10}$ copies/mL, and the median baseline CD4+ cell count was 330 x 10^6 cells/L (range: 6 to 1505 x 10^6 cells/L).

In the study, patients who were at risk of discontinuing therapy due to intolerance of ritonavir oral solution (e.g. taste aversion) were allowed to switch to the capsule formulation. Of the 44 patients taking ritonavir oral solution, 23 switched to the 100 mg capsule formulation and exceeded the weight-based ritonavir dose without changes in observed safety.

At week 24, 73.8% of the paediatric patients had at least 1.0 $\log_{10}$ HIV-1 RNA decrease from baseline. The proportion of paediatric patients reaching undetectable viral load (< 50 HIV-1 RNA copies/mL) was 50.0%, and the proportion of paediatric patients with < 400 HIV-1 RNA copies/mL was 63.8%. The mean change in plasma HIV-1 RNA from baseline was -1.98 $\log_{10}$ copies/mL. The mean CD4+ cell count increase from baseline was 117 x 10^6 cells/L.

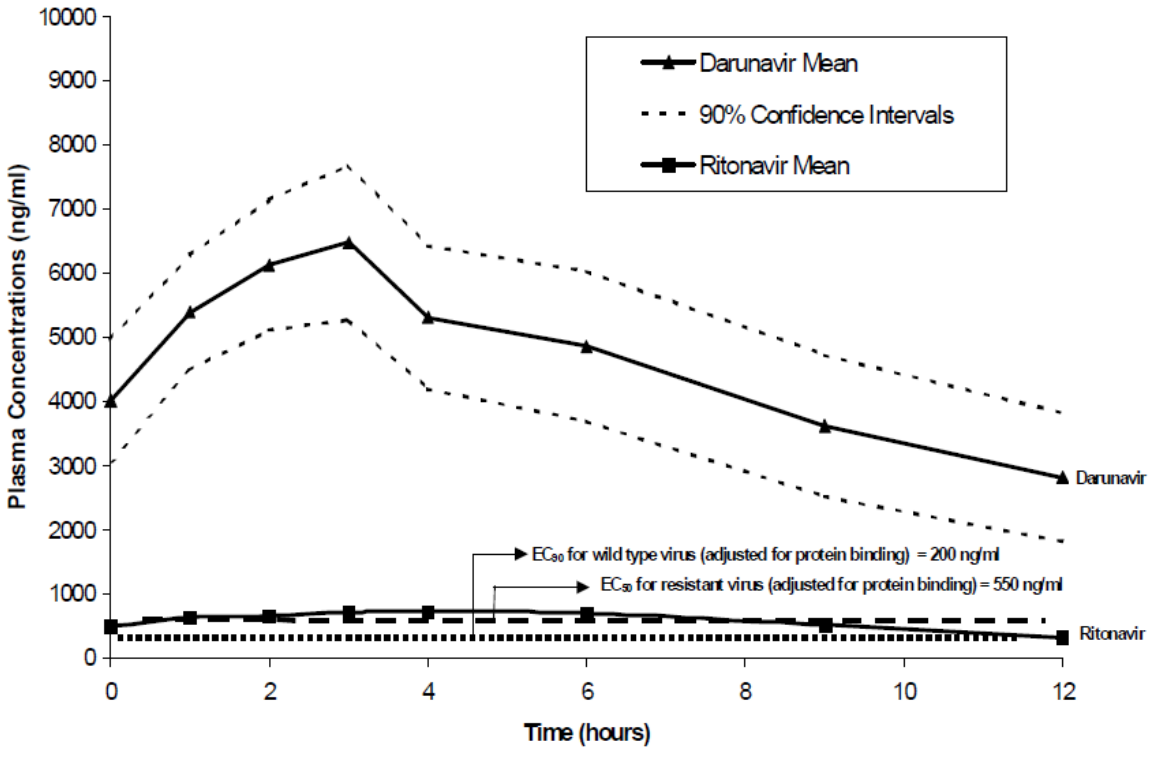
5.2 Pharmacokinetic properties

The pharmacokinetic properties of darunavir, co-administered with ritonavir, have been evaluated in healthy adult volunteers and in HIV-1 infected patients. Exposure to darunavir was higher in HIV-1 infected patients than in healthy subjects.

For combination use with cobicistat and darunavir please refer to the cobicistat data sheet.

Darunavir is primarily metabolized by cytochrome P450 3A (CYP3A). Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

Figure 4. Mean Steady-State Plasma Concentration-Time Profiles of Darunavir and Ritonavir at 600/100 mg b.i.d. at Week 4 (Integrated data from POWER 1 and POWER 2, Primary 24Week Analysis)¶



¶ Mean plasma concentration-time profiles were derived from population pharmacokinetic analysis.

Absorption

Maximum plasma concentration of darunavir in the presence of low-dose ritonavir is generally achieved within 2.5 to 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 b.i.d. 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 b.i.d. (see section 4.4).

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

Distribution

Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma alpha-1-acid glycoprotein. The apparent volume of distribution of darunavir using population pharmacokinetic analysis was 122 L.

Biotransformation

In vitro experiments with human liver microsomes indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolised by the hepatic CYP system and primarily 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/rtv dose was due to the parent drug. 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 wildtype HIV.

Elimination

After a 400/100 mg ^{14}C-darunavir/rtv 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

Paediatrics

The pharmacokinetics of darunavir in combination with ritonavir in 74 treatment-experienced paediatric patients, aged 6 to < 18 years and weighing at least 20 kg, showed that the administered weight-based dosages resulted in darunavir exposure comparable to that in adults receiving darunavir/rtv 600/100 mg b.i.d. (see section 4.2). Median (range) darunavir AUC_{12h} and C_{0h} values in this paediatric population were 63,670 (33,527; 115,360) nanog.h/mL and 3,888 (1,836; 7,821) nanog.h/mL, 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).

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

No pharmacokinetic data are available in subjects with severe renal impairment or end stage renal disease.

Results from a mass balance study with ^{14}C-darunavir/rtv showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine as unchanged drug. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis.

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 to 60 mL/min, n = 20) (see sections 4.2 4.4).

For combination use with cobicistat and darunavir please refer to the cobicistat data sheet.

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 steady-state pharmacokinetic parameters 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, darunavir unbound concentrations were approximately 50% and 100% higher, respectively, in mild and moderate hepatic impairment, compared with those in healthy subjects. The clinical relevance of this increase in unbound darunavir concentrations is unknown. Therefore, darunavir should be used with caution in mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see sections 4.2 and 4.4).

Pregnancy and postpartum

Treatment with darunavir and ritonavir

The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 600/100 mg b.i.d and darunavir/ritonavir 800/100 mg q.d. as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum. Reduction in darunavir exposure was more pronounced in the once daily group as compared to the twice daily group across both 2nd and 3rd trimester of pregnancy. 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.

Twice daily dose regimen group
In women receiving darunavir/ritonavir 600/100 mg b.i.d during the 2nd 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 3rd 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.

Once daily dose regimen group
In women receiving darunavir/ritonavir 800/100 mg q.d during the 2nd 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 3rd 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 and cobicistat

The exposure to total darunavir and cobicistat after intake of darunavir/cobicistat 800/150 mg q.d. as part of an antiretroviral regimen was substantially lower during the second and third trimester of pregnancy compared with 6 to 12 weeks postpartum (see table below). The decrease in unbound (i.e., active) darunavir pharmacokinetic parameters (C_{max} and AUC_{24h}) during pregnancy compared to postpartum was less pronounced than for total darunavir.

Pharmacokinetics of total darunavir (mean ± SD)	2nd Trimester of pregnancy n = 7	3rd Trimester of pregnancy n = 6	Postpartum n = 6
C_{max}, nanog/mL	4340 ± 1616	4910 ± 970	7918 ± 2199
AUC_{24h}, nanog/mL	47293 ± 19058	47991 ± 9879	99613 ± 34862
C_{min}, nanog/mL	168 ± 149	184 ± 99	1538 ± 1344

In women receiving darunavir/cobicistat 800/150 mg q.d. during the 2nd trimester of pregnancy, mean intra-individual values for total darunavir C_{max}, AUC_{24h} and C_{min} were 49%, 56% and 92% lower, respectively, as compared with postpartum; during the 3rd trimester of pregnancy, total darunavir C_{max}, AUC_{24h} and C_{min} values were 37%, 50% and 89% lower, respectively, as compared with postpartum.

Interactions with medicinal products

Darunavir and ritonavir are both inhibitors of the CYP3A and CYP2D6 isoforms, and inhibitors of P-gp. Co-administration of darunavir and ritonavir with medicinal products primarily metabolized by CYP3A, CYP2D6, or transported by P-gp may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see sections 4.3, 4.4 and 4.5).

Darunavir, ritonavir and cobicistat are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir, ritonavir and cobicistat, resulting in lowered plasma concentrations of darunavir, ritonavir and cobicistat. Darunavir boosted with cobicistat is more sensitive to CYP3A4 induction than darunavir boosted with ritonavir (see sections 4.3 and 4.5). Co-administration of darunavir and ritonavir and other drugs that inhibit CYP3A may decrease the clearance of darunavir, ritonavir and cobicistat and may result in increased plasma concentrations of darunavir, ritonavir and cobicistat (see section 4.5).

For combination use with cobicistat and darunavir please refer to the cobicistat data sheet.

Drug interaction studies were performed with darunavir and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of darunavir on the concentration of darunavir or drug are summarized in Table 2 (see section 4.5).

5.3 Preclinical safety data

Carcinogenicity

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Systemic exposures at the highest dose (based on plasma AUC) were approximately 0.5-fold (mice) and 0.75-fold (rats) relative to humans at the recommended therapeutic dose of darunavir/ritonavir (600/100 mg b.i.d).

The incidences of hepatocellular adenomas were statistically significantly increased at all doses in male mice; at the mid and high dose in female mice and male rats; and at the high dose in female rats. The incidence of hepatocellular carcinomas was significantly increased at the high dose in

male mice; and male and female rats. The relevance of these findings for humans is limited. An increase in the incidence of thyroid follicular cell adenomas was noted in male rats. This is considered rodent specific and of no relevance to humans.

Genotoxicity

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.

Reproductive toxicity

In a study conducted in rats, there were no effects on mating with darunavir treatment up to 1000 mg/kg/day, but exposure levels were below (AUC - 0.5-fold) that in humans at the clinically recommended dose. The number of corporea lutea and hence the number of live young was lower for females at 1000 mg/kg/day darunavir, and correlated with lower maternal body weight; the NOAEL for effects on fertility was 200 mg/kg/day darunavir (corresponding to an exposure level 0.3–fold that in humans at the recommended clinical dose).

In animal studies with darunavir treatment up to 1000 mg/kg/day, there was no teratogenicity with darunavir in mice, rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. However, the exposure levels in mice and rats were about half those with the recommended clinical dose in humans, and only 5% in rabbits. In a pre- and post-natal rat study the pups had lower birth weight following maternal treatment with 1000 mg/kg/day darunavir.

Juvenile toxicity

In a pre- and post-natal development assessment in rats, darunavir with and without ritonavir, caused a transient reduction in body weight gain of the offspring during lactation. This was attributed to drug exposure via the milk. No post weaning functions were affected with darunavir alone or in combination with ritonavir.

In juvenile rats directly dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age, mortality was observed and, in some of the animals, convulsions. Within this age range exposures in plasma, liver and brain were dose and age dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood brain barrier. No treatment related mortalities were noted in juvenile rats dosed at 1000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats. In humans, the activity of drug-metabolising enzymes approaches adult values by 3 years of age.

6. Pharmaceutical Particulars

6.1 List of excipients

Darunavir Mylan film coated tablet also contains:

- Colloidal silicon dioxide
- Microcrystalline cellulose
- Crospovidone
- Sodium starch glycolate
- Hypromellose
- Magnesium stearate
- Purified water
- Polyvinyl alcohol
- Titanium dioxide
- Macrogol/PEG
- Talc

Darunavir Mylan is lactose and gluten free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

HDPE Bottle - 2 years.

Blister pack – 3 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

White HDPE bottle with child resistant PP closure. Pack size of 60.

White HDPE bottle with PP screw cap. Pack size of 100.

PVC/PE/PVdC-Alu Blister. Pack size of 60 or 100.

Not all pack types may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Customer Services Freephone: 0800 579 811

9. Date of First Approval

10 November 2016

10. Date of Revision of the Text

31 July 2020

Summary table of changes

Section	Summary of new information

6.3	3 year shelf life for PVC/PE/PVdC-Alu Blister
6.5	Addition of PVC/PE/PVdC-Alu Blister pack.