1. PRODUCT NAME
Darunavir Mylan 600mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 600 mg of darunavir (corresponding to 650.461 mg of darunavir ethanolate).

For excipients, see *List of Excipients*.

3. PHARMACEUTICAL FORM
Film-coated tablet.

White to off-white, film coated, oval shaped, biconvex tablet, debossed with 'M' on one side and 'DE6' on the other side.

4. CLINICAL INFORMATION

4.1 Indications
DARUNAVIR MYLAN (darunavir), co-administered with ritonavir "DARUNAVIR MYLAN/ritonavir (rtv)", in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV–1 strains resistant to more than one protease inhibitor.

The following points should be considered when initiating therapy with DARUNAVIR MYLAN/rtv:
- The use of other active agents with DARUNAVIR MYLAN/rtv is associated with a greater likelihood of treatment response
- The risk and benefits of DARUNAVIR MYLAN/rtv have not been established in treatment-naïve adult patients or pediatric patients

4.2 Dosage and Administration
DARUNAVIR MYLAN 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 MYLAN/rtv.

After therapy with DARUNAVIR MYLAN has been initiated, patients should be advised not to alter the dosage, dosage form, or discontinue therapy without instruction of their physician.

Dosage – Adults
The recommended dosage of DARUNAVIR MYLAN is 600 mg twice daily (b.i.d.) taken with ritonavir 100 mg b.i.d. and with food.

The type of food does not affect the exposure to darunavir. Ritonavir is used as a pharmacokinetic enhancer of darunavir (see *Interactions* and *Pharmacokinetic Properties*).

Children (less than 12 years of age) and adolescents (12 to 17 years of age): DARUNAVIR MYLAN/rtv is not approved for use in these populations.

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 *Pregnancy, Breast-feeding and Fertility* and *Pharmacokinetic Properties-Special Populations – Pregnancy and Postpartum*).

Missed dose(s)
The following guidance is based on the half-life of darunavir in the presence of ritonavir and the recommended dosing interval of approximately 12 hours (twice daily regimen).

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

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

Special populations
Elderly (65 years of age and older)
Limited information is available on the use of DARUNAVIR MYLAN in patients 65 and older. Therefore DARUNAVIR MYLAN should be used with caution in this age group. (see *Warnings and Precautions* and *Pharmacokinetic Properties – Elderly*)

Renal impairment
No dose adjustment is required in patients with renal impairment (see *Warnings and Precautions* and *Pharmacokinetic Properties*).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. There are no data regarding the use of DARUNAVIR MYLAN when co-administered to patients with severe hepatic impairment; therefore, specific dosage recommendations cannot be made. DARUNAVIR MYLAN should be used with caution in patients with severe hepatic impairment (see *Warnings and Precautions* and *Pharmacokinetic Properties*).

Administration
Method of administration: oral administration.

DARUNAVIR MYLAN must be taken with food. The type of food does not affect the exposure to DARUNAVIR MYLAN (see *Pharmacokinetic Properties – Absorption*).

4.3 Contraindications
Hypersensitivity to darunavir or to any of the excipients.

Darunavir and ritonavir are inhibitors of the cytochrome P450 3A (CYP3A) isoform. DARUNAVIR MYLAN/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). Examples include alfuzosin, 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 *Interactions*).

Patients taking DARUNAVIR MYLAN should not use products containing potent CYP3A inducers such as rifampin 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.

4.4 Warnings and Precautions

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.

DARUNAVIR MYLAN/rtv is not approved for use in antiretroviral treatment in naïve patients and in children.

Elderly: As limited information is available on the use of DARUNAVIR MYLAN in patients aged 65 and over, caution should be exercised in the administration of DARUNAVIR MYLAN in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy (see *Pharmacokinetic Properties*).

The absolute oral bioavailability of a single 600 mg dose of DARUNAVIR MYLAN alone was approximately 37% and increased to approximately 82% in the presence of 100 mg ritonavir b.i.d. 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 MYLAN was given orally in combination with ritonavir at 100 mg b.i.d. Therefore, DARUNAVIR MYLAN should only be used in combination with low dose ritonavir as a pharmacokinetic enhancer (see *Pharmacokinetic Properties*).

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

Severe skin reactions

During the darunavir/ritonavir clinical development program (N = 3063), 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; during post-marketing experience, toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), and acute generalized exanthematous pustulosis have been reported very rarely (< 0.01%). Discontinue DARUNAVIR MYLAN 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 MYLAN/rtv (see *Adverse Reactions*). 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 MYLAN/rtv was 0.5%.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing DARUNAVIR MYLAN/rtv + raltegravir compared to subjects receiving DARUNAVIR MYLAN/rtv without raltegravir or raltegravir without DARUNAVIR MYLAN/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 MYLAN should be used with caution in patients with a known sulfonamide allergy. In clinical studies with DARUNAVIR MYLAN/rtv, the incidence and severity of rash was similar in patients with or without a history of sulfonamide allergy.

Patients with coexisting conditions

<u>Hepatic impairment</u>

There are no data regarding the use of DARUNAVIR MYLAN in patients with severe hepatic impairment; therefore, specific dosage recommendations cannot be made. DARUNAVIR MYLAN

should be used with caution in patients with severe hepatic impairment. Based on data that demonstrated that the steady-state pharmacokinetic parameters of darunavir in subjects with mild and moderate hepatic impairment were comparable with those in healthy subjects, no dose adjustment is required in patients with mild or moderate hepatic impairment (see Dosage and *Administration* and *Pharmacokinetic Properties*).

Hepatotoxicity

Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with DARUNAVIR MYLAN/rtv. During the darunavir/ritonavir clinical development program (N = 3063), hepatitis was reported in 0.5% of patients receiving combination therapy with DARUNAVIR MYLAN/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.

Appropriate laboratory testing should be conducted prior to initiating therapy with DARUNAVIR MYLAN 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 MYLAN treatment.

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 MYLAN should prompt consideration of interruption or discontinuation of treatment.

Renal impairment

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 hemodialysis or peritoneal dialysis (see Dosage and *Administration* and *Pharmacokinetic Properties*).

Hemophiliac patients

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

Metabolic disorders

Hyperglycemia/Diabetes mellitus

New onset diabetes mellitus, hyperglycemia, or exacerbation of existing diabetes mellitus has been reported in patients receiving antiretroviral therapy, including PIs. In some of these patients the hyperglycemia 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 hyperglycemia.

Consideration should be given to measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate. (see *Adverse Reactions*).

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, generalized 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 and autoimmune hepatitis 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 *Adverse Reactions)*.

Interactions with medicinal products
Darunavir when used in combination with ritonavir is an inhibitor of CYP3A, CYP2D6 and P-gp. Co-administration of DARUNAVIR MYLAN and ritonavir 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 *Contraindications* and *Interactions*).

Darunavir and ritonavir are metabolized by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lower plasma concentrations of darunavir and ritonavir. Co-administration with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (see *Interactions*). Co-administration of DARUNAVIR MYLAN/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 Interactions).

4.5 Interactions
DARUNAVIR MYLAN should be used in combination with low dose ritonavir as a pharmacokinetic enhancer.

The interaction profile of DARUNAVIR MYLAN depends on whether ritonavir is used as pharmacokinetic enhancer. DARUNAVIR MYLAN may therefore have different recommendations for concomitant medications depending on whether DARUNAVIR MYLAN is boosted with ritonavir. The dosing recommendations for DARUNAVIR MYLAN/rtv that are listed below.

DARUNAVIR MYLAN should not be used in combination with other antiretrovirals that also require pharmacokinetic boosting with ritonavir.

Darunavir when used in combination ritonavir is an inhibitor of CYP3A, CYP2D6 and P-gp. Co-administration of DARUNAVIR MYLAN/rtv and 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. Co-administration of DARUNAVIR MYLAN/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.

Darunavir and ritonavir are metabolized by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lower plasma concentrations of darunavir and ritonavir. Co-administration with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir.

Drug-drug interactions presented by drug class including drug name examples are presented below. This list of examples of drug-drug interactions is not comprehensive and therefore the label of each drug that is

co-administered with DARUNAVIR MYLAN 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.

Antiretroviral medicinal products *Integrase strand transfer inhibitors*
Dolutegravir
DARUNAVIR MYLAN/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 MYLAN/rtv co-administered with dolutegravir can be used without dose adjustment.

Elvitegravir
When DARUNAVIR MYLAN/rtv (600/100 mg b.i.d.) is used in combination with elvitegravir, the dose of elvitegravir should be 150 mg once daily.
The pharmacokinetics and dosing recommendations for other doses of darunavir have not been established. Therefore, co-administration of DARUNAVIR MYLAN/rtv in doses other than 600/100 mg b.i.d. and elvitegravir is not recommended.
Co-administration of DARUNAVIR MYLAN/rtv 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 MYLAN co-administered with low dose ritonavir and raltegravir can be used without dose adjustments.

Nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs)
Didanosine
DARUNAVIR MYLAN/rtv (600/100 mg b.i.d.) did not significantly affect didanosine exposure.
The combination of DARUNAVIR MYLAN co-administered with low dose ritonavir and didanosine can be used without dose adjustments. It is recommended that didanosine be administered on an empty stomach. Didanosine should be administered 1 hour before or 2 hours after DARUNAVIR MYLAN/rtv (which are administered with food).

Tenofovir disoproxil fumarate
The results of an interaction trial with tenofovir (tenofovir disoproxil fumarate 300 mg once daily [q.d.]) demonstrated that the systemic exposure of tenofovir was increased by 22% when co-administered with Darunavir/rtv (300/100 mg b.i.d.). This finding is not considered to be clinically relevant. There was no change in the urinary excretion of tenofovir or darunavir during co-administration. Tenofovir did not have a significant influence on darunavir exposure. No dose adjustments of DARUNAVIR MYLAN, ritonavir or tenofovir disoproxil fumarate are required when these drugs are co-administered.

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 medicinal compounds and DARUNAVIR MYLAN/rtv.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
Delavirdine
Co-administration of DARUNAVIR MYLAN/rtv and delavirdine may increase darunavir and delavirdine concentrations (inhibition of CYP3A).

The appropriate doses of DARUNAVIR MYLAN/rtv and delavirdine have not been established. The combination of DARUNAVIR MYLAN/rtv and delavirdine is not recommended.

Etravirine
In an interaction trial between Darunavir/rtv (600/100 mg b.i.d.) and etravirine, there was a 37% decrease in etravirine exposure in the presence of DARUNAVIR MYLAN/rtv and no relevant change in exposure to darunavir. Therefore, DARUNAVIR MYLAN/rtv can be co-administered with etravirine 200 mg b.i.d. without dose adjustments.

Efavirenz
An interaction trial between Darunavir/rtv (300/100 mg b.i.d.) and efavirenz (600 mg q.d.) has been performed. In the presence of efavirenz, a decrease of 13% for darunavir exposure was observed. Exposure to efavirenz was increased by 21% when administered in combination with Darunavir/rtv. Since this difference is considered not to be clinically relevant, the combination of DARUNAVIR MYLAN/rtv and efavirenz can be used without dose adjustments.

Nevirapine
The results of an interaction trial with Darunavir/rtv (400/100 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 MYLAN/rtv.

Since this difference is not considered to be clinically relevant, the combination of DARUNAVIR MYLAN/rtv and nevirapine can be used without dose adjustments.

Rilpivirine
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 MYLAN/rtv.

Since this difference is not considered to be clinically relevant, the combination of DARUNAVIR MYLAN/rtv and rilpivirine can be used without dose adjustments.

HIV protease inhibitors (PIs)
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 MYLAN was given orally in combination with ritonavir at 100 mg b.i.d.
Therefore, DARUNAVIR MYLAN should only be used in combination with a pharmacokinetic enhancer such as low dose ritonavir (see *Warnings and Precautions* and *Pharmacokinetic Properties*).

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%.

The appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer DARUNAVIR MYLAN/rtv with lopinavir/ritonavir.

Saquinavir
In an interaction trial between Darunavir (400 mg b.i.d.), saquinavir (1000 mg b.i.d.) and ritonavir (100 mg b.i.d.), darunavir exposure was decreased by 26% in the presence of saquinavir/rtv; saquinavir

exposure was not affected by the presence of DARUNAVIR MYLAN/rtv.
It is not recommended to combine saquinavir and DARUNAVIR MYLAN, with or without low dose ritonavir.

Atazanavir
An interaction trial between Darunavir/rtv (400/100 mg b.i.d.) and atazanavir (300 mg q.d.) demonstrated that systemic exposure to darunavir and atazanavir was not significantly affected when co-administered.
Atazanavir can be co-administered with DARUNAVIR MYLAN/rtv.

Indinavir
In an interaction trial between Darunavir/rtv (400/100 mg b.i.d.) and indinavir (800 mg b.i.d.), darunavir exposure was increased by 24% in the presence of indinavir/rtv; indinavir exposure was increased by 23% in the presence of DARUNAVIR MYLAN/rtv.
When used in combination with DARUNAVIR MYLAN/rtv, dose adjustment of indinavir from 800 mg b.i.d. to 600 mg b.i.d. may be warranted in case of intolerance.

Other HIV PIs
The co-administration of DARUNAVIR MYLAN/rtv and PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir have not been studied.
Therefore, such co-administration is not recommended.

CCR5 antagonist
When used in combination with DARUNAVIR MYLAN/rtv, 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 medicinal products

Acid reducing agents
Antacids
e.g. Aluminum/magnesium hydroxide, calcium carbonate
No interaction is expected between antacids and DARUNAVIR MYLAN/rtv.
DARUNAVIR MYLAN/rtv and antacids can be used concomitantly without dose adjustments.

H2-receptor antagonists
e.g. Cimetidine, famotidine, nizatidine, ranitidine
Co-administration of ranitidine (150 mg b.i.d.) and DARUNAVIR MYLAN/rtv (400/100 mg b.i.d.) did not affect the exposure to darunavir.
DARUNAVIR MYLAN/rtv can be co-administered with H2-receptor antagonists without dose adjustments.

Proton pump inhibitors
e.g. Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
Co-administration of omeprazole (20 mg q.d.) and DARUNAVIR MYLAN/rtv (400/100 mg b.i.d.) did not affect the exposure to darunavir. DARUNAVIR MYLAN/rtv and proton pump inhibitors can be co-administered without dose adjustment.

Alpha 1-adrenoreceptor antagonist
Alfuzosin
Exposure to alfuzosin may be increased when co-administered with DARUNAVIR MYLAN/rtv. Concomitant use of DARUNAVIR MYLAN/rtv with alfuzosin is contraindicated.

Antianginals/ Antiarrhythmics

Ranolazine

Exposure to ranolazine may be increased (CYP3A inhibition) when co-administered with DARUNAVIR MYLAN/rtv.

Concomitant use of DARUNAVIR MYLAN/rtv with ranolazine is contraindicated.

Ivabradine

Concomitant use of DARUNAVIR MYLAN/rtv with ivabradine is contraindicated.

Amiodarone, bepridil, disopyramide, dronedarone, flecainide, mexiletine, propafenone, systemic lidocaine, and quinidine

Exposure to these antiarrhythmics may be increased when co-administered with DARUNAVIR MYLAN/rtv.

Caution is warranted and therapeutic drug monitoring of antiarrhythmics is recommended when available.

Concomitant use of DARUNAVIR MYLAN/rtv with dronedarone is contraindicated.

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).

It is recommended that the lowest dose of digoxin should initially be prescribed and digoxin dose should be titrated to obtain the desired clinical effect when co-administered with DARUNAVIR MYLAN/rtv. Serum digoxin concentrations should be monitored to assist in the titration.

Antibacterial

Clarithromycin

An interaction trial between Darunavir/rtv (400/100 mg b.i.d.) and clarithromycin (500 mg b.i.d.) showed an increase in exposure to clarithromycin by 57%, while exposure to darunavir was not affected.

DARUNAVIR MYLAN/rtv 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. Consult the prescribing information for clarithromycin for the recommended dosage.

Anticoagulants

Direct Oral Anticoagulants (DOACs): apixaban, dabigatran etexilate, edoxaban, rivaroxaban

DOACs are primarily metabolized by CYP3A4 and/or transported by P-gp. Co-administration with DARUNAVIR MYLAN/rtv 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 apixaban and rivaroxaban, is not recommended with DARUNAVIR MYLAN/rtv.

The results of a drug-drug interaction study between darunavir 800 mg, ritonavir 100 mg and dabigatran etexilate 150 mg in healthy participants showed a 1.7-fold increase in dabigatran plasma AUC after single dosing of darunavir and ritonavir, and a 1.2-fold increase in dabigatran plasma AUC after repeated dosing of darunavir and ritonavir. The study demonstrated a 1.6-fold increase in dabigatran plasma Cmax after single dosing of darunavir and ritonavir, and a 1.2-fold increase in dabigatran plasma Cmax after repeated dosing of darunavir and ritonavir.

Clinical monitoring and/or dose reduction of the DOAC should be considered when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with DARUNAVIR MYLAN/rtv.

The results of a drug-drug interaction study between darunavir/cobicistat 800/150 mg and 538 dabigatran etexilate 150 mg in healthy participants showed a 2.6-fold increase in dabigatran plasma AUC after single dosing of darunavir/cobicistat, and a 1.9-fold increase in dabigatran plasma AUC after repeated dosing of

darunavir/cobicistat. The study demonstrated a 2.6-fold increase in dabigatran plasma Cmax after single dosing of darunavir/cobicistat and a 2.0-fold increase in dabigatran plasma Cmax after repeated dosing of darunavir/cobicistat.

Clinical monitoring is required when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with DARUNAVIR MYLAN/cobi. A dose reduction of the DOAC may be needed.

Warfarin
Warfarin concentrations may be affected when co-administered with DARUNAVIR MYLAN/rtv.
It is recommended that the international normalized ratio (INR) is monitored when warfarin is combined with DARUNAVIR MYLAN/rtv.

Anticonvulsants
Phenobarbital and phenytoin
Phenobarbital and phenytoin are inducers of CYP450 enzymes. DARUNAVIR MYLAN/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 MYLAN.

Carbamazepine
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 MYLAN/rtv is recommended. If there is a need to combine DARUNAVIR MYLAN/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 MYLAN/rtv.

Clonazepam
Co-administration of DARUNAVIR MYLAN/rtv with clonazepam may increase concentrations of clonazepam.
Clinical monitoring is recommended when co-administering DARUNAVIR MYLAN/rtv with clonazepam.

Antidepressants
Paroxetine and sertraline
In an interaction trial between paroxetine (20 mg q.d.) or sertraline (50 mg q.d.) and Darunavir/rtv (400/100 mg b.i.d.), the exposure to darunavir was not affected by the presence of sertraline or paroxetine. Exposure to sertraline and paroxetine, was decreased by 49% and 39%, respectively, in the presence of DARUNAVIR MYLAN/rtv.
If SSRIs are co-administered with DARUNAVIR MYLAN/rtv, the recommended approach is a careful dose 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 MYLAN/rtv should be monitored for an antidepressant response.

Amitriptyline, desipramine, imipramine, nortriptyline, and trazodone
Concomitant use of DARUNAVIR MYLAN/rtv and these antidepressants may increase concentrations of the antidepressant (inhibition of CYP2D6 and/or CYP3A).
Clinical monitoring is recommended when co-administering DARUNAVIR MYLAN/rtv with these antidepressants and a dose adjustment of the antidepressant may be needed.

Antiemetics
Domperidone
Use with caution: monitor for domperidone adverse reactions.

Antifungals
Itraconazole, isavuconazole, ketoconazole, posaconazole, and voriconazole
Itraconazole, isavuconazole, ketoconazole, posaconazole, and voriconazole are moderate to potent inhibitors of CYP3A and/or some are substrates of CYP3A.
Concomitant systemic use of these antifungals with DARUNAVIR MYLAN/rtv may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of some of these antifungals may be increased by DARUNAVIR MYLAN/rtv. This was confirmed in an interaction trial where the concomitant administration of ketoconazole (200 mg b.i.d.) with Darunavir/rtv (400/100 mg b.i.d.) increased exposure of ketoconazole and darunavir by 212% and 42%, respectively.
Plasma concentrations of voriconazole may be decreased in the presence of DARUNAVIR MYLAN/rtv. Voriconazole should not be administered to patients receiving DARUNAVIR MYLAN/rtv unless an assessment of the benefit/risk ratio justifies the use of voriconazole.

Clinical monitoring is recommended when co-administering DARUNAVIR MYLAN/rtv with posaconazole or isavuconazole.

When co-administration is required the daily dose of ketoconazole or itraconazole should not exceed 200 mg

Clotrimazole and fluconazole
Co-administration of DARUNAVIR MYLAN/rtv with these antifungals may increase concentrations of darunavir, ritonavir, and/or the antifungal.
Clinical monitoring is recommended when co-administering DARUNAVIR MYLAN/rtv with these antifungals.

Anti-gout
Colchicine
Concomitant use of colchicine and DARUNAVIR MYLAN/rtv may increase the exposure to colchicine. The following dose adjustments are recommended for colchicine. For the treatment of gout-flares in patients on DARUNAVIR MYLAN/rtv, 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 MYLAN/rtv, 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 MYLAN/rtv, 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 MYLAN/rtv with colchicine in patients with renal or hepatic impairment is contraindicated.

Antihistamines
Astemizole, terfenadine
Exposure to these antihistamines may be increased when co-administered with DARUNAVIR MYLAN/rtv. Concomitant use of DARUNAVIR MYLAN/rtv with astemizole and terfenadine is contraindicated.

Antimalarial
Artemether/lumefantrine
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 affected. The exposure to artemether and its active metabolite,

dihydroartemisinin, decreased by 16% and 18%, respectively. The combination of DARUNAVIR MYLAN/rtv and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.

Antimycobacterials

Rifampin and rifapentine

Co-administration of DARUNAVIR MYLAN/rtv with rifampin and rifapentine may decrease darunavir concentrations (induction of CYP3A), which may result in loss of therapeutic effect of DARUNAVIR MYLAN.

Co-administration of DARUNAVIR MYLAN/rtv with rifampin is contraindicated.

Co-administration of DARUNAVIR MYLAN/rtv with rifapentine is not recommended.

Rifabutin

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 MYLAN/rtv, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for DARUNAVIR MYLAN/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.

Antineoplastics

Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine

The plasma concentrations of these antineoplastics are expected to increase with co-administration of DARUNAVIR MYLAN/rtv (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 MYLAN/rtv.

Concomitant use of everolimus or irinotecan and DARUNAVIR MYLAN/rtv is not recommended.

Antiplatelets

Clopidogrel

Co-administration of DARUNAVIR MYLAN/rtv with clopidogrel is expected to decrease clopidogrel active metabolite plasma concentration, which may reduce the antiplatelet activity of clopidogrel. Co-administration of DARUNAVIR MYLAN/rtv with clopidogrel is not recommended.

Prasugrel

DARUNAVIR MYLAN/rtv is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite of prasugrel.

Antipsychotics/neuroleptics

Lurasidone

Concomitant use of lurasidone and DARUNAVIR MYLAN/rtv may increase the exposure to lurasidone (inhibition of CYP3A4).

Concomitant use of DARUNAVIR MYLAN/rtv with lurasidone is contraindicated.

Pimozide

Concomitant use of pimozide and DARUNAVIR MYLAN/rtv may increase the exposure to pimozide (inhibition of CYP3A and CYP2D6).

Concomitant use of DARUNAVIR MYLAN/rtv with pimozide is contraindicated.

Perphenazine
Co-administration of DARUNAVIR MYLAN/rtv and perphenazine may increase concentrations of the neuroleptic (inhibition of CYP3A or CYP2D6).
Clinical monitoring is recommended when co-administering DARUNAVIR MYLAN/rtv with perphenazine and a lower dose of the neuroleptic should be considered.

Risperidone, thioridazine
Concomitant use of risperidone or thioridazine and DARUNAVIR MYLAN/rtv 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 MYLAN/rtv.

Quetiapine
Concomitant use of quetiapine and DARUNAVIR MYLAN/rtv may increase the exposure to quetiapine (inhibition of CYP3A).
The quetiapine dose should be substantially reduced when co-administered with DARUNAVIR MYLAN. For details, refer to the quetiapine prescribing information.

β-Blockers
Carvedilol, metoprolol, timolol
Co-administration of DARUNAVIR MYLAN/rtv and beta-blockers may increase concentrations of the beta-blocker (inhibition of CYP2D6).
Clinical monitoring is recommended when co-administering DARUNAVIR MYLAN/rtv with beta-blockers and a lower dose of the beta-blocker should be considered.

Calcium channel blockers
Amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil
The exposure to calcium channel blockers may increase when DARUNAVIR MYLAN/rtv are used concomitantly (inhibition of CYP2D6 and/or CYP3A).
Caution is warranted and careful clinical monitoring is recommended.

Contraceptives
Ethinylestradiol and norethindrone
The results of an interaction trial between Darunavir/rtv (600/100 mg b.i.d.) and ethinylestradiol and norethindrone demonstrated that at steady-state systemic exposures to ethinylestradiol and norethindrone are decreased by 44% and 14%, respectively.

Ethinylestradiol and drospirenone
The effect of DARUNAVIR MYLAN/rtv on drospirenone exposure is not known.
When DARUNAVIR MYLAN/rtv is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential of hyperkalemia.
No data are available to make recommendations on the use of DARUNAVIR MYLAN/rtv with other hormonal contraceptives. Therefore, additional or alternative (non-hormonal) methods of contraception are recommended.

Corticosteroids
Corticosteroids primarily metabolized by CYP3A *(betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone)*. Concomitant use of corticosteroids and DARUNAVIR MYLAN/rtv 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 MYLAN/rtv with corticosteroids. Alternatives should be considered, particularly for long term use.
For co-administration of cutaneously-administered corticosteroids sensitive to CYP3A inhibition, refer to the prescribing information of the corticosteroid for conditions or uses that augment its systemic absorption.

Systemic dexamethasone
Systemic dexamethasone induces CYP3A and thereby may decrease darunavir exposure. This may result in loss of therapeutic effect.
Therefore, this combination should be used with caution.

Endothelin receptor antagonist
Bosentan
Concomitant use of bosentan and DARUNAVIR MYLAN/rtv may increase plasma concentrations of bosentan.
In patients who have been receiving DARUNAVIR MYLAN/rtv 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 MYLAN/rtv, discontinue the use of bosentan at least 36 hours prior to initiation of DARUNAVIR MYLAN/rtv. After at least 10 days following the initiation of DARUNAVIR MYLAN/rtv, resume bosentan at 62.5 mg q.d. or q.o.d. based upon individual tolerability.

Ergot alkaloids
e.g., Ergotamine, ergonovine, dihydroergotamine, and methylergonovine
Exposure to the ergot alkaloids may be increased when co-administered with DARUNAVIR MYLAN/rtv.
Concomitant use of DARUNAVIR MYLAN/rtv with ergot alkaloids is contraindicated.

Gastrointestinal motility agent
Cisapride
Exposure to cisapride may be increased when co-administered with DARUNAVIR MYLAN/rtv.
Concomitant use of DARUNAVIR MYLAN/rtv with cisapride is contraindicated.

Hepatitis C virus (HCV) direct-acting antivirals
Boceprevir
In an interaction trial between Darunavir/rtv (600/100 mg b.i.d.) and boceprevir (800 mg three times daily), darunavir exposure was reduced by 44% and boceprevir exposure was reduced by 32%.
It is not recommended to co-administer DARUNAVIR MYLAN/rtv with boceprevir.

Elbasvir/Grazoprevir
Concomitant use of elbasvir/grazoprevir and DARUNAVIR MYLAN/rtv may increase the exposure to grazoprevir (inhibition of CYP3A).
Concomitant use of DARUNAVIR MYLAN/rtv with elbasvir/grazoprevir is contraindicated.

Glecaprevir/Pibrentasvir
Concomitant use of glecaprevir/pibrentasvir and DARUNAVIR MYLAN/rtv may increase the exposure to glecaprevir and pibrentasvir (inhibition of P-gp, BCRP and/or OATP1B1/3).
Co-administration of DARUNAVIR MYLAN/rtv with glecaprevir/pibrentasvir is not recommended.

Herbal product
St. John's wort
Co-administration of DARUNAVIR MYLAN/rtv with products containing St. John's wort (*Hypericum perforatum*) may cause significant decreases in darunavir concentrations (induction of CYP3A), which may result in loss of therapeutic effect to DARUNAVIR MYLAN.

Co-administration of DARUNAVIR MYLAN/rtv with products containing St. John's wort (*Hypericum perforatum*) is contraindicated.

HMG-CoA reductase inhibitors

Atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin

HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A metabolism, are therefore expected to have markedly increased plasma concentrations when co-administered with DARUNAVIR MYLAN/rtv. Increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis.

Concomitant use of DARUNAVIR MYLAN/rtv with lovastatin and simvastatin is contraindicated.

The results of an interaction trial with atorvastatin show that atorvastatin (10 mg q.d.) in combination with Darunavir/rtv (300/100 mg b.i.d.) provides an exposure to atorvastatin, which is only 15% lower than that obtained with atorvastatin (40 mg q.d.) alone.

When administration of atorvastatin and DARUNAVIR MYLAN/rtv is desired, it is 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.

DARUNAVIR MYLAN/rtv (600/100 mg b.i.d.) increased exposure to a single dose of pravastatin (40 mg) by approximately 80%, but only in a subset of subjects. When administration of pravastatin and DARUNAVIR MYLAN/rtv is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effects while monitoring safety.

An interaction study evaluating DARUNAVIR MYLAN/rtv (600/100 mg b.i.d.) in combination with rosuvastatin (10 mg q.d.) resulted in an increase in rosuvastatin exposure.

When administration of rosuvastatin and Darunavir Mylan/rtv 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.

Other lipid modifying agents

Lomitapide

DARUNAVIR MYLAN/rtv is expected to increase the exposure of lomitapide when co-administered.

Co-administration is contraindicated.

Immunosuppressants

Cyclosporin, everolimus, sirolimus, tacrolimus

Exposure to these immunosuppressants may be increased when co-administered with DARUNAVIR MYLAN/rtv.

Therapeutic drug monitoring of the immunosuppressive agent is recommended when co-administered with DARUNAVIR MYLAN/rtv.

Concomitant use of everolimus and DARUNAVIR MYLAN/rtv is not recommended.

Inhaled beta-agonist

Salmeterol

Concomitant use of salmeterol and DARUNAVIR MYLAN/rtv is not recommended.

The combination may result in increased risk of cardiovascular adverse events with salmeterol, including QT prolongation, palpitations and sinus tachycardia.

Narcotic analgesics/treatment of opioid dependence

Buprenorphine/naloxone

The results of an interaction trial with Darunavir/rtv and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when administered with DARUNAVIR MYLAN/rtv. Exposure of the active metabolite, norbuprenorphine, increased by 46%.

No dose adjustment for buprenorphine was required. Careful clinical monitoring is recommended if DARUNAVIR MYLAN/rtv and buprenorphine are co-administered.

Fentanyl, oxycodone, tramadol
Co-administration of DARUNAVIR MYLAN/rtv with fentanyl, oxycodone or tramadol may increase concentrations of the analgesic.
Clinical monitoring is recommended when co-administering DARUNAVIR MYLAN/rtv with these analgesics.

Methadone
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 MYLAN/rtv. However, clinical monitoring is recommended as maintenance therapy may need to be adjusted in some patients.

Opioid antagonist
Naloxegol
Co-administration of DARUNAVIR MYLAN/rtv with naloxegol is contraindicated.

PDE-5 inhibitors

Treatment of erectile dysfunction:
Avanafil, sildenafil, tadalafil, vardenafil
In an interaction trial a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with Darunavir/rtv (400/100 mg b.i.d.).
Concomitant use of PDE-5 inhibitors for the treatment of erectile dysfunction with DARUNAVIR MYLAN/rtv should be done with caution. If concomitant use of DARUNAVIR MYLAN/rtv 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 MYLAN/rtv and avanafil is not recommended.

Treatment of pulmonary arterial hypertension:
Sildenafil, tadalafil
A safe and effective dose of sildenafil when combined with DARUNAVIR MYLAN/rtv 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).
Therefore, co-administration of DARUNAVIR MYLAN/rtv with sildenafil when used for pulmonary arterial hypertension is contraindicated.
For the treatment of pulmonary arterial hypertension with tadalafil co-administered with DARUNAVIR MYLAN/rtv, a dose adjustment for tadalafil is warranted. In patients who have been receiving DARUNAVIR MYLAN/rtv 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 MYLAN/rtv, discontinue the use of tadalafil at least 24 hours prior to initiating DARUNAVIR MYLAN/rtv and avoid the use of tadalafil during the initiation of DARUNAVIR MYLAN/rtv. After at least 1 week following the initiation of DARUNAVIR MYLAN/rtv, resume tadalafil at 20 mg q.d. and increase to 40 mg q.d. based upon individual tolerability.

Pharmacokinetic enhancer
DARUNAVIR MYLAN should be used in combination with a pharmacokinetic enhancer such as low dose ritonavir.
DARUNAVIR MYLAN should not be used in combination with other antiretrovirals that also require pharmacokinetic boosting with ritonavir.

Platelet aggregation inhibitors
Ticagrelor
Co-administration of DARUNAVIR MYLAN/rtv with ticagrelor may increase concentrations of ticagrelor. Co-administration of DARUNAVIR MYLAN/rtv and ticagrelor is not recommended.

Sedatives/hypnotics
Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem Co-administration of DARUNAVIR MYLAN/rtv with these sedatives/hypnotics may increase concentrations of the sedative/hypnotic (inhibition of CYP3A).
Co-administration of DARUNAVIR MYLAN/rtv with oral midazolam or triazolam is contraindicated.
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.
Clinical monitoring is recommended when co-administering DARUNAVIR MYLAN/rtv with the other sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered.

Treatment of premature ejaculation
Co-administration of DARUNAVIR MYLAN/rtv with dapoxetine is contraindicated.

Urinary antispasmodics
Fesoterodine, solifenacin
Use with caution: monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary.

4.6 Pregnancy, Breast-feeding and Fertility
Pregnancy
There are no adequate and well-controlled studies on pregnancy outcome with darunavir in pregnant women. Studies in animals have not shown evidence of developmental toxicity or effect on reproductive function and fertility.

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. For darunavir, sufficient first trimester exposures are available to allow detection of at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

Darunavir/ritonavir (600/100 mg twice 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 (6-12 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 *Pharmacokinetic Properties-Special Populations – Pregnancy and Postpartum*).
DARUNAVIR MYLAN/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 nursing infants, mothers should be instructed not to breastfeed if they are receiving DARUNAVIR MYLAN.

Fertility
There was no effect on mating or fertility with DARUNAVIR MYLAN treatment in rats.

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 and should be borne in mind when considering a patient's ability to drive or operate machinery.

4.8 Adverse Reactions
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of darunavir based on the comprehensive assessment of the available adverse event information. A causal relationship with darunavir cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The overall safety profile of DARUNAVIR MYLAN is based on all available clinical trial and post-marketing data, and is consistent with the data presented below.
Due to the need for co-administration of DARUNAVIR MYLAN with ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

Adverse reactions to Darunavir/rtv identified in clinical trials in adults
Adverse reactions to Darunavir/rtv 600/100 mg b.i.d. identified in antiretroviral treatment-experienced adult patients
The safety assessment is based on all safety data from the Phase 3 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 ARs reported during treatment with DARUNAVIR/rtv were mild in severity. The most frequent (≥ 5%) ARs of moderate to severe (grade 2-4) intensity were diarrhea, hypertriglyceridemia, hypercholesterolemia, nausea, abdominal pain, vomiting, hepatic enzymes increased, and rash.

The most frequent (≥ 1%) severe (grade 3 or 4) ARs were related to laboratory abnormalities. All other grade 3 or 4 ARs were reported in less than 1% of the patients. 4.7% of the patients discontinued treatment due to ARs.

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

Table 1: Adverse Reactions at least Grade 2 Intensity Reported in TITAN Trial (96 weeks)

System Organ Class Adverse 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%
Diarrhea	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		
Pruritus	1.0%	1.0%
Rash Urticaria+	5.0%	2.0%
	0.3%	0%
Musculoskeletal and Connective Tissue Disorders		
Myalgia	1.0%	0.7%
Metabolism and Nutrition Disorders	1.7%	2.0%
Anorexia Diabetes mellitus	1.7%	0.3%
General Disorders and Administration Site Conditions	3.4%	1.0%
Asthenia Fatigue	2.0%	1.3%
Immune System Disorders	0.3%	0%
Immune reconstitution syndrome		
Reproductive System and Breast Disorders	0.3%	0.3%
Gynecomastia		
Psychiatric Disorders	0.7%	0%
Abnormal dreams		

* Excluding laboratory abnormalities reported as ARs.
# Optimized Background Regimen.
\+ Adverse reactions identified from post-marketing experience.

Laboratory abnormalities, grade 2-4, considered ARs, in antiretroviral treatment-experienced HIV-1 infected adult patients in the TITAN trial are shown in Table 2:

Table 2: Laboratory abnormalities, grade 2-4, considered ARs in TITAN 96 week analyses

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	> 2.5 to ≤ 5.0 x ULN	6.9%	4.8%
Grade 2	> 5.0 to ≤ 10.0 x ULN	2.4%	2.4%
Grade 3	> 10.0 x ULN	1.0%	1.7%
Grade 4			
AST	> 2.5 to ≤ 5.0 x ULN	5.5%	6.2%
Grade 2	> 5.0 to ≤ 10.0 x ULN	2.4%	1.7%
Grade 3	> 10.0 x ULN	0.7%	1.7%
Grade 4			

ALP Grade 2 Grade 3 Grade 4	> 2.5 to ≤ 5.0 x ULN > 5.0 to ≤ 10.0 x ULN > 10.0 x ULN	0.3% 0.3% 0%	0% 0.3% 0%
Triglycerides Grade 2 Grade 3 Grade 4	500 - 750 mg/dl 751 - 1200 mg/dl > 1200 mg/dl	10.4% 6.9% 3.1%	11.4% 9.7% 6.2%
Total cholesterol* Grade 2 Grade 3	240 - 300 mg/dl > 300 mg/dl	24.9% 9.7%	23.2% 13.5%
LDL cholesterol* Grade 2 Grade 3	160 - 190 mg/dl ≥ 191 mg/dl	14.4% 7.7%	13.5% 9.3%
Elevated glucose levels Grade 2 Grade 3 Grade 4	126 - 250 mg/dl 251 - 500 mg/dl > 500 mg/dl	10.0% 1.4% 0.3%	11.4% 0.3% 0%
Pancreatic lipase Grade 2 Grade 3 Grade 4	> 1.5 to ≤ 3.0 x ULN > 3.0 to ≤ 5.0 x ULN > 5.0 x ULN	2.8% 2.1% 0.3%	3.5% 0.3% 0%
Pancreatic amylase Grade 2 Grade 3 Grade 4	> 1.5 to ≤ 2.0 x ULN > 2.0 to ≤ 5.0 x ULN > 5.0 x ULN	6.2% 6.6% 0%	7.3% 2.8% 0%

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

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience. The frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports.

In Table 3, adverse reactions identified during post-marketing experience are presented by frequency category based on spontaneous reporting rates.

Table 3: Post-marketing ARs Presented by Frequency Category Based on Spontaneous Reporting Rates

System Organ Class	Adverse Reaction	Frequency
Skin and subcutaneous tissue disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Very rare
	Toxic epidermal necrolysis	Very rare

	Acute generalized exanthematous pustulosis	Very rare
Renal and urinary disorders	Crystal nephropathy	Very rare

Effects of combination antiretroviral therapy
Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, hyperglycemia, and hyperlactatemia.
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 reconstitution inflammatory syndrome). Autoimmune disorders such as Graves' disease and autoimmune hepatitis have also been reported in the context of immune reconstitution inflammatory syndrome (see *Warnings and Precautions)*.

There have been reports of increased spontaneous bleeding in hemophilia patients receiving PIs.
Increased CPK, myalgia, myositis, and rarely, rhabdomyolysis have been reported with the use of HIV protease inhibitors, particularly in combination with NRTIs.

Although a casual relationship has not been definitively established, protease inhibitors may contribute to increase in blood sugar levels and even diabetes in HIV patients. Close monitoring of blood glucose level is recommended.

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 (see *Warnings and Precautions*). The pharmacokinetic exposure in co-infected patients was comparable to that in patients without co-infection.

4.9 Overdose
Symptoms and signs
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.

Treatment
There is no specific antidote for overdose with DARUNAVIR MYLAN. Treatment of overdose with DARUNAVIR MYLAN consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Antivirals for systemic use, ATC code: J05AE10.

Mechanism of action
Darunavir is an inhibitor of the dimerization 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 tightly binds to the HIV-1 protease with a K_D of 4.5 x 10^{-12} M. Darunavir shows resilience to

the effects of HIV protease inhibitors Resistance-Associated Mutations (RAMs). Darunavir is not an inhibitor of any of 13 tested human cellular proteases.

Pharmacodynamic effects

Microbiology

Antiviral activity in vitro

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM. These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 μM to > 100 μM.

The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir showed synergistic antiviral activity when studied in combination with the protease inhibitors ritonavir, nelfinavir, or amprenavir and additive antiviral activity when studied in combination with the protease inhibitors indinavir, saquinavir, lopinavir, atazanavir, or tipranavir, the N(t)RTIs zidovudine, lamivudine, zalcitabine, didanosine, stavudine, abacavir, emtricitabine, or tenofovir, the NNRTIs etravirine, nevirapine, delavirdine, rilpivirine, 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 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23-50-fold) harbored 2 to 4 amino acid substitutions in the protease gene. The decreased susceptibility to darunavir of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations.

In vitro selection of darunavir-resistant HIV-1 (range: 53-641-fold change in EC_{50} values [FC]) from 9 HIV-1 strains harboring multiple PI 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. A minimum of 8 of these darunavir *in vitro* selected mutations, from which at least 2 were already present in the protease prior to selection, were required in the HIV-1 protease to render a virus resistant (FC > 10) to darunavir.

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 and POWER 2 trials and in the POWER 3 analysis, only the subgroups with > 10 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 PIs remain susceptible to darunavir.

Seven of the 9 darunavir-resistant viruses selected from PI-resistant viruses had phenotypic data for tipranavir. Six of those showed a FC < 3 for tipranavir, indicative of limited cross-resistance between these 2 protease inhibitors.

Cross-resistance between darunavir and the nucleoside/nucleotide reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors, the entry inhibitors, or the integrase inhibitors, is unlikely because the viral targets for those inhibitors are different.

Clinical studies
Clinical trials described in this section were performed with DARUNAVIR co-administered with low dose ritonavir.

Description of clinical studies in adults
Efficacy of DARUNAVIR/rtv 600/100 mg b.i.d. in treatment-experienced 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 3 trial TITAN in treatment-experienced, lopinavir/rtv naïve patients and on the analyses of 96 week data from the Phase 2b trials POWER 1, 2 and 3, in patients with high level of PI resistance.
TITAN is a randomized, controlled, open-label Phase 3 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 optimized 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 18-68), 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 – 831 x 10^6 cells/L).

Table 4 below shows the efficacy data of the 48 week and 96 week analyses from the TITAN trial.

Table 4: Efficacy Data of 48 Week and 96 Week Analyses (TITAN Trial)

	At week 48[a]			**At week 96[b]**		
Outcomes	**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)	-1.95	-1.72	-0.23[f] (-0.44; -0. 02)[d]	–1.71	–1.52	–0.19[f] (–0.40; 0.03)

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 a normal approximation of 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 ITT and OP populations; furthermore superiority of DARUNAVIR/rtv over the lopinavir/rtv arm was demonstrated ($p = 0.008$). 70.8% of patients on DARUNAVIR/rtv reached less than 50 HIV-1 RNA copies/mL versus 60.3% in the lopinavir/rtv arm.

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 populations; 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.

POWER 1 and POWER 2 are randomized, controlled Phase 2b trials in adult patients with a high level of PI resistance consisting of 2 parts: an initial partially blinded, dose-finding part and a second long term part in which all patients randomized 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 RNA > 1000 copies/mL, had prior treatment with PI(s), NNRTI(s) and NRTI(s), had at least 1 primary (i.e., major) PI mutation at screening and were on a stable PI-containing regimen at screening for at least 8 weeks. Randomization 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 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 - 73), 89% were male, 81% white, 10% black and 7% hispanic. The mean baseline plasma HIV-1 RNA was 4.61 log10 copies/mL and the median baseline CD4+ cell count was 153 x 10^6 cells/L (range 3 – 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 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 log10 versus baseline, was evaluated in patients receiving DARUNAVIR/rtv plus an optimized 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%. Twenty-three percent of the control patients used dual-boosted PIs. Approximately 47% of all patients used enfuvirtide and 35% of the use was in patients who were ENF-naïve.

POWER 3*:* additional data on the efficacy of DARUNAVIR/rtv 600/100 mg b.i.d. have been obtained in treatment-experienced adult patients participating in the non-randomized trial TMC114-C215. 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 were the same as and baseline characteristics were comparable to those of POWER 1 and POWER 2. The mean baseline plasma HIV-1 RNA was 4.58 log10 copies/mL and the median CD4+ cell count was 120 x 10^6 cells/L (range 0 – 831 x 10^6 cells/L). The median darunavir FC was 3.2. Patients had a prior exposure to a mean of 5 PIs, 6 NRTIs and 2 NNRTIs, 32% had prior use of enfuvirtide.

Table 5 below shows the efficacy data of the 48 week analyses from the pooled POWER 1 and POWER 2 trials as well as from POWER 3.

Table 5: Efficacy Data of the 48 Week Analyses (Pooled POWER 1, POWER 2 and POWER 3 Trial)

Outcomes	**POWER 1 and POWER 2 pooled data**			**POWER 3**
	DARUNAVIR/rtv 600/100 mg b.i.d. N = 131	**Control N = 124**	**Treatment difference (95% CI of difference)**	**DARUNAVIR/rtv 600/100 mg b.i.d. N = 334**
HIV-1 RNA log10 mean change from baseline (log10 copies/mL)[a]	-1.69	-0.37	-1.32(-1.58; -1.05)	-1.62
HIV-1 RNA > 1 log10 below baseline[d]	81 (61.8%)	20 (16.1 %)	45.7%(35.0%; 56.4%)[e]	196 (58.7%)
HIV-1 RNA < 400 copies/mL[d]	72 (55.0%)	18 (14.5 %)	40.4%(29.8%; 51.1%)[e]	183 (54.8%)
HIV-1 RNA < 50 copies/mL[d]	59 (45.0%)	14 (11.3 %)	33.7%(23.4%; 44.1%)[e]	155 (46.4%)
CD4+ cell count mean change from baseline (× 10^6/L)[c]	103	17	86[b](57; 114)	105

[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.

In the pooled POWER 1 and POWER 2 analysis, the proportion of patients in the DARUNAVIR/rtv (600/100 mg b.i.d.) arm provided superior decreases in log10 viral load from baseline compared to the comparator arm. At week 48, the proportion of patients in the DARUNAVIR/rtv arm resulted in 62% of patients with a decrease of at least 1.0 log10 in viral load, compared to 16% in the comparator arm. The proportion of patients with HIV-1 RNA < 50 copies/mL was 45% in the DARUNAVIR/rtv arm compared to 11% for the comparator arm.

The 48 week efficacy POWER 3 analysis confirmed the viral load reduction and CD4+ increase observed in the POWER 1 and POWER 2 trials. Of the 334 patients included in the week 48 analysis, 59% had a virologic response defined as a decrease of at least 1.0 log10 in plasma viral load versus baseline and 46% of the patients reached less than 50 HIV-1 RNA copies/mL.

Analyses of data through 96 weeks of treatment in the POWER trials demonstrated sustained antiretroviral efficacy and immunological benefit. Treatment with DARUNAVIR/rtv (600/100 mg b.i.d.) resulted in 56.5% (POWER 1 and 2) and 52.2% (POWER 3) of patients with a decrease of at least 1 log10 in HIV-1 RNA from baseline. 38.9% (POWER 1 and 2) and 42.1% (POWER 3) of patients reached an HIV-1 RNA level < 50 copies/mL. At 96 weeks, 49.6% (POWER 1 and 2) and 50.0% (POWER 3) of patients reached less than 400 HIV-1 RNA copies/mL. The mean decrease in HIV-1 RNA level compared to baseline was 1.58 (POWER 1 and 2) and 1.43 (POWER 3) $\log_{10}$ copies/mL and a mean increase in CD4+ cell count of 133 x 10^6 cells/L (POWER 1 and 2) and 103 x 10^6 cells/L (POWER 3) was observed. Out of the 206 patients who responded with complete viral suppression (< 50 copies/mL) at week 48, 177 patients (86% of the responders at week 48) remained responders at week 96.

In vivo selection of viral resistance during DARUNAVIR/rtv therapy

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/ritonavir 400/100 mg b.i.d. developed primary (i.e., major) 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.

In vivo cross-resistance with other HIV protease inhibitors

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 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 PIs could not be studied in the POWER and DUET trials, since most of the baseline viruses were already resistant to these PIs. Patients with no susceptible 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 600/100 mg 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 (POWER and DUET Trials)

Number of mutations at baseline*	All % (n/N)	No/non-naïve use of ENF % (n/N)	Naïve use of ENF % (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% (20/171)	7% (10/135)	28% (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 (POWER and DUET Trials)

Baseline darunavir phenotype	All % (n/N)	No/non-naïve use of ENF % (n/N)	Naïve use of ENF % (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 the treatment history and to resistance testing results where available.

5.2 Pharmacokinetic Properties

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

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

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

The absolute oral bioavailability of a single 600 mg dose of DARUNAVIR alone was approximately 37% and increased to approximately 82% in the presence of 100 mg 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 *Warnings and Precautions*).
When administered without food, the relative bioavailability of DARUNAVIR in the presence of low-dose ritonavir is 30% lower as compared to intake with food. Therefore, DARUNAVIR tablets should be taken with ritonavir and with food. The type of food does not affect exposure to darunavir.

Distribution
Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma alpha-1-acid glycoprotein.

Metabolism
In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by the hepatic CYP system and almost exclusively by isozyme CYP3A4. A ^{14}C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg DARUNAVIR/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 feces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces 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
Elderly (65 years of age and older)
Population pharmacokinetic analysis in HIV-infected patients showed that DARUNAVIR pharmacokinetics are not considerably different in the age range (18-75 years) evaluated in HIV infected patients (see *Warnings and Precautions*).

Renal impairment
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.
Although DARUNAVIR has not been studied in patients with renal impairment, population pharmacokinetic analysis showed that the pharmacokinetics of DARUNAVIR were not significantly affected in HIV infected patients with moderate renal impairment (CrCl between 30 - 60 mL/min, n = 20) (see *Dosage and Administration* and *Warnings and Precautions*).

Hepatic impairment
Darunavir is primarily metabolized 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. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see *Dosage and Administration* and *Warnings and Precautions*).

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

Pregnancy and postpartum
The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 600/100 mg b.i.d as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum (see Table 6). 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.

Table 6: Pharmacokinetic Results of Total Darunavir After Administration of Darunavir/Ritonavir at 600/100 mg bid as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

Pharmacokinetics of total darunavir (mean ± SD)	**2nd Trimester of pregnancy n=12[a]**	**3rd Trimester of pregnancy n=12**	**Postpartum (6-12 Weeks) n=12**
C_{max}, ng/mL	4668 ± 1097	5328 ± 1631	6659 ± 2364
AUC_{12h}, ng.h/mL	39370 ± 9597	45880 ± 17360	56890 ± 26340
C_{min}, ng/mL[b]	1922 ± 825	2661 ± 1269	2851 ± 2216

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

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.

6. PHARMACEUTICAL INFORMATION

6.1 List of Excipients
Core tablet:
Hypromellose,
Silicified microcrystalline cellulose,
Crospovidone,
Colloidal silicon dioxide,
Magnesium stearate.

Film coat:
Polyvinyl alcohol part hydrolysed,
Titanium dioxide,
Macrogol/PEG,
Talc.

6.2 Incompatibilities
Not applicable

6.3 Shelf Life
24 months

6.4 Storage Conditions
Do not store above 30°C. Store in the original container. Discard 60 days after the first opening

6.5 Dosage Form and Packaging Available
Round blue opaque HDPE bottle containing 60 tablets with a desiccant and closed with a blue opaque polypropylene cap.

7. MANUFACTURER
Mylan Laboratories Limited
Plot No. H12 & 13, MIDC Waluj Industrial Area,
Chhatrapati Sambhajinagar,
Maharashtra 431136, India

8. PRODUCT REGISTRATION HOLDER
NVS Regulatory Services Sdn Bhd,
Unit 19g, 7th Floor, Block 2,
Worldwide Business Centre,
Jalan Tinju 13/50,
40675 Shah Alam, Selangor, Malaysia

9. DATE OF REVISION OF THE TEXT
August 2026