1. Name of the finished pharmaceutical product

INN Name: Darunavir and Ritonavir Tablets 400 mg/ 50 mg

Trade Name: NA

Strength: 400 mg/50 mg

Pharmaceutical form: Solid oral dosage form

2. Qualitative and quantitative composition

Each Film coated tablets contains 433.640 mg of Darunavir Ethanolate equivalent to 400 mg of Darunavir and Ritonavir USP 50 mg, Silicified Microcrystalline Cellulose USP-NF (Prosolv SMCC HD90), Crospovidone , USP/NF (Polyplasdone XL-10), Colloidal silicon dioxide , USP/NF (Aerosil 200), Magnesium Stearate (LIGAMED MF-2-V), Copovidone, (Plasdone S 630), Sorbitan mono Laurate, (span 20), Dibasic calcium phosphate anhydrous, (A-Tab), Sodium Stearyl fumarate, Opadry yellow 16C82767, Purified Water.

3. Pharmaceutical form

Dosage form: Film coated Tablet

Description:

Yellow, capsule shaped, bevel edged, biconvex film coated tablets debossed with 'H' on one side and 'D8' on the other side.

4. Clinical particulars

4.1 Therapeutic indications

INDICATIONS AND USAGE

Darunavir and Ritonavir 400 mg/50 mg tablets are indicated as a pharmacokinetic enhancer for protease inhibitors in a combination therapy with other antiretroviral agents for the treatment of HIV-1 infected patients.

Consideration should be given to official treatment guidelines for HIV-1 infected patients.

4.2 Posology and method of administration

Therapy should be initiated by a health care provider experienced in the management of HIV infection. After therapy with Darunavir and Ritonavir Tablets 400 mg/50 mg has been initiated,

Patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their health care provider.

Posology

Darunavir

Darunavir (as ethanolate) 400 mg Tablets must always be given orally with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The product information of ritonavir must therefore be consulted prior to initiation of therapy with Darunavir (as ethanolate) 400 mg tablets.

PI-experienced adult

The recommended dose regimen is 400 mg (1 tablet of Darunavir (as ethanolate) 600mg Tablets) twice daily taken with ritonavir 100 mg twice daily, taken with food.

PI- *naïve and experienced pediatric patients from the age of 3 years (with a body weight of at least 15 kg).*

The weight-based dose of darunavir and ritonavir tablets 400 mg/ 50mg in pediatric patients is provided in the table below. Pediatric dosing may require co-administration of tablets of different strengths to achieve the recommended doses depending on weight band. Not all doses may be achieved with this formulation. Careful instructions to caregivers when recommending a combination of different strength tablets is critical to ensure appropriate dosing.

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

Recommended dose for PI-naïve paedriatic patients (3 to 17 years of age)* with darunavir tablets and ritonavir		
Body weight (kg)	**Dose (once daily with food)**	**Dose (twice daily with food)**
≥15kg-<30kg	600 mg darunavir/100 mg ritonavir once daily	375 mg darunavir/50 mg ritonavir twice daily
≥30 kg-<40 kg	675 mg darunavir/100 mg ritonavir once daily	450 mg darunavir/60 mg ritonavir twice daily
≥40 kg	800 mg darunavir/100 mg ritonavir once daily	600 mg darunavir/100 mg ritonavir twice daily

*When genotypic testing is not feasible, a twice daily dosing regimen is recommended in HIV protease inhibitor-experienced patients.

Advice on missed doses

If a dose of darunavir and/or ritonavir is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of darunavir and ritonavir tablets 400 mg/ 50 mg with food as soon as possible. If this is noticed later than 12 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

This guidance is based on the 15-hour half-life of darunavir in the presence of ritonavir and the recommended dosing interval of approximately 24 hours.

Special populations

Elderly

Limited information is available in this population, and therefore, darunavir should be used with caution in this age group.

Renal impairment

No dose adjustment is required for darunavir/ritonavir in patients with renal impairment.

Hepatic impairment

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

Pediatric population

Dose adjustments cannot be achieved with Darunavir (as ethanolate) 600mg Tablets. Other formulations/tablet strengths of darunavir may be required.

Darunavir/ritonavir should not be used in children below 3 years of age or weighing less than 15 kg.

Method of administration

Patients should be instructed to take darunavir with low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir.

Ritonavir

Ritonavir 25 mg Tablets should be prescribed by physicians who are experienced in the treatment of HIV infection.

Ritonavir 25 mg Tablets is administered orally and should be ingested with food. Ritonavir 25 mg Tablets should be swallowed whole and not chewed, broken or crushed.

As Ritonavir 25 mg Tablets is used as a pharmacokinetic enhancer for other protease inhibitors the Summary of Product Characteristics for the particular protease inhibitor must be consulted.

The following HIV-1 protease inhibitors can be used with ritonavir as a pharmacokinetic enhancer at the noted doses.

Adults and adolescents:

Amprenavir 600 mg twice daily with ritonavir 100 mg twice daily

Atazanavir 300 mg once daily with ritonavir 100 mg once daily

Fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily

Lopinavir co-formulated with ritonavir (lopinavir/ritonavir) 400 mg/100 mg or 800 mg/200 mg

Saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily in ART experienced patients.

Initiate treatment with saquinavir 500 mg twice daily with ritonavir 100 mg twice daily for the first 7 days, then saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily in ART- naïve patients.

Tipranavir 500 mg twice daily with ritonavir 200 mg twice daily. Tipranavir with ritonavir should not be used in treatment-naïve patients.

Darunavir 600 mg twice daily with ritonavir 100 mg twice daily in antiretroviral treatment (ART) experienced patients.

Darunavir 800 mg once daily with ritonavir 100 mg once daily may be used in some ART experienced patients. Refer to the darunavir SmPC for further information on once daily dosing in ART experienced patients.

Darunavir 800 mg once daily with ritonavir 100 mg once daily in ART-naïve patients

For use in adults more suitable formulations containing a higher amount of the active, i.e. 100mg tablets, may be available.

Pediatric patients:

Recommended doses are 2 x 25 mg to 2 x 50 mg (i.e. 2 x 2 tablets) ritonavir per day depending on the concurrently used PI.

For children who are undergoing anti-tuberculosis treatment with rifampicin, higher dosages of ritonavir may be needed for pharmacokinetic enhancement of the combined protease inhibitor. Please refer to the product information of the protease inhibitors approved for co-administration with ritonavir.

Ritonavir 25 mg tablets should only be used in children who can swallow tablets whole. Other, more suitable formulations may be available for children less than 5 years of age or other children not able to swallow tablets whole.

Renal impairment:

Since the renal clearance of ritonavir is negligible, a decrease in the total body clearance is not expected in patients with renal impairment. Depending on the specific protease inhibitor with which it is co-administered, ritonavir may be appropriate for use with caution in patients with renal insufficiency. For specific dosing information in patients with renal impairment, refer to the summary of product characteristics (SmPC) of the co-administered protease inhibitor.

Hepatic impairment:

Ritonavir should not be given to patients with decompensated liver disease. In the absence of pharmacokinetic studies in patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation, caution should be exercised when ritonavir is used as a pharmacokinetic enhancer as increased levels of the co-administered PI may occur. Specific recommendations for use of ritonavir as a pharmacokinetic enhancer in patients with hepatic impairment are dependent on the protease inhibitor with which it is co-administered. The SmPC of the co-administered PI should be reviewed for specific dosing information in this patient population.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Patients with severe (Child-Pugh Class C) hepatic impairment.

Combination of rifampicin with darunavir with concomitant low dose ritonavir.

Co-administration with the combination product lopinavir/ritonavir.

Co-administration with herbal preparations containing St John's wort (Hypericum perforatum)

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

- alfuzosin (alpha 1-adrenoreceptor antagonist)
- amiodarone, bepridil, dronedarone, quinidine, ranolazine, systemic lidocaine (antiarrhythmic/antianginals)
- astemizole, terfenadine (antihistamines)
- colchicine when used in patients with renal and/or hepatic impairment (antigout)
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- cisapride (gastrointestinal motility agent)
- pimozide, quetiapine, sertindole (antipsychotics/neuroleptics)
- triazolam, midazolam administered orally (sedatives/hypnotics) (for caution on parenterally administered midazolam)
- sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil (PDE-5 inhibitors)

- simvastatin and lovastatin (HMG-CoA reductase inhibitors)
- ticagrelor (antiplatelet).

Ritonavir

Hypersensitivity to ritonavir or to any of the excipients.

Consult the Summary of Product Characteristics of the co-administered drug for other possible contraindications.

Ritonavir 25 mg Tablets should not be given to patients with decompensated liver disease.

In vitro and *in vivo* studies have demonstrated that ritonavir is a potent inhibitor of CYP3A- and CYP2D6- mediated biotransformations. The following medicines are contraindicated when used with ritonavir and, unless otherwise noted, the contraindication is based on the potential for ritonavir to inhibit metabolism of the co-administered medicinal product, resulting in increased exposure to the co-administered product and risk of clinically significant adverse effects.

The enzyme-modulating effect of ritonavir may be dose dependent.

Medicinal Product Class	**Medicinal Products within Class**	**Rationale**
Concomitant medicinal product levels increased or decreased		
α1-Adrenoreceptor Antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension
Analgesics	Pethidine, piroxicam, propoxyphene	Increased plasma concentrations of nor pethidine, piroxicam and propoxyphene. Thereby, increasing the risk of serious respiratory depression or hematologic abnormalities, or other serious adverse effects from these agents.
Antiarrthymics	Fusidic Acid	Increased plasma concentrations of fusidic acid and ritonavir.
Antifungal	Voriconazole	Concomitant use of ritonavir (400 mg twice daily and more) and voriconazole is contraindicated due to a reduction in voriconazole plasma concentrations and possible loss of effect

Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Antimycobacterial	Rifabutin	Concomitant use of ritonavir dosed as an antiretroviral agent (600 mg twice daily) and rifabutin is contraindicated due to an increase of rifabutin serum concentrations and risk of adverse reactions including uveitis. Recommendations regarding use of ritonavir dosed as a pharmacokinetic enhancer with rifabutin
Antipsychotics/ Neuroleptics	Clozapine, pimozide	Increased plasma concentrations of clozapine and pimozide. Thereby, increasing the risk of serious hematologic abnormalities, or other serious adverse effects from these agents.
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischemia.
GI motility agent	Cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent.
HMG Co-A Reductase Inhibitor	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis

PDE5 inhibitor	Avanafil	Increased plasma concentrations of avanafil
	Sildenafil	Contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only. Increased plasma concentrations of sildenafil. Thereby, increasing the potential for sildenafil-associated adverse events (which include hypotension and syncope). for co-administration of sildenafil in patients with erectile ysfunction.
	Vardenafil	Increased plasma concentrations of vardenafil
Sedatives/hypnotics	Clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam	Increased plasma concentrations of clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents. (For caution on parenterally administered midazolam, see section Interaction with other medicinal products and other forms of interaction)
Ritonavir medicinal product level decreased		
Herbal Preparation	St. John's Wort	Herbal preparations containing St. John's wort (Hypericum perforatum) due to the risk of decreased plasma concentrations and reduced clinical effects of ritonavir

4.4 Special warnings and precautions for use

Darunavir

Transmission

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

Severe skin reactions

Severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been uncommonly reported. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens - Johnson syndrome has been rarely (< 0.1%) reported, and during post-marketing experience toxic epidermal necrolysis and acute generalized exanthematous pustulosis have been reported. Symptoms can include, but are not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia. Darunavir should be discontinued immediately if signs or symptoms of severe skin reactions develop.

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

Hepatotoxicity

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

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

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

Hepatic impairment

The safety and efficacy of darunavir have not been established in patients with severe underlying liver disorders and darunavir is therefore contraindicated in patients with severe hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, this medicine should be used with caution in patients with mild or moderate hepatic impairment.

Renal impairment

No special precautions or dose adjustments for darunavir/ritonavir are required in patients with renal impairment. As darunavir and ritonavir tablets 400mg/ 50mg are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Therefore, no special precautions or dose adjustments are required in these patients.

Hemophiliac patients

There have been reports of increased bleeding, including spontaneous skin hematomas and haemarthrosis in patients with hemophilia type A and B treated with PIs. In some patient's 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.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment.

For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Osteonecrosis

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

Opportunistic infections

Patients receiving darunavir or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Immune reconstitution inflammatory syndrome

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

Interactions with medicinal products

Efavirenz in combination with darunavir/ritonavir 800/100 mg once daily may result in sub-optimal darunavir Cmin. If efavirenz is to be used in combination with darunavir/ritonavir a twice daily dosing regimen is recommended in HIV protease inhibitor-experienced patients.

Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A and P-glycoprotein.

Excipients

Each tablet contains 3.655 mg of FD&C yellow #6/Sunset yellow FCF Aluminum Lake, a coloring agent which may cause allergic reactions.

Ritonavir

Opportunistic infections

Ritonavir is not a cure for HIV-1 infection or AIDS. Patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection.

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

As ritonavir is used as a pharmacokinetic enhancer with other PIs, full details on the warnings and precautions relevant to that particular PI should be considered, therefore the summary of product characteristics for the particular PI must be consulted.

Some of the below warnings originate in the use of ritonavir as antiretroviral agent at higher doses than those recommended for pharmacokinetic enhancement. Respective effects of ritonavir when used as a pk enhancer might hence be less pronounced.

Patients with chronic diarrhea or malabsorption: Extra monitoring is recommended when diarrhea occurs. The relatively high frequency of diarrhea during treatment with ritonavir may compromise the absorption and efficacy (due to decreased compliance) of ritonavir or other concurrent medicinal products. Serious persistent vomiting and/or diarrhea associated with ritonavir use might also compromise renal function. It is advisable to monitor renal function in patients with renal function impairment.

Hemophilia: there have been reports of increased bleeding, including spontaneous skin hematomas and haemarthroses, in hemophiliac patients type A and B treated with protease inhibitors. In some patient's additional factor VIII was given. In more than a half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Hemophiliac patients should therefore be made aware of the possibility of increased bleeding.

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

Pancreatitis: Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and ritonavir therapy should be discontinued if a diagnosis of pancreatitis is made.

Immune Reactivation 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 few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, and Pneumocystis jiroveci 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 reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

Liver disease: Ritonavir should not be given to patients with decompensated liver disease. For patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be

monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal disease: Since the renal clearance of ritonavir is negligible, decrease in the total body clearance is not expected in patients with renal impairment. For specific dosing information in patients with renal impairment, refer to the Summary of Product Characteristics (SmPC) of the co-administered protease inhibitor.

Renal failure, renal impairment, elevated creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with concomitant use of tenofovir disoproxil fumarate in clinical practice.

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

PR interval prolongation: Ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicinal products known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving ritonavir. Ritonavir should be used with caution in such patients.

Interactions with other medicinal products

Full details on the warnings and precautions relevant to a particular PI must be considered, therefore the summary of product characteristics, for the particular PI must be consulted to determine if the information below is applicable.

PDE5 inhibitors: Particular caution should be used when prescribing sildenafil or tadalafil for the treatment of erectile dysfunction in patients receiving ritonavir. Co-administration of ritonavir with these medicinal products is expected to substantially increase their concentrations and may result in associated adverse reactions such as hypotension and prolonged erection.

Concomitant use of avanafil or vardenafil with ritonavir is contraindicated. Concomitant use of sildenafil with ritonavir is contraindicated in pulmonary arterial hypertension patients.

HMG-CoA reductase inhibitors: The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism, thus concomitant use of ritonavir with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised and reduced doses should be considered if ritonavir is used concurrently with atorvastatin, which is metabolized to a lesser extent by CYP3A. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir, the lowest doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent of CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Colchicine

Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir.

Digoxin: Particular caution should be used when prescribing ritonavir in patients taking digoxin since co-administration of ritonavir with digoxin is expected to increase digoxin levels. The increased digoxin levels may lessen over time.

In patients who are already taking digoxin when ritonavir is introduced, the digoxin dose should be reduced to one-half of the patients' normal dose and patients need to be followed more closely than usual for several weeks after initiating co-administration of ritonavir and digoxin.

In patients who are already taking ritonavir when digoxin is introduced, digoxin should be introduced more gradually than usual. Digoxin levels should be monitored more intensively than usual during this period, with dose adjustments made, as necessary, based on clinical, electrocardiographic and digoxin level findings.

Ethinyl estradiol: Barrier or other non-hormonal methods of contraception should be considered when administering ritonavir at therapeutic or low doses as ritonavir is likely to reduce the effect

and change the uterine bleeding profile when co-administered with estradiol-containing contraceptives.

Glucocorticoids: Concomitant use of ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression

Trazodone: Particular caution should be used when prescribing ritonavir in patients using trazodone. Trazodone is a CYP3A4 substrate and co-administration of ritonavir is expected to increase trazodone levels. Adverse reactions of nausea, dizziness, hypotension and syncope have been observed in single dose interaction studies in healthy volunteers

Rivaroxaban: It is not recommended to use ritonavir in patients receiving rivaroxaban, due to the risk of increased bleeding.

Bedaquiline: Strong CYP3A4 inhibitors such as protease inhibitors may increase bedaquiline exposure which could potentially increase the risk of bedaquiline-related adverse reactions. Therefore, combination of bedaquiline with ritonavir should be avoided. However, if the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (refer to the bedaquiline summary of product characteristics).

Delamanid

Co-administration of delamanid with a strong inhibitor of CYP3A (ritonavir) may increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co- administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (refer to the delamanid Summary of Product Characteristics).

Saquinavir: Doses of ritonavir higher than 100 mg twice daily should not be used. Higher doses of ritonavir have been shown to be associated with an increased incidence of adverse reactions.

Co-administration of saquinavir and ritonavir has led to severe adverse reactions, mainly diabetic ketoacidosis and liver disorders, especially in patients with pre-existing liver disease.

Saquinavir/ritonavir should not be given together with rifampicin, due to the risk of severe hepatotoxicity (presenting as increased hepatic transaminases) if the three medicines are given together.

Tipranavir: Co-administration of tipranivir with 200 mg of ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity.

Doses of ritonavir lower than 200 mg twice daily should not be used as they might alter the efficacy profile of the combination.

Fosamprenavir: Co-administration of fosamprenavir with ritonavir in doses greater than 100 mg twice daily has not been clinically evaluated. The use of higher ritonavir doses might alter the safety profile of the combination and therefore is not recommended.

Atazanavir: Co-administration of atazanavir with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and therefore is not recommended. Only when atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted. Refer to the atazanavir summary of product characteristics for further details.

Excipients

This medicinal product contains 0.95 mmol (21.93 mg) sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

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

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

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

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

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

Medicinal products that affect darunavir/ritonavir exposure

Darunavir and ritonavir are metabolised by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of these compounds and consequently that of darunavir, leading to

loss of therapeutic effect and possible development of resistance. CYP3A inducers that are contraindicated include rifampicin, St John's wort and lopinavir.

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

Interaction table

Interactions between darunavir/ritonavir and antiretroviral and non-antiretroviral medicinal products are listed in the table below (not determined as "ND"). The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 80-125% range.

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

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
HIV ANTIRETROVIRALS		
Integrase strand transfer inhibitors		
Dolutegravir	darunavir ↔ dolutegravir AUC ↓ Cmax ↓	Darunavir co-administered with low dose ritonavir and dolutegravir can be used without dose adjustment.

Elvitegravir	darunavir AUC ↔ Cmax ↔ elvitegravir AUC ↔ Cmin ↔ Cmax ↔	When darunavir co-administered with low dose ritonavir (600/100 mg twice daily) 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 or with elvitegravir/cobicistat have not been established. Therefore, co-administration of darunavir with low dose ritonavir in doses other than 600/100 mg twice daily and elvitegravir is not recommended. Co-administration of darunavir with low dose 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 and raltegravir can be used without dose adjustments.
Nucleo(s/t)ide reverse transcriptase inhibitors (NRTIs)		
Didanosine	darunavir AUC ↔ Cmin ↔ Cmax ↔ didanosine AUC ↓ Cmax ↓	Darunavir co-administered with low dose ritonavir and didanosine can be used without dose adjustments. Didanosine is to be administered on an empty stomach, thus it should be administered 1 hour before or 2 hours after darunavir/ritonavir given with food.

Tenofovir disoproxil fumarate	#darunavir AUC ↑ Cmin ↑ Cmax ↑ tenofovir AUC ↑ Cmin ↑ Cmax ↑ (↑ tenofovir from effect on MDR-1 transport in the renal tubules)	Monitoring of renal function may be indicated when darunavir co- administered with low dose ritonavir is given in combination with tenofovir, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.
Abacavir Emtricitabine Lamivudine Stavudine Zidovudine	Not studied. Based on the different elimination pathways of the other NRTIs zidovudine, emtricitabine, stavudine, lamivudine, that are primarily renally excreted, and abacavir for which metabolism is not mediated by CYP450, no interactions are expected for these medicinal compounds and darunavir	Darunavir co-administered with low dose ritonavir can be used with these NRTIs without dose adjustment.
Non-nucleo(s/t)ide reverse transcriptase inhibitors (NNRTIs)		
Efavirenz	#darunavir AUC ↓ Cmin ↓ Cmax ↓ efavirenz AUC ↑ Cmin ↑ Cmax ↑ (↑ efavirenz from CYP3A inhibition) (↓ darunavir from CYP3A induction)	Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when darunavir co-administered with low dose ritonavir is given in combination with efavirenz. Efavirenz in combination with darunavir/ritonavir 800/100 mg once daily may result in sub-optimal darunavir C_{min}. If efavirenz is to be used in combination with darunavir/ ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used.

Etravirine	darunavir AUC ↑ Cmin ↔ Cmax ↔ etravirine AUC ↓ Cmin ↓ Cmax ↓	Darunavir co-administered with low dose ritonavir and etravirine 200 mg twice daily can be used without dose adjustments.
Nevirapine	#darunavir: concentrations were consistent with historical data nevirapine AUC ↑ Cmin ↑ Cmax ↑ (↑ nevirapine from CYP3A inhibition)	Darunavir co-administered with low dose ritonavir and nevirapine can be used without dose adjustments.
Rilpivirine	darunavir AUC ↔ Cmin ↓ Cmax↔ rilpivirine AUC ↑ Cmin ↑ Cmax ↑	Darunavir co-administered with low dose ritonavir and rilpivirine can be used without dose adjustments.
HIV Protease inhibitors (PIs) - without additional co-administration of low dose ritonavir†		
Atazanavir	#darunavir AUC ↔ Cmin ↔ Cmax↔ atazanavir AUC ↔ Cmin ↑ Cmax ↓	Darunavir co-administered with low dose ritonavir and atazanavir can be used without dose adjustments.
Indinavir	#darunavir AUC ↑ Cmin ↑ Cmax ↑ indinavir AUC ↑ Cmin ↑ Cmax↔	When used in combination with darunavir co-administered with low dose ritonavir, dose adjustment of indinavir from 800 mg twice daily to 600 mg twice daily may be warranted in case of intolerance.

Saquinavir	#darunavir AUC ↓ Cmin ↓ Cmax ↓ saquinavir AUC ↓ Cmin ↓ Cmax ↓	It is not recommended to combine darunavir co-administered with low dose ritonavir with saquinavir.
Lopinavir/ritonavir	darunavir AUC ↓ Cmin ↓ Cmax ↓ lopinavir AUC ↑ 9% lopinavir Cmin ↑ 23% lopinavir Cmax ↓ 2%	Due to a decrease in the exposure (AUC) of darunavir by 40%, appropriate doses of the combination have not been established. Hence, concomitant use of darunavir co-administered with low dose ritonavir and the combination product lopinavir/ritonavir is contraindicated.
CCR5 ANTAGONIST		
Maraviroc	darunavir, ritonavir concentrations were consistent with historical data maraviroc AUC ↑ Cmax ↑	The maraviroc dose should be 150 mg twice daily when co-administered with darunavir co-administered with low dose ritonavir
ANAESTHETIC		
Alfentanil	Not studied The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by darunavir co- administered with low dose ritonavir	The concomitant use with darunavir co-administered with low dose ritonavir may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.
ANTIANGINA/ANTIARRHYTHMIC		

Disopyramide Flecainide Mexiletine Propafenone Amiodarone Bepridil Dronedarone Lidocaine (systemic) Quinidine Ranolazine	Not studied. Darunavir is expected to increase these antiarrhythmic plasma concentrations. (CYP3A inhibition)	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with darunavir co-administered with low dose ritonavir. Darunavir co-administered with low dose ritonavir and amiodarone, bepridil, dronedarone, systemic lidocaine, quinidine, or ranolazine is contraindicated.
Digoxin	digoxin AUC ↑ Cmax ↑ (↑ digoxin from probable inhibition of P-gp)	Given that digoxin has a narrow therapeutic index, it is recommended that the lowest possible dose of digoxin should initially be prescribed in case digoxin is given to patients on darunavir/ritonavir therapy. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject.
ANTIBIOTIC		
Clarithromycin	#darunavir AUC ↓ Cmin ↑ Cmax ↓ clarithromycin AUC ↑ Cmin ↑ Cmax ↑ (↑ clarithromycin from CYP3A inhibition and possible P-gp inhibition)	Caution should be exercised when clarithromycin is combined with darunavir co-administered with low dose ritonavir. For patients with renal impairment the product information of clarithromycin should be consulted for the recommended dose.
ANTICOAGULANTS		

Apixaban Dabigatran etexilate Rivaroxaban	Not studied. Co-administration of darunavir with these anticoagulants may increase concentrations of the anticoagulant. (CYP3A and/or P-gp inhibition)	The use of darunavir co-administered with low dose ritonavir and these anticoagulants is not recommended.
Warfarin	Not studied. Warfarin concentrations may be affected when co-administered with darunavir with low dose ritonavir.	It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with darunavir co-administered with low dose ritonavir.
ANTICONVULSANTS		
Phenobarbital Phenytoin	Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir (induction of CYP450 enzymes).	Darunavir co-administered with low dose ritonavir should not be used in combination with these medicines.
Carbamazepine	darunavir AUC ↔ Cmin ↓ Cmax ↔ carbamazepine AUC ↑ Cmin ↑ Cmax ↑	No dose adjustment for darunavir/ritonavir is recommended. If there is a need to combine darunavir /ritonavir and carbamazepine, patients should be monitored for potential carbamazepine-related adverse events. Carbamazepine concentrations should be monitored and its dose should be titrated for adequate response. Based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of darunavir/ritonavir.
ANTIDEPRESSANTS		

Paroxetine	#darunavir AUC ↔ Cmin ↔ Cmax ↔ paroxetine AUC ↓ Cmin ↓ Cmax ↓	If antidepressants are co-administered with darunavir co-administered with low dose ritonavir, the recommended approach is a dose titration of the antidepressant based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of these antidepressants who start treatment with darunavir with low dose ritonavir should be monitored for antidepressant response.
Sertraline	#darunavir AUC ↔ Cmin ↓ Cmax ↔ sertraline AUC ↓ Cmin ↓ Cmax ↓	
Amitriptyline Desipramine Imipramine Nortriptyline Trazodone	Concomitant use of darunavir co-administered with low dose ritonavir and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or CYP3A inhibition).	Clinical monitoring is recommended when co-administering darunavir with low dose ritonavir with these antidepressants and a dose adjustment of the antidepressant may be needed.
ANTIFUNGALS		
Voriconazole	Not studied. Ritonavir may decrease plasma concentrations of voriconazole. (induction of CYP450 enzymes)	Voriconazole should not be combined with darunavir co-administered with low dose ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Ketoconazole	#darunavir AUC ↑ Cmin ↑ Cmax ↑ ketoconazole AUC ↑ Cmin ↑ Cmax ↑ (CYP3A inhibition).	Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of ketoconazole should not exceed 200 mg.

Fluconazole Posaconazole	Not studied. Darunavir may increase antifungal plasma concentrations (P-gp inhibition) and posaconazole or fluconazole may increase darunavir concentrations. (CYP3A inhibition).	Caution is warranted and clinical monitoring is recommended.
Clotrimazole	Not studied. Concomitant systemic use of clotrimazole and darunavir co-administered with low dose ritonavir may increase plasma concentrations of darunavir. darunavir AUC24h ↑ (based on population pharmacokinetic model)	Caution is warranted and clinical monitoring is recommended, when co-administration of clotrimazole is required.
Itraconazole	Not studied. Concomitant systemic use of itraconazole and darunavir co-administered with low dose ritonavir may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of itraconazole may be increased by darunavir co-administered with low dose ritonavir. (CYP3A inhibition).	Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of itraconazole should not exceed 200 mg.
ANTIGOUT MEDICINES		

Colchicine	Not studied. Concomitant use of colchicine and darunavir co-administered with low dose ritonavir may increase the exposure to colchicine.	A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with darunavir co-administered with low dose ritonavir is required. Patients with renal or hepatic impairment should not be given colchicine with darunavir co-administered with low dose ritonavir.
ANTIMALARIALS		
Artemether/Lumefantrine	darunavir AUC ↔ Cmin ↓ Cmax ↔ Artemether AUC ↓ Cmin ↔ Cmax ↓ dihydroartemisinin AUC ↓ Cmin ↔ Cmax ↓ lumefantrine AUC ↑ Cmin ↑ Cmax ↑	The combination of darunavir and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Not studied. Rifapentine and rifampicin are strong CYP3A inducers and cause decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction).	The combination of rifampicin and darunavir with concomitant low dose ritonavir is contraindicated The combination of rifapentine and darunavir with concomitant low dose ritonavir is not recommended.

Rifabutin	darunavir AUC ↑ Cmin ↑ Cmax ↑ rifabutin AUC↑ Cmax ↔ (Rifabutin is an inducer and substrate of CYP3A.)	A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg once every other day) and increased monitoring for rifabutin related adverse events is warranted in patients receiving the combination with darunavir co-administered with ritonavir. In case of safety issues, a further increase of the dosing interval for rifabutin and/or monitoring of rifabutin levels should be considered. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients. Based upon the safety profile of darunavir/ritonavir, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for darunavir/ritonavir.
ANTINEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine Everolimus	Not studied. Darunavir is expected to increase these antineoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when co-administered with darunavir with low dose ritonavir resulting in the potential for increased adverse events usually associated with these agents. Caution should be exercised when combining one of these antineoplastic agents with darunavir with low dose ritonavir Concominant use of everolimus and darunavir co-administered with low dose ritonavir is not recommended.

ANTIPLATELETS		
Ticagrelor	Not studied. Co-administration with darunavir boosted with low dose ritonavir may lead to a substantial increase in exposure to ticagrelor.	Concomitant administration of darunavir with low dose ritonavir with ticagrelor is contraindicated. Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended.
ANTIPSYCHOTICS/NEUROLEPTICS		
Quetiapine	Not studied. Due to CYP3A inhibition by darunavir, concentrations of the antipsychotics/neuroleptics are expected to increase.	Concomitant administration of darunavir with low dose ritonavir and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased concentrations of quetiapine may lead to coma.
Risperidone Thioridazine Pimozide Sertindole	Not studied. Darunavir is expected to increase these antipsychotic plasma concentrations. (CYP2D6 inhibition and/or P-gp)	A dose decrease may be needed for these drugs when co-administered with darunavir co-administered with low dose ritonavir. Concominant administration of darunavir with low dose ritonavir and pimozide or sertindole is contraindicated.
β-BLOCKERS		
Carvedilol Metoprolol Timolol	Not Studied. Darunavir is expected to increase these β- blocker plasma concentrations. (CYP2D6 inhibition)	Clinical monitoring is recommended when co- administering darunavir with β- blockers. A lower dose of the β- blocker should be considered.
CALCIUM CHANNEL BLOCKERS		
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Not studied. Darunavir co- administered with low dose ritonavir can be expected to increase the plasma concentrations of calcium channel blockers. (CYP3A and/or CYP2D6 inhibition)	Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with darunavir with low dose ritonavir
CORTICOSTEROIDS		

Fluticasone Budesonide	darunavir AUC ↓ Cmin ↓ Cmax ↓ fluticasone propionate AUC ↑ Cmin ↑ Cmax ↑	Concomitant administration of darunavir/ritonavir and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid which is not a substrate for CYP3A (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period.
Dexamethasone (systemic)	Not studied. Dexamethasone may decrease plasma concentrations of darunavir. (CYP3A induction)	Systemic dexamethasone should be used with caution when combined with darunavir co- administered with low dose ritonavir.
Prednisone	Not studied. Darunavir may increase plasma concentrations of prednisone. (CYP3A inhibition)	Concomitant use of darunavir with low dose ritonavir and prednisone 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 with low dose ritonavir with corticosteroids.
ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Not studied. Concomitant use of bosentan and darunavir co- administered with low dose ritonavir may increase plasma	When administered concomitantly with darunavir and low dose ritonavir, the patient's tolerability of bosentan should be monitored.
HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS		

Boceprevir	darunavir AUC ↓ Cmin ↓ Cmax ↓ boceprevir AUC ↓ Cmin ↓ Cmax ↓	It is not recommended to co-administer darunavir with low dose ritonavir and boceprevir.
Simeprevir	darunavir AUC ↑ Cmin ↑ Cmax ↔ simeprevir AUC ↑ Cmin ↑ Cmax ↑	It is not recommended to co-administer darunavir with low dose ritonavir and simeprevir.
Dasabuvir+ ombitasvir/paritaprevir/ritonavir	darunavir Cmax ↓ AUC ↓ Cmin ↓ dasabuvir Cmax↔ AUC↔ Cmin ↔ ombitasvir Cmax↔ AUC ↔ Cmin↔ paritaprevir Cmax ↑ AUC ↑ Cmin ↑	The recommended dose of darunavir is 800 mg once daily, without ritonavir, when administered at the same time as ombitasvir/ paritaprevir/ritonavir + dasabuvir (ritonavir dose in ombitasvir/paritaprevir/ ritonavir will provide darunavir pharmacokinetic enhancement). This regimen can be used in the absence of extensive PI resistance (i.e. lack of darunavir associated RAMs). Darunavir combined with ombitasvir/paritaprevir/ ritonavir + dasabuvir is not recommended in patients with extensive PI resistance.

Ombitasvir/paritaprevir/ritonavir	darunavir Cmax ↔ AUC ↔ Cmin ↔ ombitasvir Cmax↔ AUC ↔ Cmin↔ paritaprevir Cmax ↑ AUC ↑ Cmin ↑	No dose adjustment needed for dasabuvir+ombitasvir/paritaprevir/ ritonavir. Treatment with darunavir +ombitasvir/paritaprevir/ritonavir without dasabuvir is not recommended due to a larger increase of paritaprevir plasma concentrations in the absence of dasabuvir.
Ledipasvir	Darunavir Cmax ↔ AUC↔ Cmin↔ Ledipasvir Cmax↑ AUC↑ Cmin ↑	No dose adjustment is required.
Sofosbuvir	Darunavir Cmax ↔ AU C ↔ Cmin ↔ Sofosbuvir Cmax ↑ AUC ↑ GS-331007 Cmax ↔ AUC ↔	No dose adjustment is required.
Daclatasvir	Darunavir AUC: ↔ Cmax: ↔ Cmin: ↔ Daclatasvir AUC ↔ Cmax ↔	No dose adjustment is required.

HERBAL PRODUCTS		
St John's wort *(Hypericum perforatum)*	Not studied. St John's wort is expected to decrease the plasma concentrations of darunavir at ritonavir (CYP450 induction)	Darunavir co-administered with low dose ritonavir must not be used concomitantly with products containing St John's wort (*Hypericum perforatum*). If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Darunavir exposure (and also ritonavir exposure) may increase on stopping St John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort.
HMG CO-A REDUCTASE INHIBITORS		
Lovastatin Simvastatin	Not studied. Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with darunavir/ritonavir. (CYP3A inhibition)	Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of darunavir, co-administered with low dose ritonavir, with lovastatin and simvastatin is therefore contraindicated
Atorvastatin	atorvastatin AUC ↑ Cmin ↑ Cmax ↑	When administration of atorvastatin and darunavir co- administered with low dose ritonavir is desired, it is recommended to start with an atorvastatin dose of 10 mg once daily. A gradual dose increase of atorvastatin may be tailored to the clinical response.
Pravastatin	pravastatin AUC ↑ Cmax ↑	When administration of pravastatin and darunavir co- administered with low dose ritonavir is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effect while monitoring for safety.

Rosuvastatin	rosuvastatin AUC ↑ Cmax ↑	When administration of rosuvastatin and darunavir, co- administered with low dose ritonavir is required, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.
H2-RECEPTOR ANTAGONISTS		
Ranitidine	#darunavir AUC ↔ Cmin ↔ Cmax ↔	Darunavir, co-administered with low dose ritonavir, can be co- administered with H2-receptor antagonists without dose adjustments.
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus	Not studied. Exposure to these immunosuppressants will be increased when co-administered with darunavir/ritonavir. (CYP3A inhibition)	Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs. Concomitant use of everolimus and darunavir, co-administered with low dose ritonavir is not recommended.
INHALED BETA AGONISTS		
Salmeterol	Not studied. Concomitant use of salmeterol and darunavir, co-administered with low dose ritonavir may increase plasma concentrations of salmeterol.	Concomitant use of salmeterol and darunavir, co-administered with low dose ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS / TREATMENT OF OPIOID DEPENDENCE		

Methadone	R (-) methadone AUC ↓ Cmin ↓ Cmax ↓	No adjustment of methadone dosage is required when initiating co-administration with darunavir/ritonavir. However, increased methadone dose may be necessary when concomitantly administered for a longer period of time due to induction of metabolism by ritonavir. Therefore, clinical monitoring is recommended, as maintenance therapy may need to be adjusted in some patients.
INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
Buprenorphine/naloxone	buprenorphine AUC ↓ Cmin ↔ Cmax ↓ Norbuprenorphine AUC ↑ Cmin ↑ Cmax ↑ naloxone AUC ↔ Cmax ↔	The clinical relevance of the increase in norbuprenorphine pharmacokinetic parameters has not been established. Dose adjustment for buprenorphine may not be necessary when co-administered with darunavir/ritonavir but a careful clinical monitoring for signs of opiate toxicity is recommended.
OESTROGEN-BASED CONTRACEPTIVES		
Ethinylestradiol Norethindrone 35 µg/1 mg once daily	ethinylestradiol AUC ↓ Cmin ↓ Cmax ↓ norethindrone AUC ↓ Cmin ↓ Cmax ↔	Alternative or additional contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with darunavir and low dose ritonavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.
PROTON PUMP INHIBITORS		

Omeprazole 20 mg once daily	#darunavir AUC ↔ Cmin ↔ Cmax ↔	Darunavir, co-administered with low dose ritonavir, can be co- administered with proton pump inhibitors without dose adjustments.
PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS		
For the treatment of erectile dysfunction Avanafil Sildenafil Tadalafil Vardenafil	↑ PDE-5 inhibitors	The combination of avanafil and darunavir with low dose ritonavir is contraindicated. Concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with darunavir co-administered with low dose ritonavir should be done with caution.
PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS		
		If concomitant use of darunavir, co-administered with low dose ritonavir, with sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended.

For the treatment of pulmonary arterial hypertension Sildenafil Tadalafil	Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and darunavir co-administered with low dose ritonavir may increase plasma concentrations of sildenafil or tadalafil. (CYP3A inhibition)	A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with darunavir and low dose ritonavir has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope). Therefore, co-administration of darunavir with low dose ritonavir and sildenafil when used for the treatment of pulmonary arterial hypertension is contraindicated. Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with darunavir and low dose ritonavir is not recommended.
SEDATIVES/HYPNOTICS		

Buspirone Clorazepate Diazepam Estazolam Flurazepam Triazolam Zoldipem	Not studied. Sedative/hypnotics are extensively metabolised by CYP3A. Co-administration with darunavir/ritonavir may cause a large increase in the concentration of these medicines.	Clinical monitoring is recommended when co- administering darunavir with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. Darunavir co-administered with low dose ritonavir is contraindicated with triazolam.
Midazolam	Based on data for other CYP3A inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally with darunavir co-administered with low dose ritonavir. If parenteral midazolam is co- administered with darunavir co-administered with low dose ritonavir it may cause a large increase in the concentration of this benzodiazepine. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.	Darunavir co-administered with low dose ritonavir is contraindicated with orally administered midazolam whereas, caution should be used with co- administration of darunavir with low dose ritonavir and parenteral midazolam. If parenteral midazolam is co-administered with darunavir with a low dose ritonavir, it should be done in an intensive care unit (ICU) or similar setting, which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.

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

Ritonavir

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Co-administration of ritonavir and medicinal products primarily metabolized by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. For select medicinal products (e.g. alprazolam) the inhibitory effects of ritonavir on CYP3A4 may decrease over time. Ritonavir also has a high affinity for P-glycoprotein and may inhibit this transporter. The inhibitory effect of ritonavir (with or without other protease inhibitors) on P-gp activity may decrease over time (e.g. digoxin and fexofenadine - see table "Ritonavir effects on non-antiretroviral medicinal products" below). Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolized by these pathways, and may result in decreased systemic exposure to such medicinal products, which could decease or shorten their therapeutic effect.

Important information regarding medicinal product interactions when ritonavir is used as a pharmacokinetic enhancer is also contained in the summary of product characteristics of the co-administered protease inhibitor.

Medicinal products that affect ritonavir levels

Serum levels of ritonavir can be reduced by concomitant use of herbal preparations containing St John's wort (Hypericum perforatum). This is due to the induction of medicinal product metabolizing enzymes by St John's wort. Herbal preparations containing St John's wort must not be used in combination with ritonavir. If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Ritonavir levels may increase on stopping St John's wort. The dose of ritonavir may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort.

Serum levels of ritonavir may be affected by select co-administered medicinal products (eg delavirdine, efavirenz, phenytoin and rifampicin). These interactions are noted in the medicinal product interaction tables below.

Medicinal products that are affected by the use of ritonavir

Interactions between ritonavir and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in the tables below.

Medicinal Product Interactions – Ritonavir with Protease Inhibitors

Co-administered Medicinal Product	**Dose of Co-administered Medicinal Product (mg)**	**Dose of ritonavir (mg)**	**Medicinal Product Assessed**	**AUC**	**Cmin**
Amprenavir	600 q12h	100 q12h	Amprenavir[2]	↑ 64%	↑ 5 fold
	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 600 mg amprenavir twice daily with ritonavir 100 mg twice daily. For further information, physicians should refer to the amprenavir Summary of Product Characteristics.				
Atazanavir	300 q24h	100 q24h	Atazanavir Atazanavir[1]	↑ 86% ↑ 2 fold	↑ 11 fold ↑ 3-7 fold
	Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 300 mg atazanavir once dailywith ritonavir 100 mg once daily in treatment experienced patients. For further information, physicians should refer to the Summary of Product Characteristics for atazanavir products.				
Darunavir	600, single	100 q12h	Darunavir	↑ 14 fold	
	Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeutic effect. Ritonavir doses higher than 100 mg twice daily have not been studied with darunavir. For further information, refer to the Summary of Product Characteristics for darunavir products.				
Fosamprenavir	700 q12h	100 q12h	Amprenavir	↑ 2.4 fold	↑ 11 fold
	Ritonavir increases the serum levels of amprenavir (from fosamprenavir) as a result of CYP3A4 inhibition. Fosamprenavir must be given with ritonavir to ensure its therapeutic effect. Clinical trials confirmed the safety and efficacy of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily. Ritonavir doses higher than 100 mg twice daily have not been studied with fosamprenavir. For further information, physicians should refer to the fosamprenavir Summary of Product Characteristics.				
Indinavir	800 q12h 400 q12h	100 q12h 400 q12h	Indinavir[3] Ritonavir Indinavir[3]	↑ 178% ↑ 72% ↔	ND ND ↑ 4 fold

			Ritonavir	↔	↔
	Ritonavir increases the serum levels of indinavir as a result of CYP3A4 inhibition. Appropriate doses for this combination, with respect to efficacy and safety, have not been established. Minimal benefit of ritonavir-mediated pharmacokinetic enhancement is achieved with doses higher than 100 mg twice daily. In cases of co-administration of ritonavir (100 mg twice daily) and indinavir (800 mg twice daily) caution is warranted as the risk of nephrolithiasis may be increased.				
Saquinavir	1000 q12h	100 q12h	Saquinavir4 Ritonavir	↑ 15-fold ↔	↑ 5-fold ↔
	400 q12h	400 q12h	Saquinavir4 Ritonavir	↑ 17-fold ↔	ND ↔
	Ritonavir increases the serum levels of saquinavir as a result of CYP3A4 inhibition. Saquinavir should only be given in combination with ritonavir. Ritonavir100 mg twice dailywith saquinavir 1000 mg twice daily provides saquinavir systemic exposure over 24 hours similar to or greater than those achieved with saquinavir 1200 mg three times daily without ritonavir. In a clinical study investigating the interaction of rifampicin 600 mg once daily and saquinavir 1000 mg with ritonavir 100 mg twice daily in healthy volunteers, severe hepatocellular toxicity with transaminase elevations up to > 20-fold the upper limit of normal after 1 to 5 days of co-administration was noted. Due to the risk of severe hepatoxicity, saquinavir/ritonavir should not be given together with rifampicin. For further information, physicians should refer to the saquinavir Summary of Product Characteristics.				
Tipranavir	500 q12h	200 q12h	Tipranavir Ritonavir	↑ 11 fold ↓ 40%	↑ 29 fold ND
	Ritonavir increases the serum levels of tipranavir as a result of CYP3A inhibition. Tipranavir must be given with low dose ritonavir to ensure its therapeutic effect. Doses of ritonavir less than 200 mg twice daily should not be used with tipranavir as they might alter the efficacy of the combination. For further information, physicians should refer to the tipranavir Summary of Product Characteristics.				

ND: Not determined.

1. Based on cross-study comparison to 400 mg atazanavir once daily alone.
2. Based on cross-study comparison to 1200 mg amprenavir twice daily alone.
3. Based on cross-study comparison to 800 mg indinavir three times daily alone.

4. Based on cross-study comparison to 600 mg saquinavir three times daily alone.

Medicinal Product Interactions – Ritonavir with Antiretroviral Agents Other Than Protease Inhibitors

Co-administered Medicinal Product	**Dose of Co-administered Medicinal Product (mg)**	**Dose of ritonavir (mg)**	**Medicinal Product Assessed**	**AUC**	**Cmin**
Didanosine	200 q12h	600 q12h 2 h later	Didanosine	↓ 13%	↔
	As ritonavir is recommended to be taken with food and didanosine should be taken on an empty stomach, dosing should be separated by 2.5 h. Dose alterations should not be necessary.				
Delavirdine	400 q8h	600 q12h	Delavirdine[1] Ritonavir	↔ ↑ 50%	↔ ↑ 75%
	Based on comparison to historical data, the pharmacokinetics of delavirdine did not appear to be affected by ritonavir. When used in combination with delavirdine, dose reduction of ritonavir may be considered.				
Efavirenz	600 q24h	500 q12h	Efavirenz Ritonavir	↑ 21% ↑ 17%	
	A higher frequency of adverse reactions (eg, dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is co-administered with ritonavir dosed as an antiretroviral agent.				
Maraviroc	100 q12h	100 q12h	Maraviroc	↑ 161%	↑ 28%
	Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition.Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the Summary of Product Characteristics for maraviroc.				
Nevirapine	200 q12h	600 q12h	Nevirapine Ritonavir	↔ ↔	↔ ↔
	Co-administration of ritonavir with nevirapine does not lead to clinically relevant changes in the pharmacokinetics of either nevirapine or ritonavir.				
Raltegravir	400 single	100 q12h	Raltegravir	↓ 16%	↓ 1%
	Co-adminsitration of ritonavir and raltegravir results in a minor reduction in raltegravir levels				
Zidovudine	200 q8h	300 q6h	Zidovudine	↓ 25%	ND
	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary.				

ND: Not determined

1. Based on parallel group comparison.

Ritonavir effects on Non-Antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of ritonavir (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products Cmax
Alpha1-Adrenoreceptor Antagonist				
Alfuzosin	Ritonavir co-administration is likely to result in increased plasma concentrations of alfuzosin and is therefore **contraindicated**.			
Amphetamine Derivatives				
Amphetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir			
Analgesics				
Buprenorphine Norbuprenorphine Glucuronide metabolites	16 q24h	100 q12h	↑ 57% ↑ 33% ↔	↑ 77% ↑ 108% ↔
	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmaco-dynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine or ritonavir may therefore not be necessary when the two are dosed together. When ritonavir is used in combination with another protease inhibitor and buprenorphine, the SmPC of the co-administered protease inhibitor should be reviewed for specific dosing information.			
Pethidine, piroxicam, propoxyphene	Ritonavir co-administration is likely to result in increased plasma concentrations of pethidine, piroxicam, and propoxyphene and is therefore **contraindicated**			
Fentanyl	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir.			
Methadone[1]	5, single dose	500 q12h,	↓ 36%	↓ 38%
	Increased methadone dose may be necessarywhen concomitantly			

	administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer due to induction of glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.			
Morphine	Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.			
Antiarrthymics				
Amiodarone, bepridil, dronedarone, encainide, flecanide, propafenone, quinidine	Ritonavir co-administration is likely to result in increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecanide, propafenone, and quinidine and is therefore **contraindicated**			
Digoxin	0.5 single IV dose 0.4 single oral dose	300 q12h, 3 days 200 q12h, 13 days	↑ 86% ↑ 22%	ND ↔
	This interaction may be due to modification of P-glycoprotein mediated digoxin efflux by ritonavir dosed as an antriretroviral agent or as a pharmacokinetic enhancer. Increased digoxin levels observed in patients receiving ritonavir may lessen over time as induction develops			
Antiasthmatic				
Theophylline[1]	3 mg/kg q8h	500 q12h	↓ 43%	↓ 32%
	An increased dose of theophyline may be required when co-administered with ritonavir, due to induction of CYP1A2.			
Anticancer agents				
Dasatinib, nilotinib, vincristine, vinblastine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse reactions.			
Anticoagulant				
Rivaroxaban	10, single dose	600 q12h	↑ 153%	↑ 55%
	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmaco-dynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.			
Warfarin S-Warfarin R-Warfarin	5, single dose	400 q12h	↑ 9% ↓ 33%	↓ 9% ↔
	Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little pharmacokinetic effect is noted on S-			

	warfarin when co-administered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation, therefore it is recommended that anticoagulation parameters are monitored when warfarin is co- administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.			
Anticonvulsants				
Carbamazepine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of carbamazepine. Careful monitoring of therapeutic and adverse effects is recommended when carbamazepine is concomitantly administered with ritonavir.			
Divalproex, lamotrigine, phenytoin	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants. Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are concomitantly administered with ritonavir. Phenytoin may decrease serum levels of ritonavir.			
Antidepressants				
Amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir			
Desipramine	100, single oral dose	500 q12h	↑ 145%	↑ 22%
	The AUC and Cmax of the 2-hydroxymetabolite were decreased 15 and 67%, respectively. Dosage reduction of desipramine is recommended when co-administered with ritonavir dosed as an antiretroviral agent.			
Trazodone	50, single dose	200 q12h	↑ 2.4-fold	↑ 34%
	An increase in the incidence in trazodone-related adverse reactions was noted when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. If trazodone is co- administered with ritonavir, the combination			

	should be used with caution, initiating trazodone at the lowest dosage and monitoring for clinical response and tolerability.			
Anti-gout treatments				
Colchicine	Concentrations of colchicine are expected to increase when coadministered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition) in patients with renal and/or hepatic impairment Refer to the colchicine prescribing information			
Antihistamines				
Astemizole, terfenadine	Ritonavir co-administration is likely to result in increased plasma concentrations of astemizole and terfenadine and is therefore **contraindicated**			
Fexofenadine	Ritonavir may modify P-glycoprotein mediated fexofenadine efflux when dosed as an antriretroviral agent or as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine. Increased fexofenadine levels may lessen over time as induction develops.			
Loratadine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratidine is concomitantly administered with ritonavir.			
Anti-infectives				
Fusidic Acid	Ritonavir co-administration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore **contraindicated**			
Rifabutin[1] 25-*O*-desacetyl rifabutin metabolite	150 daily	500 q12h,	↑ 4-fold ↑ 38-fold	↑ 2.5-fold ↑ 16-fold
	Due to the large increase in rifabutin AUC, the concomitant use of rifabutin with ritonavir dosed as an antiretroviral agent is **contraindicated**. The reduction of the rifabutin dose to 150 mg 3 times per week may be indicated for select PIs when co-administered with ritonavir as a pharmacokinetic enhancer. The summary of product characteristics of the co-administered			

	protease inhibitor should be consulted for specific recommendations. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV-infected patients.			
Rifampicin	Although rifampicin may induce metabolism of ritonavir, limited data indicate that when high doses of ritonavir (600 mg twice daily) is co-administered with rifampicin, the additional inducing effect of rifampicin (next to that of ritonavir itself) is small and may have no clinical relevant effect on ritonavir levels in high-dose ritonavir therapy. The effect of ritonavir on rifampicin is not known.			
Voriconazole	200 q12h 200 q12h	400 q12h 100 q12h	↓ 82% ↓ 39%	↓ 66% ↓ 24%
	Concomitant use of ritonavir dosed as an antiretroviral agent and voriconazole is **contraindicated** due to reduction in voriconazole concentrations. Co-administration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.			
Atovaquone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.			
Bedaquiline	No interaction study is available with ritonavir only. In an interaction study of single-dose bedaquiline and multiple dose lopinavir/ritonavir, the AUC of bedaquiline was increased by 22%. This increase is likely due to ritonavir and a more pronounced effect may be observed during prolonged co-administration. Due to the risk of bedaquiline related adverse events, co-administration should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogrammonitoring and monitoring of transaminases is recommended and refer to the bedaquiline Summary of Product Characteristics).			

Clarithromycin 14-OH clarithromycin metabolite	500 q12h	200 q8h	↑ 77% ↓ 100%	↑ 31% ↓ 99%
	Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be co- administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. For patients with renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 ml/min the dose should be reduced by 50%, for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75%.			
Delamanid	No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30% increased. Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (refer to the delamanid Summary of Product Characteristics			
Erythromycin, itraconazole	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of erythromycin and itraconazole. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is used concomitantly administered with ritonavir.			
Ketoconazole	200 daily	500 q12h	↑ 3.4-fold	↑ 55%
	Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole. Due to an increased incidence of gastrointestinal and hepatic adverse reactions, a dose reduction of ketoconazole should be considered when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.			
Sulfamethoxazole/Trimethoprim[2]	800/160, single dose	500 q12h	↓ 20% / ↑ 20%	↔

	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.
Antipsychotics/Neuroleptics	
Clozapine, pimozide	Ritonavir co-administration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore **contraindicated**.
Haloperidol, risperidone, thioridazine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir
Quetiapine	Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of ritonavir and quetiapine is contraindicated as it may increase quetiapine-related toxicity.
β2-agonist (long acting)	
Salmetarol	Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmetarol is expected. Therefore concomitant use is not recommended.
Calcium channel antagonists	
Amlodipine, diltiazem, nifedipine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.
Ergot Derivatives	
Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Ritonavir co-administration is likely to result in increased plasma concentrations of ergot derivatives and is therefore **contraindicated**.
Endothelin antagonists	
Bosentan	Co-administration of bosentan and ritonavir may increase steady state bosentan maximum concentrations (Cmax) and area under the curve (AUC).
GI motility agent	

Cisapride	Ritonavir co-administration is likely to result in increased plasma concentrations of cisapride and is therefore **contraindicated**.			
HCV Protease Inhibitor				
Simeprevir	200 qd	100 q12h	↑ 7.2-fold	↑ 4.7-fold
	Ritonavir increases plasma concentrations of simeprevir as a result of CYP3A4 inhibition. It is not recommended to co-administer ritonavir with simeprevir.			
HMG Co-A Reductase Inhibitors				
Atorvastatin, fluvastatin, lovastatin, pravstatin, rosuvastatin, simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is **contraindicated**. Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.			
Hormonal contraceptive				
Ethinyl estradiol	50 µg, single dose	500 q12h	↓ 40%	↓ 32%
	Due to reductions in ethinyl estradiol concentrations, barrier or other non-hormonal methods of contraception should be considered with concomitant ritonavir use when dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the			

	effectiveness of estradiol-containing contraceptives.			
Immunosupressants				
Cyclosporine, tacrolimus, everolimus	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of cyclosporine, tacrolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.			
Phosphodiesterase (PDE5) inhibitors				
Avanafil	50, single dose	600 q12h	↑ 13-fold	↑ 2.4-fold
	Concomitant use of avanafil with ritonavir is contraindicated.			
Sildenafil	100, single dose	500 q12h	↑ 11-fold	↑ 4-fold
	Concomitant use of sildenafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution and in no instance should sildenafil doses exceed 25 mg in 48 hours. Concomitant use of sildenafil with ritonavir is **contraindicated** in pulmonary arterial hypertension patients.			
Tadalafil	20, single dose	200 q12h	↑ 124%	↔
	The concomitant use of tadalafil with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution at reduced doses of no more than 10 mg tadalafil every 72 hours with increased monitoring for adverse reactions. When tadalafil is used concurrentlywith ritonavir in patients with pulmonary arterial hypertension, refer to the tadalafil SmPC			
Vardenafil	5, single dose	600 q12h	↑ 49-fold	↑ 13-fold
	The concomitant use of vardenafil with ritonavir is contraindicated.			
Sedatives/hynoptics				
Clorazepate, diazepam, estazolam, flurazepam, oral and parenteral midazolam and triazolam	Ritonavir co-administration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam and is therefore **contraindicated** Midazolam is extensively metabolised by CYP3A4. Co-administration with ritonavir may cause a large increase in the concentration of this benzodiazepine. No medicinal product interaction study has been performed for the co-administration of ritonavir with			

	benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, ritonavir should not be co-administered with orally administered midazolam, whereas caution should be used with co-administration of ritonavir and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3 – 4-fold increase in midazolam plasma levels. If ritonavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.			
Triazolam	0.125, single dose	200, 4 doses	↑ > 20 fold	↑ 87%
	Ritonavir co-administration is likely to result in increased plasma concentrations of triazolam and is therefore **contraindicated**.			
Pethidine Norpethidine metabolite	50, oral single dose	500 q12h	↓ 62% ↑ 47%	↓ 59% ↑ 87%
	The use of pethidine and ritonavir is **contraindicated** due to the increased concentrations of the metabolite, norpethidine, which has both analgesic and CNS stimulant activity. Elevated norpethidine concentrations may increase the risk of CNS effects (eg, seizures)			
Alprazolam	1, single dose	200 q12h, 2 days 500 q12h, 10 days	↑2.5 fold ↓ 12%	↔ ↓ 16%
	Alprazolam metabolism was inhibited following the introduction of ritonavir. After ritonavir use for 10 days, no inhibitory effect of ritonavir was observed. Caution is warranted during the first several days when alprazolam is co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.			
Buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an			

	antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.			
Sleeping agent				
Zolpidem	5	200, 4 doses	↑ 28%	↑ 22%
	Zolpidem and ritonavir may be co-administered with careful monitoring for excessive sedative effects.			
Smoke cessation				
Bupropion	150 150	100 q12h 600 q12h	↓ 22% ↓ 66%	↓ 21% ↓ 62%
	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 in vitro, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting reductions in bupropion concentrations may have onset several days after initiation of ritonavir co-administration.			
Steroids				
Fluticasone propionate aqueous nasal spray	200 µg qd	100 q12h	↑ ~350-fold	↑ ~ 25- fold
	Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression (plasma cortisol levels were noted to be decreased 86% in the above study) have been reported in patients receiving ritonavir and inhaled or intranasal fluticasone propionate; similar effects could also occur with other corticosteroids metabolised by CYP3A eg, budesonide. Consequently, concomitant administration of ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a			

	glucocorticoid, which is not a substrate for CYP3A4 (eg, beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period.			
Dexamethasone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with ritonavir.			
Prednisolone	20	200 q12h	↑ 28%	↑ 9%
	Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37 and 28% after 4 and 14 days ritonavir, respectively.			

ND: Not determined

1. Based on a parallel group comparison

2. Sulfamethoxazole was co-administered with trimethoprim.

Cardiac and neurologic events have been reported when ritonavir has been co-administered with disopyramide, mexiletine or nefazadone. The possibility of medicinal product interaction cannot be excluded.

In addition to the interactions listed above, as ritonavir is highly protein bound, the possibility of increased therapeutic and toxic effects due to protein binding displacement of concomitant medicinal products should be considered.

Further information regarding medicinal product interactions when ritonavir is used a pharmacokinetic enhancer is also contained in the Summary of Product Characteristics of the co-administered protease inhibitor.

Proton pump inhibitors and H_2-receptor antagonists: proton pump inhibitors and H_2-receptor antagonists (e.g. omeprazole or ranitidine) may reduce concentrations for co-administered protease inhibitors. For specific information regarding the impact of co-administration of acid reducing agents, refer to the SmPC of the co-administered protease inhibitor. Based on interaction studies with the ritonavir boosted protease inhibitors (lopinavir/ritonavir, atazanavir), concurrent

administration of omeprazole or ranitidine does not significantly modify ritonavir efficacy as a pharmacokinetic enhancer despite a slight change of exposure (about 6 - 18%).

4.6 Pregnancy and lactation

Darunavir

Pregnancy

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

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

Breast-feeding

Studies in rats have demonstrated that darunavir is excreted in milk and at high levels (1,000 mg/kg/day) resulted in toxicity. It is not known whether darunavir is excreted in human milk. The most recent official treatment guidelines (e.g. those issued by WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Fertility

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

Ritonavir

A limited number (> 800) of pregnant women were exposed to ritonavir during pregnancy; a very limited number (< 300) were exposed during the first trimester. These data largely refer to exposures where ritonavir was used in combination therapy as a pharmacokinetic enhancer for other PIs. These limited data indicate no increase in the rate of birth defects compared to rates observed in population- based birth defect surveillance systems. Animal data have shown reproductive toxicity. The use of ritonavir may be considered in pregnancy only when the benefits outweigh the risk to the fetus.

Ritonavir adversely interacts with oral contraceptives (OCs). Therefore, an alternative, effective and safe method of contraception should be used during treatment.

Breast-Feeding

It is not known whether this medicine is excreted in human milk. Milk excretion has not been measured in the animal studies, however a study in rats showed some effects on offspring development during lactation which are compatible with excretion of ritonavir in milk in that species. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances

Fertility

No human data on the effect of ritonavir on fertility are available. Animal studies do not indicate harmful effects of ritonavir on fertility.

4.7 Effects on ability to drive and use machines

Darunavir

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

Ritonavir

No studies on the effects on the ability to drive and use machines have been performed. As somnolence and dizziness are known undesirable effects, this should be taken into account when driving or using machinery.

4.8 Undesirable effects

Darunavir

Summary of the safety profile

The most frequent adverse reactions with darunavir/ritonavir reported in clinical trials, and as spontaneous reports are diarrhoea, nausea, rash, headache and vomiting. The most frequent serious reactions are acute renal failure, myocardial infarction, immune reconstitution inflammatory syndrome, thrombocytopenia, osteonecrosis, diarrhoea, hepatitis and pyrexia.

Tabulated list of adverse reactions

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

Adverse reactions in clinical trials and post-marketing

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

rare	syncope, convulsion, ageusia, sleep phase rhythm disturbance
Eye disorders	
uncommon	conjunctival hyperaemia, dry eye
rare	visual disturbance
Ear and labyrinth disorders	
uncommon	vertigo
Cardiac disorders	
uncommon	myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia
rare	acute myocardial infarction, sinus bradycardia, palpitations
Vascular disorders	
uncommon	hypertension, flushing
Respiratory, thoracic and mediastinal disorders	
uncommon	dyspnoea, cough, epistaxis, throat irritation
rare	rhinorrhoea
Gastrointestinal disorders	
very common	diarrhoea
common	vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence
uncommon	pancreatitis, gastritis, gastroesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia
rare	stomatitis, haematemesis, cheilitis, dry lip, coated tongue
Hepatobiliary disorders	
common	increased alanine aminotransferase
uncommon	hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-glutamyltransferase
Skin and subcutaneous tissue disorders	
common	rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus
uncommon	angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation

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

Description of selected adverse reactions

Rash

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

During the clinical development program of raltegravir in treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing darunavir + raltegravir compared to those containing darunavir without raltegravir or raltegravir without darunavir. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy

Musculoskeletal abnormalities

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

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

Immune reconstitution inflammatory syndrome

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

Bleeding in haemophiliac patients

There have been reports of increased spontaneous bleeding in haemophiliac patients receiving antiretroviral protease inhibitors

Paediatric population

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

Other special populations

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

Co-infected patients receiving darunavir co-administered with ritonavir are more likely to have baseline and treatment emergent hepatic transaminase elevations than those without chronic viral hepatitis.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

Ritonavir

Adverse reactions associated with the use of ritonavir as a pharmacokinetic enhancer are dependent on the specific co-administered PI. For information on adverse reactions refer to the SmPC of the specific co-administered PI.

The following adverse reactions were reported from clinical trials and post-marketing experience in adult patients with ritonavir dosed as antiretroviral agent

The most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances (including paresthesia and oral paresthesia) and fatigue/asthenia.

The following adverse reactions of moderate to severe intensity with possible or probable relationship to ritonavir have been reported. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness: very common (> 1/10); common (> 1/100 to < 1/10); uncommon (> 1/1000 to < 1/100); rare (> 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).

Events noted as having frequency not known were identified via post-marketing surveillance.

Undesirable effects in clinical studies and post-marketing in adult patients		
System Order Class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Common	Decreased white blood cells, decreased haemoglobin, decreased neutrophils, increased eosinophils, thrombocytopenia
	Uncommon	Increased neutrophils
Immune system disorders	Common	Hypersenstitivity including urticaria and face oedema
	Rare	Anaphylaxis

Metabolic and nutritional disorders	Common	Hypercholesterolaemia, hypertriglyceridaemia, gout, oedema and peripheral oedema, dehydration (usually associated with gastrointestinal symptoms)
	Uncommon	Diabetes mellitus
	Rare	Hyperglycaemia
Nervous system disorders	Very common	Dysgeusia, oral and peripheral paraesthesia, headache, dizziness, peripheral neuropathy
	Common	Insomnia, anxiety, confusion, disturbance in attention, syncope, seizure
Eye disorders	Common	Blurred vision
Cardiac disorders	Uncommon	Myocardial infarction
Vascular disorders	Common	Hypertension, hypotension including orthostatic hypotension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	Very common	Pharyngitis, oropharyngeal pain, cough
Gastrointestinal disorders	Very common	Abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance, vomiting, dyspepsia
	Common	Anorexia, flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
Hepatobiliary disorders	Common	Hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice)
Skin and subcutaneous tissue disorders	Very common	Pruritus, rash (including erythematous and maculopapular)
	Common	Acne
	Rare	Stevens Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculosketal and connective tissue disorders	Very common Common	Arthralgia and back pain Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
Renal and urinary disorders	Common Uncommon	Increased urination, renal impairment (e.g. oliguria, elevated creatinine) Acute renal failure
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Very common Common	Fatigue including asthenia, flushing, feeling hot Fever, weight loss
Investigations	Common Uncommon	Increased amylase, decreased free and total thyroxin Increased glucose, increased magnesium, increased alkaline phosphatase

Description of selected adverse reactions

Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretrovirals.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy

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

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis.

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

Paediatric populations

The safety profile of ritonavir in children is similar to that seen in adults

4.9 Overdose

Darunavir

Human experience of acute overdose with darunavir co-administered with low dose ritonavir is limited. Single doses up to 1,600 mg of darunavir tablets in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

There is no specific antidote for overdose with darunavir. Treatment of overdose with darunavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis.

Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

Ritonavir

Symptoms

Human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg/day for two days and reported paraesthesia, which resolved after the dose was decreased. A case of renal failure with eosinophilia has been reported.

The signs of toxicity observed in animals (mice and rats) included decreased activity, ataxia, dyspnoea and tremors.

Management

There is no specific antidote for overdose with ritonavir. Treatment of overdose with ritonavir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Due to the solubility characteristics and possibility of trans intestinal elimination, it is proposed that management of overdose could entail gastric lavage and

administration of activated charcoal. Since ritonavir is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.**5.**

Pharmacological properties

5.1 Pharmacodynamic properties

Pharmaco-dynamic properties

Darunavir

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

Mechanism of action

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

Antiviral activity *in vitro*

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC50 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 EC50 values ranging from < 0.1 to 4.3 nM. These EC50 values are well below the 50% cellular toxicity concentration range of 87 μM to> 100 μM.

Resistance

Clinical trial data showed that virologic response to darunavir co-administered with low dose ritonavir was decreased when 3 or more darunavir RAMs (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) were present at baseline or when these mutations developed during treatment.

Increasing baseline darunavir fold change in EC50 (FC) was associated with decreasing virologic response. A lower and upper clinical cut-off of 10 and 40 were identified. Isolates with baseline FC≤ 10 are susceptible; isolates with FC > 10 to 40 have decreased susceptibility; isolates with FC > 40 are resistant.

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

Cross-resistance

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

In the virologic failures observed in clinical trials there was no cross-resistance with other PIs.

Clinical efficacy

A randomised, controlled, open-label Phase III trial compared darunavir co-administered with ritonavir (600/100 mg twice daily) versus lopinavir/ritonavir (400/100 mg twice daily) in 595 ART-experienced, lopinavir naïve HIV-1 infected adult patients; both arms used an Optimised Background Regimen (OBR) consisting of at least 2 antiretrovirals (NRTIs with or without NNRTIs). Results showed that 60.4% of patients in the darunavir/ritonavir arm had HIV-1 RNA < 50 copies/ml at week 96 compared to 55.2% in the lopinavir/ritonavir arm [difference: 5.2%, 95% CI (-2.8; 13.1)].

Another Phase III, randomised, open-label trial compared darunavur/ritonavir 800/100 mg once daily versus darunavir/ritonavir 600/100 mg twice daily in 590 ART-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a screening HIV-1 RNA > 1,000 copies/ml. Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs. Efficacy analysis based on 48 weeks of treatment showed virologic response, defined as the percentage of patients with plasma HIV-1 RNA level< 50 copies/ml, with darunavir/ritonavir 800/100 mg once daily treatment was non-inferior (at the pre-defined 12% non-inferiority margin) compared to darunavir/ritonavir 600/100 mg twice daily for both ITT and OP populations.

Two randomised, controlled trials, each enrolling 255 patients, compared darunavir co-administered with ritonavir (600/100 mg twice daily) with a control group receiving an investigator-selected PI(s) regimen in HIV-1 infected patients who had previously failed more than 1 PI containing regimen. An OBR consisting of at least 2 NRTIs with or without enfuvirtide (ENF) was used in both trials. Analyses of data through 96 weeks of treatment in the two trials

demonstrated sustained antiretroviral efficacy and immunologic benefit with 38.9% of patients in the darunavir/ritonavir arm having HIV RNA < 50 copies/ml at week 96 compared to 8.9% in the control arm [difference: 30.1%, 95% CI (20.1; 40.0)]. Out of the 59 patients who responded with complete viral suppression (< 50 copies/ml) at week 48, 47 patients (80% of the responders at week 48) remained responders at week 96.

Baseline genotype or phenotype and virologic outcome

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

Paediatric patients

An open-label, Phase II trial evaluated the pharmacokinetics, safety, tolerability, and efficacy of darunavir with low dose ritonavir in 80 ART-experienced HIV-1 infected paediatric patients aged 6 to 17 years and weighing at least 20 kg. These patients received darunavir/ritonavir twice daily in combination with other antiretroviral agents. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 log10 versus baseline. According to the TLOVR non-virologic failure censored algorithm 24 (30.0%) patients experienced virological failure, of which 17 (21.3%) patients were rebounders and 7 (8.8%) patients were non-responders.

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

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

Pregnancy and postpartum

Darunavir/ritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 34 pregnant women (17 in each arm) during the second and third trimesters, and postpartum. Virologic response was preserved throughout the study period in both arms. No mother to child transmission occurred in the infants born to the 29 subjects who stayed on the antiretroviral treatment through delivery. There were no new clinically relevant safety findings compared with the known safety profile of darunavir/ritonavir in HIV-1 infected adults.

Ritonavir

Pharmacokinetic enhancement by ritonavir is based on ritonavir's activity as a potent inhibitor of CYP3A- mediated metabolism. The degree of enhancement is related to the metabolic pathway of the co-administered protease inhibitor and the impact of the co-administered protease inhibitor on the metabolism of ritonavir. Maximal inhibition of metabolism of the co-administered protease inhibitor is generally achieved with ritonavir doses of 100 mg daily to 200 mg twice daily, and is dependent on the co-administered protease inhibitor. For additional information on the effect of ritonavir on co-administered protease inhibitor metabolism, see Section 4.5 and refer to the summary of product characteristics of the particular co-administered PIs.

Effects on the Electrocardiogram

QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 45 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) difference in QTcF from placebo was 5.5 (7.6) for 400 mg twice daily ritonavir. The Day 3 ritonavir exposure was approximately 1.5 fold higher than that observed with the 600 mg twice daily dose at steady state. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec.

Modest prolongation of the PR interval was also noted in subjects receiving ritonavir in the same study on Day 3. The mean changes from baseline in PR interval ranged from 11.0 to 24.0 msec in the 12 hour interval post dose. Maximum PR interval was 252 msec and no second or third degree heart block was observed.

Resistance

Ritonavir-resistant isolates of HIV-1 have been selected in vitro and isolated from patients treated with therapeutic doses of ritonavir.

Reduction in the antiretroviral activity of ritonavir is primarily associated with the protease mutations V82A/F/T/S and I84V. Accumulation of other mutations in the protease gene (including at positions 20, 33, 36, 46, 54, 71, and 90) can also contribute to ritonavir resistance. In general, as mutations associated with ritonavir resistance accumulate, susceptibility to select other PIs may decrease due to cross-resistance. The summary of product characteristics of other protease inhibitors or official continuous updates should be consulted for specific information regarding protease mutations associated with reduced response to these agents.

Clinical efficacy and safety data Ritonavir was the first protease inhibitor (approved in 1996) for which efficacy was proven in a study with clinical endpoints. The effects of ritonavir (alone or combined with other antiretroviral agents) on biological markers of disease activity such as CD4 cell count and viral RNA were evaluated in several studies involving HIV-1 infected patients. However, due to ritonavir's metabolic inhibitory properties its use as a pharmacokinetic enhancer of other protease inhibitors is the prevalent use of ritonavir in clinical practice.

Pharmacokinetic properties

Darunavir

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 α1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG and, therefore, higher plasma concentrations.

Darunavir is primarily metabolised by CYP3A. Ritonavir inhibit 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.

Following single dose administration of Darunavir (as ethanolate) 600mg Tablets in healthy volunteers, the mean (± SD) darunavir Cmax value was 8667 (± 2182) µg/ml, and the corresponding value for AUC was 101867 (± 40859) µg.h/ml. The mean (± SD) darunavir tmax value was 3.92 (± 1.02) hours.

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

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 α1-acid glycoprotein.

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

Biotransformation

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

Elimination

After a 400/100 mg 14C-darunavir with ritonavir dose, approximately 79.5% and 13.9% of the administered dose of 14C-darunavir could be retrieved in faeces and urine, respectively.

Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in faeces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir.

The intravenous clearance of darunavir alone (150 mg) and in the presence of low dose ritonavir was 32.8 l/h and 5.9 l/h, respectively.

Special populations

Paediatric population

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

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 14 treatment- experienced paediatric patients, aged 3 to < 6 years and weighing at least 15 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving darunavir/ritonavir 600/100 mg twice daily.The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 12 ART-naïve paediatric patients, aged 12 to < 18 years and weighing at least 40 kg, showed that darunavir/ritonavir 800/100 mg once daily results in darunavir exposure that was comparable to that achieved in adults receiving darunavir/ritonavir 800/100 mg once daily. Therefore the same once daily dosage may be used in treatment-experienced adolescents aged 12 to < 18 years and weighing at least 40 kg without darunavir resistance associated mutations (DRV-RAMs)* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l. DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 10 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 14 kg to< 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving darunavir/ritonavir 800/100 mg once daily. In addition, pharmacokinetic modeling and simulation of darunavir exposures in paediatric patients across the ages of 3 to < 18 years confirmed the darunavir exposures as observed in the clinical studies and allowed the

identification of weight-based Darunavir/ritonavir once daily dosing regimens for paediatric patients weighing at least 15 kg that are either ART-naïve or treatment-experienced paediatric patients without DRV-RAMs* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

Elderly

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

Gender

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

Renal impairment

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

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

Hepatic impairment

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

Pregnancy and postpartum

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

Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 600/100 mg twice daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum			
Pharmacokinetics of total darunavir (mean ± SD)	**Second trimester of pregnancy (n=11)[a]**	**Third trimester of pregnancy (n=11)**	**Postpartum (6-12 weeks) (n=11)**
Cmax, ng/ml	4,601 ± 1,125	5,111 ± 1,517	6,499 ± 2,411
AUC12h, ng.h/ml	38,950 ± 10,010	43,700 ± 16,400	55,300 ± 27,020
Cmin, ng/ml[a]	1,980 ± 839.9	2,498 ± 1,193	2,711 ± 2,268

a n=10 for AUC12h

b excluding Cmin value below LLOQ, n=10 for reference

Pharmacokinetic results of total darunavir after administration of darunavir/ritonavir at 800/100 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy and postpartum			
Pharmacokinetics of total darunavir (mean ± SD)	**Second trimester of pregnancy (n=16)**	**Third Trimester of pregnancy (n=14)**	**Postpartum (6-12 weeks) (n=15)**
Cmax, ng/ml	4,988 ± 1,551	5,138 ± 1,243	7,445 ± 1,674
AUC12h, ng.h/ml	61,303 ± 16,232	60,439 ± 14,052	94,529 ± 28,572
Cmin, ng/ml[a]	1,193 ± 509	1,098 ± 609	1,572 ± 1,108

a n=12 for postpartum, n=15 for second trimester and n=14 for third trimester

In women receiving darunavir/ritonavir 600/100 mg twice daily during the second trimester of pregnancy, mean intra-individual values for total darunavir Cmax, AUC12h and Cmin were 28%, 24% and 17% lower, respectively, as compared with postpartum; during the third trimester of

pregnancy, total darunavir Cmax, AUC12h and Cmin values were 19%, 17% lower and 2% higher, respectively, as compared with postpartum.

In women receiving darunavir/ritonavir 800/100 mg once daily during the second trimester of pregnancy, mean intra-individual values for total darunavir Cmax, AUC12h and Cmin were 34%, 34% and 32% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir Cmax, AUC12h and Cmin values were 31%, 35% and 50% lower, respectively, as compared with postpartum.

Ritonavir

Absorption:

There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailability have not been determined.

No pharmacokinetic data are available for Ritonavir 25 mg Tablets. A bioequivalence study was conducted with Ritonavir 100 mg tablets, which are proportionally similar to Ritonavir 25 mg Tablets in composition.Following single dose administration of Ritonavir 100 mg Tablets in healthy subjects (n=42) under fed conditions, the mean (±SD) ritonavir Cmax value was 594 ng/ml (±307) and the corresponding value for AUC was 5238 ng.h/ml (±2365). The mean ritonavir tmax value was 5.44 hours (± 1.79).

Effects of food on oral absorption:

Food slightly decreases the bioavailability of the ritonavir tablets. Administration of a single 100 mg dose of ritonavir with a moderate fat meal (857 kcal, 31% calories from fat) or a high fat meal (907 kcal, 52% calories from fat) was associated with a mean decrease of 20-23% in ritonavir AUC and Cmax.

Distribution:

The apparent volume of distribution (VB/F) of ritonavir is approximately 20 - 40 L after a single 600 mg dose. The protein binding of ritonavir in human plasma is approximately 98 - 99% and is constant over the concentration range of 1.0 – 100 µg /ml. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities.

Tissue distribution studies with 14C-labelled ritonavir in rats showed the liver, adrenals, pancreas, kidneys and thyroid to have the highest concentrations of ritonavir. Tissue to plasma ratios of

approximately 1 measured in rat lymph nodes suggests that ritonavir distributes into lymphatic tissues. Ritonavir penetrates minimally into the brain.

Metabolism:

Ritonavir was noted to be extensively metabolised by the hepatic cytochrome P450 system, primarily by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform. Animal studies as well as in vitro experiments with human hepatic microsomes indicated that ritonavir primarily underwent oxidative metabolism. Four ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent compound. However, the AUC of the M-2 metabolite was approximately 3% of the AUC of parent compound.

Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (and other products metabolised by CYP3A4) and other protease inhibitors may influence the pharmacokinetics of ritonavir.

Elimination:

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir. In these studies renal elimination was not found to be a major route of elimination of ritonavir. This was consistent with the observations in animal studies.

Special Populations: No clinically significant differences in AUC or Cmax were noted between males and females. Ritonavir pharmacokinetic parameters were not statistically significantly associated with body weight or lean body mass. Ritonavir plasma exposures in patients 50 – 70 years of age when dosed 100 mg in combination with lopinavir or at higher doses in the absence of other protease inhibitors is similar to that observed in younger adults.

Patients with impaired liver function: After multiple dosing of ritonavir to healthy volunteers (500 mg twice daily) and subjects with mild to moderate hepatic impairment (Child Pugh Class A and B, 400 mg twice daily) exposure to ritonavir after dose normalisation was not significantly different between the two groups.

Patients with impaired renal function: Ritonavir pharmacokinetic parameters have not been studied in patients with renal impairment. However, since the renal clearance of ritonavir is negligible, no changes in the total body clearance are expected in patients with renal impairment.

Paediatric patients: Ritonavir steady-state pharmacokinetic parameters were evaluated in HIV infected children above 2 years of age receiving doses ranging from 250 mg/m² twice daily to 400 mg/m² twice daily. Ritonavir concentrations obtained after 350 to 400 mg/m² twice daily in paediatric patients were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice daily. Across dose groups, ritonavir oral clearance (CL/F/m2) was approximately 1.5 to 1.7 times faster in paediatric patients above 2 years of age than in adult subjects.

Ritonavir steady-state pharmacokinetic parameters were evaluated in HIV infected children less than 2 years of age receiving doses ranging from 350 to 450 mg/m² twice daily. Ritonavir concentrations in this study were highly variable and somewhat lower than those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice daily. Across dose groups, ritonavir oral clearance (CL/F/m2) declined with age with median values of 9.0 L/h/m2 in children less than 3 months of age, 7.8 L/h/m2 in children between 3 and 6 months of age and 4.4 L/h/m2 in children between 6 and 24 months of age.

Preclinical safety data

Darunavir

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

In repeated-dose toxicology studies in mice, rats and dogs, there were only limited effects of treatment with darunavir. In rodents the target organs identified were the haematopoietic system, the blood coagulation system, liver and thyroid. In the dog, no major toxicity findings or target organs were identified up to exposures equivalent to clinical exposure at the recommended dose.

In a study conducted in rats, the number of corpora lutea and implantations were decreased in the presence of maternal toxicity. Otherwise, there were no effects on mating or fertility with darunavir treatment at exposure levels below (AUC-0.5 fold) of that in human at the clinically recommended dose. Up to same dose levels, there was no teratogenicity with darunavir in rats and

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

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

In a carcinogenicity study in mice and rats dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumours in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

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

Ritonavir

Repeated dose toxicity studies in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium (RPE) and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests. Renal changes including tubular degeneration, chronic inflammation and proteinurea were noted in rats and are felt to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials. Developmental toxicity observed in rats (embryolethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.

Ritonavir was not found to be mutagenic or clastogenic in a battery of in vitro and in vivo assays including the Ames bacterial reverse mutation assay using S. typhimurium and E. coli, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes. Long term carcinogenicity studies of ritonavir in mice and rats revealed tumourigenic potential specific for these species, but are regarded as of no relevance for humans.

6. Pharmaceutical particulars

6.1 List of excipients

Silicified Microcrystalline Cellulose USP-NF (Prosolv SMCC HD90), Crospovidone , USP/NF (Polyplasdone XL-10), Colloidal silicon dioxide , USP/NF (Aerosil 200), Magnesium Stearate (LIGAMED MF-2-V), Copovidone, (Plasdone S 630), Sorbitan mono Laurate, (span 20), Dibasic calcium phosphate anhydrous, (A-Tab), Sodium Stearyl fumarate, Opadry yellow 16C82767, Purified Water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30° C.

6.5 Nature and contents of container

Glass Vials: 30’s HDPE Container, 60’s HDPE Container & 120’s HDPE Container

6.6 Special precautions for disposal and other handling

Store below 30°C.

7. Marketing Authorisation Holder and Manufacturing Site Addresses

7.1 Name and Address of Manufacturer

M/s. Hetero Labs Limited, Unit-III
22-110, IDA,
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7.2 Name and Address of Principal

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8. Date of Revision of the text