PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

VITRAVIR 400 mg/50 mg Film coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains darunavir ethanolate equivalent to darunavir 400 mg and ritonavir 50 mg.

Excipients: Colloidal silicon dioxide; copovidone; crospovidone; microcrystalline cellulose; ferric oxide yellow, sodium chloride; sodium stearyl fumarate; sorbitan monolaurate; coating: Opadry Yellow 20C520058.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets.

A light yellow film-coated ovaloid, biconvex, bevelled edge tablet debossed with “M” on one side of the tablet and “DRL” on the other side.

WARNING:

Co-administration of VITRAVIR with certain non-sedating antihistamines, sedative hypnotics, anti-dysrhythmics or ergot alkaloid preparations may result in potentially serious and or life-threatening adverse events due to possible effects of ritonavir on the hepatic metabolism of these medicines. See Sections 4.3 and 4.4.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In combination with other antiretroviral medicines, **VITRAVIR** is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment experienced adult patients who are protease-inhibitor-naïve patients or after exclusion of darunavir resistance associated mutations (DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V). Genotypic or phenotypic testing, should guide the use of **VITRAVIR**.

There is no information on the use of darunavir in combination with ritonavir in the paediatric population *(less than 18 years of age)* for the once daily dose (see Section 4.2, 5.2 and 5.3).

4.2 Posology and method of administration

Posology:

VITRAVIR must always be given in combination with other antiretroviral medicines.

Adults:

Genotypic or phenotypic testing, should guide the use of **VITRAVIR**. Two tablets once daily are recommended in HIV protease-inhibitor-naïve patients and in treatment-experienced patients with demonstrated absence of DRV-RAMs. (This is a dosage regimen of a daily dose of darunavir/ritonavir 800 mg/100 mg). The ritonavir included in the formulation is used as a pharmacokinetic enhancer of darunavir (see Sections 4.5 and 5.2).

VITRAVIR should be given with food. The type of food does not affect the exposure to darunavir (see Section 5.2).

Children (less than 12 years of age) and adolescents (12 to 17 years of age):

The safety and efficacy of the once daily dose of **VITRAVIR** in paediatric patients has not been established.

Missed Dose(s)

In case a dose of **VITRAVIR** was missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of **VITRAVIR** with food as soon as possible. If this was 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.

Hepatic impairment:

No dose adjustment is required in patients with mild or moderate hepatic impairment. There are no data regarding the use of **VITRAVIR** when co-administered to patients with severe hepatic impairment; therefore, specific dosage recommendations cannot be made. **VITRAVIR** should not be used in

patients with severe hepatic impairment as safety and efficacy have not been demonstrated (see Section 4.3 and 4.4).

Renal impairment:

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

4.3 Contraindications

Hypersensitivity to darunavir or ritonavir or to any of the excipients of **VITRAVIR**.

VITRAVIR is contraindicated in severe liver disease.

Darunavir and ritonavir are both inhibitors of the cytochrome P450 3A (CYP3A) isoform. **VITRAVIR** should not be co-administered with medicines that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These medicines are included in the table below:

Medicines that are contraindicated with VITRAVIR	
Medicine Class: Medicine Name	Clinical Comment
Anticonvulsants: Phenobarbitone Phenytoin	Phenobarbitone and phenytoin are inducers of CYP450 enzymes. **VITRAVIR** should not be used in combination with phenobarbitone, or phenytoin, as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to **VITRAVIR** (see Section 4.5).

Antidysrhythmics: Amiodarone Bepridil Flecainide Propafenone Quinidine Encainide Digoxin	CONTRAINDICATED with **VITRAVIR** due to potential cardiac dysrhythmias.
Antihistamines: Astemizole	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmia.
Antimycobacterial: Rifampicin	Rifampicin is a potent inducer of CYP450 metabolism. **VITRAVIR** should not be used in combination with rifampicin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to **VITRAVIR** (see Section 4.5).
Rifabutin	The exposure to rifabutin and its active metabolite was increased 3-fold and the incidence of side effects was doubled when rifabutin was given at a dose of 150 mg every other day in combination with **VITRAVIR** (see Section 4.5).
Antipsychotic: Blonanserin	May result in potential increase in frequency or intensity of known neurological or other toxicities associated with blonanserin.
Endothelin receptor antagonist Bosentan	Concomitant use of bosentan and **VITRAVIR** should be avoided (see Section 4.5).

PDE-5 inhibitor: Sildenafil – when intended for the treatment of pulmonary arterial hypertension	A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope).
Antigout: Colchicine in patients with hepatic or renal impairment	Co-administration of **VITRAVIR** in patients with renal or hepatic impairment is contraindicated due to the potential risk of colchicine-induced toxic effects.
Alpha 1-adrenoreceptor antagonist: Alfuzosin	Potential for serious and/or life-threatening reactions such as hypotension.
Ergot Derivatives: Dihydroergotamine Ergonovine Ergotamine Methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischaemia of the extremities and other tissues.
GI Motility Agents: Cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmia.
Hepatitis C virus (HCV) direct-acting antivirals: **NS3-4A protease inhibitors** Boceprevir Telaprevir	It is not recommended to co-administer **VITRAVIR** with boceprevir or telaprevir (see Section 4.5).

Herbal Products: St. John's wort *(Hypericum perforatum)*	**VITRAVIR** should not be used concomitantly with products containing St. John's wort *(Hypericum perforatum)* because co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to **VITRAVIR** (see Section 4.5).
HMG-CoA reductase inhibitors: Lovastatin Simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: Pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac dysrhythmia.
Sedative/Hypnotics: Midazolam, Triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Antifungals: Ketoconazole, itraconazole and voriconazole	CONTRAINDICATED because concomitant systemic use of ketoconazole, itraconazole or voriconazole and **VITRAVIR** may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole or itraconazole may be increased by **VITRAVIR**, while the plasma concentrations of voriconazole may be decreased in the presence of **VITRAVIR** (see Section 4.5).

Buprenorphine/ naloxone	The results of an interaction trial with *darunavir/ritonavir* and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when buprenorphine/naloxone was administered with **VITRAVIR**. Exposure of the active metabolite, norbuprenorphine, increased by 46 %. No dose adjustment for buprenorphine was required. Careful clinical monitoring is recommended if **VITRAVIR** and buprenorphine are co-administered (see Section 4.5).
Long acting beta-adrenoceptor agonist: Salmeterol	May result in potential increased risk of cardiovascular adverse events associated with salmeterol.

4.4 Special warnings and precautions for use

Patients should be advised that current antiretroviral therapy, including **VITRAVIR**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Elderly

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

General

VITRAVIR must be co-administered with food to exert its therapeutic effect (see Section 4.2 and 5.2). Failure to correctly administer **VITRAVIR** with food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired antiviral effect.

The two-tablet dose of **VITRAVIR** contains 100 mg of ritonavir as a pharmacokinetic enhancer (see Section 5.2). Adding more ritonavir will not significantly affect darunavir concentrations and is not recommended.

Severe skin reactions

During the clinical development program, severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported. Stevens-Johnson syndrome has been reported; and during post marketing experience toxic epidermal necrolysis has also been reported. **VITRAVIR** should be discontinued immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia. Rash (all grades, regardless of causality) occurred in 10,3 % of patients treated with **VITRAVIR**. The discontinuation rate due to rash in patients using **VITRAVIR** was 0,5 %.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing **VITRAVIR** + raltegravir compared to subjects receiving **VITRAVIR** without raltegravir or raltegravir without **VITRAVIR**. However, rash that was considered as medicine related occurred at similar rates for all three groups.

Sulpha allergy

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

Patients with coexisting conditions

Hepatic impairment

VITRAVIR should not be used in patients with severe hepatic impairment (see Section 4.3). No dose adjustment is required in patients with mild or moderate hepatic impairment (see Sections 5.2 and 5.3).

Hepatotoxicity

Medicine-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with **VITRAVIR**. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse events. Appropriate laboratory testing should be conducted prior to initiating therapy with **VITRAVIR** 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 **VITRAVIR** treatment. Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, liver tenderness, hepatomegaly) in patients on **VITRAVIR** should prompt consideration of interruption or discontinuation of treatment.

Renal impairment

Since the renal clearance of darunavir is limited, a decrease in the elimination of **VITRAVIR** is not expected in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis (see Sections 4.2 and 5.2).

Haemophilia patients

There have been reports of increased bleeding, including spontaneous skin haematomas and hemarthrosis in patients with haemophilia type A and B treated with PIs such as **VITRAVIR**. *Haemophilia* patients should therefore be made aware of the possibility of increased bleeding.

Hyperglycaemia

New onset diabetes mellitus, hyperglycaemia, or exacerbation of pre-existing diabetes mellitus has been reported in patients receiving **VITRAVIR**.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/ accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued.

Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy

(cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving **VITRAVIR** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

Interactions with medicines

Ritonavir and darunavir in **VITRAVIR** are both inhibitors of CYP3A. Co-administration of **VITRAVIR** with medicines primarily metabolised by CYP3A may result in increased plasma concentrations of such medicines, which could increase or prolong their therapeutic effect and adverse events (see Sections 4.3 and 4.5). For medicines that are highly dependent on the metabolism by CYP3A and that have a narrow therapeutic index, such as amiodarone, bepridil, (systemic) lidocaine and quinidine, plasma concentrations of such medicines could increase when combined with **VITRAVIR**. This can lead to prolongation or increase of their therapeutic effect and adverse events (see Section 4.5).

Methadone

No adjustment of methadone dosage is required when initiating co-administration of **VITRAVIR**. However, clinical monitoring is recommended as maintenance therapy may need to be adjusted (see Section 4.5).

Oestrogen-based contraceptives

Plasma concentrations of ethinylestradiol are decreased by induction of its metabolism by ritonavir and alternative methods of non-hormonal contraception are recommended (see Section 4.5).

Allergic reactions

Allergic reactions including uticaria, skin eruptions, bronchospasm and angio-edema have been reported. Cases of anaphylaxis and Stevens-Johnson syndrome have also been reported (see boxed warning in beginning of Professional Information).

Hepatic reactions

Hepatic transaminase elevations exceeding five times the upper limit of normal, clinical hepatitis and jaundice have occurred in patients receiving **VITRAVIR** alone or in combinations with other antiretroviral medicines. There may be an increased risk of transaminase elevations in patients with underlying hepatitis B or C. Therefore, caution should be exercised when administering **VITRAVIR** to patients with pre-existing mild to moderate liver disease, liver enzyme abnormalities or hepatitis. Increased AST/ALT monitoring should be considered in these patients during the first three months of **VITRAVIR** treatment. There have been reports of hepatic dysfunction, including fatalities, particularly in patients taking multiple concomitant medications and/or with advanced AIDS. **VITRAVIR** is contraindicated in patients with severe hepatic insufficiency (see Section 4.3).

Pancreatitis

Pancreatitis has been observed in patients receiving **VITRAVIR** therapy, including those who developed hypertriglyceridemia. Fatalities have been observed. Patients with advanced HIV disease may be at increased risk of elevated blood levels of triglycerides and of 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. Patience who exhibit these signs or symptoms should be evaluated and **VITRAVIR** therapy should be discontinued if a diagnosis of pancreatitis is made.

Diabetes mellitus/hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycaemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy such as **VITRAVIR**. Some patients required either initiation or dose adjustment of insulin or oral hypoglycaemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. Patients who discontinued protease inhibitor therapy, the hyperglycaemia persisted in some cases.

Corticosteriods

Concomitant use of **VITRAVIR** and fluticasone propionate can significantly increase fluticasone propionate plasma concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects including Cushing’s syndrome and adrenal suppression have been reported when **VITRAVIR** has been co-

administered with inhaled or intranasally administered fluticasone propionate. Similar findings with concomitant administration of **VITRAVIR** and other inhaled corticosteroids that are metabolised similarly to fluticasone, such as budesonide, cannot be excluded. Particular caution should be used when administering **VITRAVIR** and any of these inhaled or intranasally administered glucorticoids (see Section 4.5).

PDE 5 inhibitors

Caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction or pulmonary hypertension in patients receiving **VITRAVIR**. Co-administration of **VITRAVIR** with these medicines is expected to increase their concentrations and may result in increased associated adverse events, such as hypotension and prolonged erection. Concomitant use of sildenafil with **VITRAVIR** is contraindicated in pulmonary arterial hypertension patients (see Section 4.3 and 4.5).

Herbal products

Patients on **VITRAVIR** should not use products containing St John's Wort (*Hypericum perforatum)* because co-administration may be expected to reduce plasma concentrations of ritonavir. This may result in loss of therapeutic effect and development of resistance (see Section 4.3).

HMG-CoA Reductase Inhibitors

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism, thus concomitant use of **VITRAVIR** with

simvastatin or lovastatin is contraindicated due to increased risk of myopathy including rhabdomyolysis. Caution must be exercised and reduced doses should be considered if **VITRAVIR** is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A4. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposures has been reported with **VITRAVIR** co-administration. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (See Table 2).

Resistance/cross-resistance

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of **VITRAVIR** therapy following loss of viral suppression may increase the likelihood of cross-resistance to the other protease inhibitors. The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Therefore, it is unknown what effect **VITRAVIR** therapy will have on the activity of concordantly or subsequently administered protease inhibitors.

Laboratory tests

VITRAVIR has been associated with alterations in triglyceride, ALT, AST, GGT, CPK and uric acid. Appropriate laboratory testing should be performed prior to initiating **VITRAVIR** therapy and at periodic intervals or if any clinical signs or symptoms occur during therapy. For comprehensive information concerning nucleoside analogues, physicians should refer to the complete product information for each of these drugs.

Haemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with haemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has been postulated although a mechanism of action has not been established.

PR interval prolongation

Ritonavir has been shown to cause modest asymptomatic prolongation of PR interval in some patients. Reports of second or third degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicines known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving ritonavir. **VITRAVIR** should be used in caution in such patients.

Fat redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement and “cushingoid appearance” have been observed in patients receiving protease inhibitors. The mechanism and long-term consequences of the events are currently unknown. A causal relationship has not been established.

Immune reconstitution syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy. During the initial phase if combination antiretroviral treatment when the immune system responds, patients may develop an inflammatory response to asymtoma or residual opportunistic infections such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* (carinii) pneumonia or tuberculosis) which may necessitate further evaluation and treatment

Lipid disorders

Treatment with **VITRAVIR** therapy in combination with saquinavir has resulted in substantial increases in the concentration of total triglyceride and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See Table 2 for additional information on potential drug interactions with **VITRAVIR** and HMG-CoA Reductase Inhibitors (hypolipidemic).

4.5 Interaction with other medicines and other forms of interaction

Combination of darunavir and ritonavir:

Darunavir and ritonavir are both inhibitors of the cytochrome CYP3A. Co-administration of **VITRAVIR** with medicines primarily metabolised by CYP3A may result in increased plasma concentrations of such medicines, which could increase or prolong their therapeutic effect and adverse events.

VITRAVIR should not be co-administered with medicines that are highly dependent on CYP3A for clearance and for which increased plasma

concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These medicines include astemizole, alfuzosin, sildenafil (when used for treatment of pulmonary arterial hypertension), midazolam, triazolam, pimozide and the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine and methylergonovine) (see Section 4.3).

Rifampicin is a potent inducer of CYP450 metabolism. **VITRAVIR** should not be used in combination with rifampicin, as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to **VITRAVIR** (see Sections 4.3 and 4.4).

VITRAVIR should not be used concomitantly with products containing St. John's wort (*Hypericum perforatum*) because co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to **VITRAVIR** (see Sections 4.3 and 4.4).

Antiretroviral medicinal products Nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs)

Didanosine

A combination of darunavir and ritonavir (600/100 mg twice daily) did not significantly affect didanosine exposure. The combination of **VITRAVIR** co-administered with low dose ritonavir and didanosine can be used without dose adjustments. As it is recommended that didanosine be administered on an empty stomach. Didanosine should be administered 1 hour before or 2 hours after **VITRAVIR** (which are administered with food).

Tenofovir

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

Other NRTIs

Based on the different elimination pathways of other NRTIs such as zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir that are primarily renally excreted, no medicine interactions are expected for these medicinal compounds and **VITRAVIR**.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Etravirine

In an interaction trial between darunavir/rtv (600/100 mg twice daily) and etravirine, there was a 37 % decrease in etravirine exposure in the presence of darunavir/rtv and no relevant change in exposure to darunavir. Therefore, **VITRAVIR** can be co-administered with etravirine 200 mg twice daily without dose adjustments.

Efavirenz

An interaction trial between darunavir/rtv (300/100 mg twice daily) and efavirenz (600 mg once daily) has been performed. In the presence of efavirenz, a decrease

of 13 % for darunavir exposure and a decrease of darunavir C_{min} by 31 % were observed. Exposure to efavirenz was increased by 21 % when administered in combination with darunavir/rtv. The combination of **VITRAVIR** and efavirenz should be used with caution.

Nevirapine

The results of an interaction trial with darunavir/rtv (400/100 mg twice daily) and nevirapine (200 mg twice daily) demonstrated that darunavir exposure was not affected when administered concomitantly with nevirapine. Exposure to nevirapine increased by 27 % (compared to historical controls) when administered in combination with darunavir/rtv. Since this difference is not considered to be clinically relevant, the combination of **VITRAVIR** and nevirapine can be used without dose adjustments.

Rilpivirine

In an interaction trial between darunavir/rtv (800/100 mg once daily) and rilpivirine (150 mg once daily), no clinically relevant effect on darunavir exposure was observed. Exposure to rilpivirine increased by 130 % (2,3-fold) when administered in combination with darunavir/rtv. Since this difference is not considered to be clinically relevant, the combination of **VITRAVIR** and rilpivirine can be used without dose adjustments.

HIV protease inhibitors (PIs)

Ritonavir

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

Lopinavir/ritonavir

Results of interaction trials with darunavir with or without ritonavir and lopinavir/ritonavir (1 200 mg darunavir twice daily with or without 100 mg ritonavir twice daily and lopinavir/ritonavir 400/100 mg twice daily or 533/133,3 mg twice daily) demonstrated a decrease in the exposure (AUC) of darunavir by 40 %. The appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer **VITRAVIR** with lopinavir/ritonavir.

Saquinavir

In an interaction trial between darunavir (400 mg twice daily), saquinavir (1 000 mg twice daily) and ritonavir (100 mg twice daily), darunavir exposure was decreased by 26 % in the presence of saquinavir/rtv; saquinavir exposure was not affected by the presence of darunavir/rtv. It is not recommended to combine saquinavir and **VITRAVIR**.

Atazanavir

An interaction trial between darunavir/rtv (400/100 mg twice daily) and atazanavir (300 mg once daily) demonstrated that systemic exposure to darunavir and

atazanavir was not significantly affected when co-administered. Atazanavir can be co-administered with **VITRAVIR**.

Indinavir

In an interaction trial between darunavir/rtv (400/100 mg twice daily) and indinavir (800 mg twice daily), darunavir exposure was increased by 24 % in the presence of indinavir/rtv; indinavir exposure was increased by 23 % in the presence of darunavir/rtv.

Other HIV protease inhibitors

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

CCR5 (Cysteine-Cysteine Chemokine Receptor 5) antagonist

When used in combination with darunavir/rtv, the dose of maraviroc should be 150 mg twice daily. An interaction trial between darunavir/rtv (600/100 mg twice daily) and maraviroc (150 mg twice daily) demonstrated that in the presence of darunavir/rtv the exposure of maraviroc was increased 4-fold. There was no apparent effect of maraviroc on darunavir/ritonavir exposure.

Other medicines:

Alfuzosin

Exposure to alfuzosin may be increased when co-administered with darunavir/rtv. Concomitant use of **VITRAVIR** with alfuzosin is contraindicated (see Section 4.3).

Antidysrhythmics (*bepridil, systemic lidocaine, quinidine and amiodarone*)

Exposure to bepridil, lidocaine, quinidine and amiodarone may be increased when co-administered with **VITRAVIR**. Use of these medicines with **VITRAVIR** is contraindicated (see Section 4.3).

Digoxin

An interaction trial with darunavir/rtv (600/100 mg twice daily) and a single dose of digoxin (0,4 mg) showed an increase of digoxin AUC_{last} of 77 % (ratio of Least Square Means (LSM) was 1,77 with a 90 % CI of 0,90 to 3,50).

The use of digoxin with **VITRAVIR** is contraindicated (see Section 4.3).

Anticoagulants

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

Anticonvulsants (phenobarbitone, phenytoin and carbamazepine)

Phenobarbitone and phenytoin

Phenobarbitone and phenytoin are inducers of CYP450 enzymes. Darunavir/rtv should not be used in combination with these medicines, as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to **VITRAVIR** (see Section 4.3).

Carbamazepine

An interaction trial between darunavir/rtv (600/100 mg twice daily) and carbamazepine (200 mg twice daily) showed that the exposure to darunavir, co-administered with ritonavir, was unaffected by carbamazepine. Ritonavir exposure (AUC12h) was decreased by 49 %. For carbamazepine, AUC12h was increased by 45 %. No dose adjustment for **VITRAVIR** is recommended. If there is a need to combine **VITRAVIR** 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 **VITRAVIR**.

Anti malarials

An interaction trial between darunavir/rtv (600/100 mg twice daily) and artemether/lumefantrine (80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours) showed an increase in exposure to lumefantrine by 2,75-fold, while exposure to darunavir was not affected. The exposure to artemether and its active metabolite, dihydroartemisinin, decreased by 16 % and 18 %, respectively. The combination of **VITRAVIR** and artemether/lumefantrine lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.

Colchicine

Concomitant use of colchicine and darunavir/rtv may increase the exposure to colchicine. The following dose adjustments are recommended for colchicine. For the treatment of gout flares in patients on darunavir/rtv, the recommended dose of

colchicine is 0,5 mg (1 tablet), followed by 0,25 mg 1 hour later. Treatment course to be repeated no earlier than 3 days. For the prophylaxis of gout flares in patients on **VITRAVIR**, the recommended dose of colchicine is 0,25 mg every day or every other day. For the treatment of familial Mediterranean fever in patients on **VITRAVIR**, the maximum dose of colchicine is 0,5 mg every day (may be given as 0,25 mg twice daily). Patients with renal or hepatic impairment should not be given colchicine with **VITRAVIR**.

Antihistamines (Astemizole)

Exposure to these antihistamines may be increased when co-administered with darunavir/rtv. Concomitant use of **VITRAVIR** with astemizole is contraindicated (see Section 4.3).

Calcium channel blockers

The exposure to calcium channel blockers (e.g., felodipine, nifedipine, nicardipine) may increase when **VITRAVIR** are used concomitantly. Caution is warranted and careful clinical monitoring is recommended.

Clarithromycin

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

For patients with renal impairment, a dose reduction of clarithromycin should be considered.

For patients with renal impairment, the following dose adjustments should be considered:

For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50 %.

For subjects with CLcr of < 30 mL/min, the dose of clarithromycin should be reduced by 75 %.

Dexamethasone

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

Bosentan

Bosentan is metabolised by cytochrome CYP3A4 and CYP2C9. Concomitant use of bosentan and **VITRAVIR** should be avoided (see Section 4.3).

Fluticasone

Concomitant use of inhaled fluticasone and **VITRAVIR** may increase plasma concentrations of fluticasone. Alternatives should be considered, particularly for long term use.

Hepatitis C virus (HCV) direct-acting antivirals:

NS3-4A protease inhibitors

Boceprevir

In an interaction trial between darunavir/rtv (600/100 mg b.i.d.) and boceprevir (800 mg three times daily), darunavir exposure was reduced by 44 % and boceprevir exposure was reduced by 32 %. It is not recommended to co-administer **VITRAVIR** with boceprevir (see Section 4.3).

Telaprevir

In an interaction trial between darunavir/rtv (600/100 mg twice daily) and telaprevir (750 mg every 8 hours), darunavir exposure was reduced by 40 % and telaprevir exposure was reduced by 35 %. It is not recommended to co-administer **VITRAVIR** with telaprevir (see Section 4.3).

HMG CoA reductase inhibitors

HMG CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A metabolism, are therefore expected to have markedly increased plasma concentrations when co-administered with darunavir/rtv. Increased concentrations of HMG CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of **VITRAVIR** with lovastatin and simvastatin is therefore not recommended (see Section 4.3).

The results of an interaction trial with atorvastatin show that atorvastatin (10 mg once daily) in combination with darunavir/rtv (300/100 mg twice daily) provides an exposure to atorvastatin, which is only 15 % lower than that obtained with atorvastatin (40 mg once daily) alone. When administration of atorvastatin and **VITRAVIR** 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. Darunavir/rtv (600/100 mg twice daily) increased exposure to a

single dose of pravastatin (40 mg) by approximately 80 %, but only in a subset of subjects. When administration of pravastatin and **VITRAVIR** is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effects while monitoring safety (see Section 4.4). An interaction study evaluating darunavir/rtv (600/100 mg twice daily) in combination with rosuvastatin (10 mg once daily) resulted in a 50 % increase in rosuvastatin exposure. It is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety (see Section 4.4).

H_2 Receptor antagonists and proton pump inhibitors

Co-administration of omeprazole (20 mg once daily) or ranitidine (150 mg twice daily) and darunavir/rtv (400/100 mg once daily) did not affect the exposure to darunavir. Based on these results, **VITRAVIR** can be co-administered with H_2 receptor antagonists and proton pump inhibitors without dose adjustments.

Inhaled beta agonist (salmeterol)

Concomitant use of salmeterol and **VITRAVIR** is not recommended. The combination may result in increased risk of cardiovascular adverse events with salmeterol, including QT prolongation, palpitations and sinus tachycardia (see Section 4.3).

Immunosuppressants (ciclosporin, tacrolimus, sirolimus)

Exposure to ciclosporin, tacrolimus, or sirolimus may be increased when co-administered with **VITRAVIR**. Therapeutic drug monitoring of the immune

suppressive agent is recommended when co-administered with **VITRAVIR** (see Section 4.4).

Ketoconazole, itraconazole and voriconazole

Ketoconazole, itraconazole and voriconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole or voriconazole and darunavir/rtv may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole or itraconazole may be increased by darunavir/rtv. This was confirmed in an interaction trial where the concomitant administration of ketoconazole (200 mg twice daily) with darunavir/rtv (400/100 mg twice daily) increased exposure of ketoconazole and darunavir by 212 % and 42 %, respectively. Concomitant use of ketoconazole, itraconazole and voriconazole with **VITRAVIR** is contraindicated (see Section 4.3).

Methadone

An interaction trial investigating the effect of darunavir/rtv (600/100 mg twice daily) on a stable methadone maintenance therapy showed an AUC decrease of 16 % for R-methadone. Based on pharmacokinetic and clinical findings, no adjustment of methadone dosage is required when initiating co-administration of **VITRAVIR**. However, clinical monitoring is recommended as maintenance therapy may need to be adjusted in some patients (see Section 4.4).

Buprenorphine/naloxone

The results of an interaction trial with darunavir/rtv and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when administered

with darunavir/rtv. Exposure of the active metabolite, norbuprenorphine, increased by 46 %. No dose adjustment for buprenorphine was required. Careful clinical monitoring is recommended if **VITRAVIR** and buprenorphine are co-administered.

Oestrogen based contraceptives

The results of an interaction trial between darunavir/rtv (600/100 mg twice daily) and ethinylestradiol and norethindrone demonstrated that at steady state systemic exposures to ethinylestradiol and norethindrone are decreased by 44 % and 14 %, respectively. Therefore, alternative methods of non-hormonal contraception **should be used** (see Section 4.4).

PDE-5 inhibitors

Treatment of erectile dysfunction

In an interaction trial a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with darunavir/rtv (400/100 mg twice daily). Concomitant use of PDE-5 inhibitors for the treatment of erectile dysfunction with **VITRAVIR** should be done with caution. If concomitant use of **VITRAVIR** with sildenafil, vardenafil, or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2,5 mg dose in 72 hours or tadalafil at a single dose not exceeding 10 mg dose in 72 hours is recommended (see Section 4.4).

Treatment of pulmonary arterial hypertension

A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension has not been established. There is an increased potential for sildenafil associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope). Therefore, co-administration of **VITRAVIR** with sildenafil when used for pulmonary arterial hypertension is contraindicated (see Section 4.3). For the treatment of pulmonary arterial hypertension with tadalafil co-administered with **VITRAVIR**, a dose adjustment for tadalafil is warranted. In patients who have been receiving darunavir/rtv for at least 1 week, start tadalafil at 20 mg, once daily and increase to 40 mg once daily based upon individual tolerability. For patients on tadalafil and initiating **VITRAVIR**, discontinue the use of tadalafil at least 24 hours prior to initiating **VITRAVIR** and avoid the use of tadalafil during the initiation of **VITRAVIR**. After at least 1 week following the initiation of **VITRAVIR**, resume tadalafil at 20 mg once daily and increase to 40 mg once daily based upon individual tolerability.

Rifabutin

Rifabutin is a substrate of CYP450 enzymes. In an interaction trial, an increase of systemic exposure to darunavir by 57 % was observed, when darunavir/rtv (600/100 mg twice daily) was administered with rifabutin (150 mg once every other day). Based on the safety profile of **VITRAVIR**, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for **VITRAVIR**. The exposure to rifabutin (sum of main compound and its active metabolite) was increased 3-fold and the incidence of side effects was doubled when rifabutin was given at a dose of 150 mg every other day in combination with **VITRAVIR** (see Section 4.3).

Selective Serotonin Reuptake Inhibitors (SSRIs)

In an interaction trial between paroxetine (20 mg once daily) or sertraline (50 mg once daily) and darunavir/rtv (400/100 mg twice daily), the exposure to darunavir was not affected by the presence of sertraline or paroxetine. Exposure to sertraline and paroxetine, was decreased by 49 % and 39 %, respectively, in the presence of darunavir/rtv. If SSRIs are co-administered with **VITRAVIR**, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with **VITRAVIR** should be monitored for antidepressant response.

Ritonavir

Medicines which increase CYP3A activity (e.g. phenobarbitone, carbamazepine, dexamethasone, phenytoin, rifampicin and rifabutin) would be expected to increase the clearance of **VITRAVIR** resulting in decreased ritonavir plasma concentrations.

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms with the following ranked order: CYP3A4 > CYP2D6 > CYP2C9 > CYP2C19 >> CYP2A6, CYP1A2, CYP2E1. There is evidence that ritonavir may induce glucuronosyl transferase, CYP1A2, CYP2C9 and CYP2C19 enzymes. Decreased plasma concentrations of the other medicine and loss of therapeutic effects during **VITRAVIR** co-administration may signify the need for dosage alteration of these medicines.

In addition to the medicines listed in Section 4.3, Table 2 below summarises some commonly prescribed medicines, separated by the type of metabolism and expected magnitude of interaction when co-administered with ritonavir. Co-administration of ritonavir in **VITRAVIR** and medicines primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicine, which could increase or prolong its therapeutic and adverse effects.

Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir. Dosage reductions may be required for those agents extensively metabolized by CYP3A.

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

Table 2: Potential effects on medicines co-administered with VITRAVIR. (Contraindicated medicines are listed in column 1)

Medicine category	**Representative medicines by potential interaction category**					
	Contra-indicated medication (see Section 4.3)	**Large[1] ↑ AUC[2] (CYP3A)**	**Moderate[1] ↑ AUC[2] (CYP2D6)**	**Moderate[1] ↑ or ↓ AUC[2] (CYP2C9/19)**	**Possible ↓ AUC[2] (Unknown CYP)**	**Possible ↓ AUC[2] (Glucuroni-dation)**
Analgesics, narcotics		Alfentanil Fentanyl	Hydro-codone Oxycodone Tramadol		Leva-methadyl (LAAM)	Codeine Hydromorphone Meperidine*

						Methadone* Morphine
Analgesics, Non steroidal				Diclofenac Flurbiprofen Ibuprofen Indomethacin Piroxicam	Nabumetone Sulindac	Ketoprofen Ketorolac Naproxen
Antidys-rhythmic	Amiodarone Encainide Flecainide Propafenone Quinidine Digoxin	Lidocaine	Diso-pyramide Mexiletine		Tocainide[11]	
Anti-ashmatic						Theophylline*
Antibiotic, macrolide		Erythro-mycin	Clarithro-mycin*			
Antibiotic, steroidal		Fusidic acid				
Anticonvulsant		Carbama zepine	Clonaze-pan Ethosuxi-mide		Pheno-barbitone	Divalproex Lamotrigine Phenytoin
Antidepressant tricyclic		Amitripty-line Clomipra mine Desipra-mine* Imipra-mine Maproti-line Nortripty-line Trimipra mine			Doxepin[11]	

Antidepressant SSRIs and non-tricyclics		Nefazodone Sertraline	Fluoxetine Paroxetine Trazodine* Venlafaxine		Fluvoxamine	Bupropion
Anti-diarrhoeal						Diphenoxylate Loperamide
Antiemetics Prokinetics	Cisapride		Ondansetron		Prochlorperazine[11] Promethazine	Metoclopramide
Antifungal agents	Voriconazole	Itraconazole Ketoconazole* Miconazole				
Anti-histamines	Astemizole	Loratadine				
Antihypertensive		Bosentan		Losartan	Doxazosin[11] Prazosin[11] Terazosin[11]	
Antimycobacterial		Rifabutin*			Ethionamide Rifampicin	
Anti-parasitics		Quinine		Proguanil	Albendazole Chloroquine Metronidazole Primaquine Pyrimethamine	Atovaquone
Anti-psychotics	Blonanserin					
Protein pump inhibitors				Lansoprazole Omeprazole		
ß-Blockers			Metoprolol Penbutolol Pindolol Timolol	Propranolol	Betaxolol[11]	

ß2-agonist (long-acting)	Salmeterol					
Calcium channel blockers	Bepridil	Amlodi-pine Diltiazem Felodi-pine Isradi-pine Nicardi-pine Nifedi-pine Nimodi-pine Nisoldi-pine Nitrendi-pine Verapa-mil				
Cancer chemothera peutic agents		Tamoxi-fen	Etoposide Paclitaxel Vinblastine Vincristine	Cyclophospha mide[3] Isosfamide[3]	Dauno-rubicin[11] Doxo-rubicin[11]	
Ergot alkaloids and derivatives	Dihydroergot amine Ergonovine[11] Ergotamine Methylergon ovine[11]	Bromo-criptine			Methyser-gide[11]	
Haemorheol ogic agent					Pentoxi-fylline	
Herbal products	St. John's Wort					
HIV antivirals		Atazanav ir Daruna-vir	Maraviroc		Nevirapine[11]	

		(Fos) amprenavir Indinavir* Saquinavir* Tipranavir				
Hypoglycaemics				Glimepiride Glipizide Glyburide Tolbutamide		
Hypolipidemics	Lovastatin Simvastatin	Atorvastatin	Rosuvastatin		Gemfibrozil	Clofibrate
Immunosuppresants		Ciclosporin Everolimus Tacrolimus Sirolimus (Rapamycin)				
Neuroleptics	Pimozide		Chloropromazine Haloperidol Perphenazine Risperidone Thioridazine			Clozapine
PDE5 inhibitor	Sildenafil indicated for PAH	Sildenafil indicated for ED Tadalafil Vardenafil				

Sedative/ hypnotics	Midazolam Triazolam	Buspi-rone	Cloraze-pate Diazepam Estazolam Flurazepam Zolpidem			Lorazepam Oxazepam Propofol Temazepam
Steroids		Dexamethasone Fluticasone*	Prednisone			Ethinyl Estradiol*
Stimulants			Dexfenfluramine Methamphetamine		Methylphenidate	

[1]Large = > 3X; Moderate = 1,5-3 X

[2]AUC = area under the plasma concentration-time curve, a measure of medicine exposure

[3]An increase in the AUC of cyclophosphamide and ifosfamide, both activated by CYP, may correspond to a decrease in the AUC of the active metabolite (s) and a possible decrease in efficacy of these medicines

[11]A possible increase in concentration is more likely when combined with ritonavir

*Clinical medicine interaction study has been performed

Alprazolam

Co-administration of alprazolam with ritonavir resulted in statistically significant decrease in mean alprazolam C_{max} values (16 %) but not in mean AUC values (12 %).

Amprenavir

Literature reports have shown that concentrations of the HIV-protease inhibitor, amprenavir are increased when co administered with ritonavir.

Bosentan

Co-administration of bosentan maximum concentrations (C_{max}) and area under the curve (AUC). Refer to the bosetan prescribing information.

Bupropion

Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels.

Buspirone

Buspirone is primarily metabolised by CYP3A4. Concurrent administration of buspirone and ritonavir is expected to substantially elevate buspirone levels.

Clarithromycin

The concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31 %, C_{min} increased by 182 % and AUC increased 77 % with essentially complete inhibition of the formation of 14-[R]-hydroxy-clarithromycin.

No dosage reduction should be necessary in patients with normal renal function. For patients with CL_{cr} < 30 to 60 mL/min the dose of clarithromycin should be reduced by 50 %. For patients with CL_{cr} < 30 mL/min the dose of clarithromycin should be decreased by 75 %. Doses of clarithromycin greater than 1 gram per day should not be co-administered with **VITRAVIR**.

Desipramine

Co-administration of ritonavir with desipramine resulted in a 145 % mean increase in the AUC of desipramine. Dosage reduction of desipramine should be considered in patients taking the combination.

Didanosine:

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 600 mg every 12 hours and didanosine (ddl) 200 mg every 12 hours resulted in a reduction of the ddl steady state C_{max} and AUC of 16 % and 13 %, respectively. In contrast, little if any effect was noted in ritonavir pharmacokinetics. Dose alteration of ddl during concomitant ritonavir therapy should be necessary; however, dosing of the two medicines should be separated by 2,5 hours to avoid formulation incompatibility.

Digoxin

A literature report has shown that co-administration of ritonavir (300 mg every 12 hours) and digoxin resulted in significantly increased digoxin levels. Therefore, digoxin is contraindicated with **VITRAVIR** (see Section 4.3).

Efavirenz

In healthy volunteers receiving 500 mg ritonavir twice daily with efavirenz 600 mg once daily, the steady state AUC of efavirenz was increased by 21 %. An associated increase in the AUC of ritonavir of 17 % was observed.

Fluticasone propionate

Concomitant use of ritonavir and fluticasone propionate may increase concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use (see Section 4.4).

Fusidic Acid

Co-administration of ritonavir with fusidic acid is expected to significantly increase fusidic acid and ritonavir concentrations in plasma.

Hypericum perforatum (St. John's Wort)

Patients on **VITRAVIR** should not concomitantly use products containing St. John's Wort (*Hypericum perforatum)* since it may be expected to result in reduced plasma concentrations of ritonavir. This effect may be due to induction of CYP3A4 and my result in the loss of therapeutic effect and development of resistance (see Sections 4.3 and 4.4).

Indinavir

Ritonavir inhibits the CYP3A-mediated metabolism of indinavir. In healthy subjects, 200 to 400 mg of ritonavir twice daily given with a single 400 mg to 600 mg indinavir dose increased the indinavir AUC by 185 to 475 % C_{max} 21 % to 110 % and C_{min} 11 to 33-fold, relative to 400 mg and 600 mg indinavir given alone. Concomitant administration of 400 mg ritonavir and 400 mg of indinavir twice daily with a meal yielded a similar indinavir AUC, a 4-fold increase in C_{min} and a 50 to 60 % decrease in C_{max} as compared to those resulting from administration of indinavir 800 mg three times daily under fasting conditions. Co-administration of

ritonavir with indinavir will result in increased indinavir serum concentrations. There are limited safety or efficacy data available on the use of this combination in patients. The risk of nephrolithiasis may be increased when doses of indinavir equal to or greater than 800 mg twice daily are given with **VITRAVIR**. Adequate hydration and monitoring of the patients is warranted.

Methadone

Co-administration of ritonavir with methadone is expected to decrease methadone concentrations. A dosage increase of methadone may be considered (see Section 4.4).

Nelfinavir

Interactions between ritonavir and nelfinavir are likely to involve both cytochrome P450 inhibition and induction. Concurrent ritonavir 400 mg twice daily significantly increases the concentrations of M8 (the major active metabolite of nelfinavir) and results in a smaller increase in nelfinavir concentrations. In a study in ten patient's nelfinavir 750 mg and ritonavir 400 mg twice daily yielded slightly higher nelfinavir AUC (160 %), C_{max} (121 %) and C_{trough} (123 %) than historical data for nelfinavir 750 mg three times daily monotherapy. The AUC of M8 was increased by 347 %.

Oral contraceptive, patch contraceptive or implants

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg every 12 hours and a fixed-combination oral contraceptive resulted in reductions of the ethinyl oestradiol mean C_{max} and mean AUC by 32 % and 40 % respectively. Increased doses of oral contraceptives or patch

contraceptives containing ethinyl oestradiol, or alternate methods of contraception, should be considered (see Section 4.4).

Rifabutin

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg every 12 hours and rifabutin resulted in an approximate 4-fold and 35-fold increase in the AUC of rifabutin and its active metabolite 25-0-deacetyl rifabutin, respectively. The significance of this interaction has been confirmed in clinical trials. Dosage reduction of rifabutin by at least three-quarters of the usual dose of 300 mg/day is recommended (e.g. 150 mg every other day or three times a week). Further dosages may be necessary (see Section 4.3).

Saquinavir

A pharmacokinetic study demonstrated that ritonavir extensively inhibits the metabolism of saquinavir resulting in greatly increased saquinavir plasma concentrations. Following approximately four weeks of a combination regimen of saquinavir (400 or 600 mg twice a day) and ritonavir (400 or 600 mg twice a day) in HIV-infected patients, saquinavir AUC values were at least 17-fold greater than historical AUC values from patients who received saquinavir 600 mg three times a day without ritonavir. When used in combination therapy for up to 24 weeks, doses greater than 400 mg twice a day of either ritonavir or saquinavir were associated with an increase in adverse events.

Sildenafil, tadalafil and vardenafil

Caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving ritonavir. Co-administration of ritonavir with these medicines is expected to increase their concentrations and may result in increased associated adverse events, such as hypotension and prolonged erection. Concomitant use of sildenafil with **VITRAVIR** is contraindicated in pulmonary arterial hypertension patients (see Section 4.3).

Sulfamethoxazole/trimethoprim

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg every 12 hours and sulfamethoxazole/trimethoprim resulted in a 20 % reduction of the sulfamethoxazole AUC and a 20 % increase of the trimethoprim AUC. Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.

Theophylline

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg every 12 hours and theophylline resulted in a 43 % decrease in the AUC of theophylline. An increased dosage of theophylline may be required.

Tobacco

Tobacco use is associated with an 18 % decrease in the AUC of ritonavir.

Trazadone

Concomitant use of ritonavir and trazadone may increase concentrations of trazadone. Adverse events of nausea, dizziness, hypotension and syncope have

been observed. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazadone should be considered.

Vincristine, vinblastine

Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse events.

Voriconazole

A study has shown that co-administration of ritonavir 400 mg every 12 hours decreased voriconazole steady-state AUC by an average of 82 %; therefore, co-administration of these drugs are contraindicated (see Section 4.3).

Warfarin

Anticoagulant metabolism may be induced, resulting in decreased concentrations of warfarin.

Zidovudine

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 300 mg every 6 hours and zidovudine (AZT) 200 mg every eight hours resulted in a reduction of the zidovudine C_{max} and AUC of 27 % and 25 %, respectively. In contrast, little if any effect was noted on ritonavir pharmacokinetics. Dose alteration of AZT during concomitant ritonavir therapy should not be necessary.

(See Table 3)

Table 3: Effect on AUC and C_{max} of co-administration of VITRAVIR with other medicines

Medicine	**Effect on Ritonavir Ritonavir dosage**	**n**	**AUC % (95 CI)**	**C_{max} % (95 CI)**
Clarithromycin 500 mg every 12 hours 4 days	200 mg every 8 hours 4 days	22	↑ 12 % (2,23 %)	↑ 15 % (2,28 %)
Didanosine 200 mg every 12 hours 4 days	600 mg every 12 hours 4 days	12	←→	←→
Fluconazole 400 mg day 1, 200 mg daily 4 days	200 mg every 6 hours 4 days	8	↑ 12 % (5,20 %)	↑ 15 % (7,22 %)
Fluoxetine 30 mg every 12 hours 8 days	600 mg single dose	16	↑ 19 % (7,34 %)	←→
Rifampin 600 mg or 300 mg daily 10 days[1]	500 mg every 12 hours 20 days	7,9	↓ -35 % (7,55 %)	↓ -25 % (-5,46 %)
Zidovudine 200 mg every 8 hours 4 days	300 mg every 6 hours 4 days	10	←→	←→

[1]Preliminary data

↑ indicates increase

↓ indicates decrease

← → Indicates no change

*Parallel group design; entries are subjects receiving combination and control regimens, respectively

4.6 Fertility, pregnancy and lactation

Pregnancy

VITRAVIR is contraindicated in pregnancy and lactation as safety has not been established.

Studies in animals do not indicate direct harmful effects of darunavir with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see Section 5.3).

A large amount (6100 live births) of pregnant women were exposed to ritonavir during pregnancy; of these, 2800 live births were exposed during the first trimester. These data largely refer to exposures where ritonavir was used in combination therapy and not at therapeutic ritonavir doses but at lower doses as a pharmacokinetic enhancer for other PIs. These 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 (see Section 5.3).

Lactation

It is not known whether darunavir or ritonavir is excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk. Because of the potential

for serious adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving **VITRAVIR**.

Carcinogenesis and mutagenesis

Long-term carcinogenicity studies of ritonavir in animal systems have not been completed. Ritonavir was not found to be mutagenic or clastogenic.

4.7 Effects on ability to drive and use machines

Dizziness and somnolence has been reported in some patients and this should be borne in mind when considering a patient's ability to drive or operate machinery (see Section 4.8).

4.8 Undesirable effects

Adverse Drug Reactions to darunavir/ritonavir identified in the ODIN trial

Adverse Drug Reactions to darunavir/rtv 800/100 mg once daily of at least moderate intensity (grade 2-4) in antiretroviral treatment experienced HIV-1 infected adult patients in the ODIN trial are mentioned in the table below.

Adverse Drug Reactions of at Least Grade 2 - ODIN trial (darunavir/rtv 800/100 mg daily + OBR#, n=[294])	
System Organ Class & Frequency category	**Adverse Drug Reaction**
Metabolism and nutrition disorders	
Frequent:	Hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hypertriglyceridaemia

Less frequent:	Diabetes mellitus, anorexia, dyslipidaemia, lipodystrophy, low density lipoprotein increased
Nervous system disorders	
Frequent:	Headache
Gastrointestinal disorders	
Frequent: Less frequent:	Diarrhoea, vomiting, nausea, abdominal pain Abdominal distension, dyspepsia, flatulence, pancreatic enzymes increased
Skin and subcutaneous tissue disorders	
Frequent: Less frequent:	Rash Pruritus
Musculoskeletal and connective tissue disorders	
Less frequent:	Myalgia
General disorders and administration site conditions	
Less frequent:	Asthenia, fatigue

* Excluding laboratory abnormalities reported as ADRs

Optimised Background Regimen

Laboratory abnormalities, considered ADRs, in antiretroviral treatment experienced HIV-1 infected adult patients of at least Grade 2 in the ODIN trial, are shown in the table below:

Laboratory Abnormalities of at least Grade 2 - ODIN trial (darunavir/rtv 800 mg daily + OBR#, n=[286]) **Worst Treatment Emergent Toxicity Grades***	
	DRV/rtv 800/100 mg once daily (N=286)
General Biochemistry	
Amylase	

Grade 2	3,1 %
Grade 3	2,4 %
Grade 4	0,3 %
Lipase	
Grade 2	1 %
Grade 3	0,3 %
Lipids and Glucose	
Glucose	
Grade 2	6,3 %
Grade 3	0,7 %
Low Density Lipoprotein Calculated	
Grade 2	7 %
Grade 3	2,8 %
Total Cholesterol	
Grade 2	7,7 %
Grade 3	2,4 %
Triglycerides	
Grade 2	3,5 %
Grade 3	1,4 %
Grade 4	0,3 %
Liver Function	
Alanine Amino Transferase	
Grade 2	1,7 %
Alkaline Phosphatase	
Grade 2	0,7 %
Aspartate Amino Transferase	
Grade 2	1,4 %
Grade 3	0,7 %

Optimised Background Regimen

* Only grading categories with observed laboratory values are listed

Additional adverse drug reactions to darunavir/rtv identified in other clinical trials:

System Organ Class	Adverse Drug Reaction	Incidence*
Immune System Disorders	Immune reconstitution syndrome	Less frequent
Psychiatric Disorders	Abnormal dreams	Less frequent
Gastrointestinal disorders	Acute pancreatitis	Less frequent
Hepato-biliary disorders	Hepatitis acute	Less frequent
Skin and subcutaneous tissue disorders	Angioedema Stevens-Johnson syndrome Urticaria	Less frequent
Reproductive System and Breast Disorders	Gynaecomastia	Less frequent

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

POST-MARKETING EXPERIENCE

Adverse drug reactions identified during post-marketing experience of darunavir/ritonavir.

System Organ Class	Adverse Drug Reaction
Immune system disorders	Hypersensitivity
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis. Acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	Osteonecrosis

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

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

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

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

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

In patients, co-infected with hepatitis B or C virus receiving darunavir/ritonavir, the incidence of adverse events and clinical chemistry abnormalities were not higher than in patients receiving darunavir/ritonavir who were not co-infected, except for increased hepatic enzymes (see Section 4.4). The pharmacokinetic exposure in co-infected patients was comparable to that in patients without co-infection.

Ritonavir:

Adverse reactions:

The most frequent reported clinical adverse events, other than asthenia, among patients receiving ritonavir were gastrointestinal and neurological disturbances

including nausea, diarrhoea, vomiting, anorexia, abdominal pain, taste perversion and circumoral and peripheral paraesthesias.

Adverse events at least possibly, probably or of unknown relationship to ritonavir are displayed by system organ class and frequencies: frequent and less frequent.

Table 4: Treatment-emergent adverse events occurring in patients receiving ritonavir and with possible, probable or unknown relationship to ritonavir in phase II/III combined studies

Organ class classification	**Frequency**	**Adverse event**
Infections and infestations	Frequent	Pharyngitis.
Blood and lymphatic system disorders	Less frequent	Anaemia, ecchymosis, leukopenia, lymphadenopathy, lymphocytosis, thrombocytopenia.
Immune system disorders	Frequent	Allergic reactions.
Endocrine disorders	Less frequent	Diabetes mellitus.
Metabolism and nutrition disorders	Frequent	Anorexia, hyperlipaemia, weight loss. Avitaminosis, cachexia, dehydration, oedema, glycosuria, gout, hypercholesterolemia, peripheral oedema, redistribution/accumulation of body fat (see Section 4.4).
Psychiatric disorders	Frequent	Anxiety, insomnia. Agitation, confusion, depression, emotional lability, euphoria, hallucinations, decreased libido, nervousness, personality disorder, abnormal thinking.

Nervous system disorders	Frequent	Circumoral paraesthesia, headache, peripheral paraesthesia, taste perversion. Dizziness, hyperesthaesia, paraesthesia, somnolence.
	Less frequent	Abnormal dreams, amnesia, aphasia, ataxia, convulsion, grand mal convulsion, inco-ordination, neuralgia, neuropathy, paralysis, parosmia, peripheral neuropathy, peripheral sensory neuropathy, taste loss, tremor, visual field defect.
Eye disorders	Frequent	Abnormal vision, amblyopia/blurred vision, blepharitis, diplopia, eye pain, iritis, photophobia, uveitis.
Ear and labyrinth disorders	Less frequent	Ear pain, hearing impairment, increased cerumen, tinnitus, vertigo.
Cardiac disorders	Less frequent	Palpitation, syncope.
Vascular disorders	Frequent	Haemorrhage, hypotension, migraine, peripheral vascular disorder, postural hypotension, tachycardia.
Respiratory, thoracic and mediastinal disorders	Frequent	Increased cough.
	Less frequent	Asthma, dyspnoea, epistaxis, hiccup, hypoventilation, interstitial pneumonia, lung disorder and rhinitis.
Gastrointestinal disorders	Frequent	Abdominal pain, diarrhoea, nausea, vomiting. Dry mouth, dyspepsia, eructation, flatulence, local throat irritation, mouth ulcer.

	Less frequent	Abdomen enlarged, abnormal stools, bloody diarrhoea cheilitis, colitis, constipation, dysphagia, oesophagitis, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal haemorrhage, gingivitis, ileitis, oral moniliasis, pancreatitis, periodontal abscess, rectal disorder, tenesmus, thirst.
Hepato-biliary disorders	Frequent	Cholangitis, hepatitis, hepatomegaly, liver damage.
Skin and subcutaneous tissue disorders	Frequent	Macropapular rash, pruritus, rash, sweating. Acne, contact dermatitis, dry skin, eczema, facial oedema, folliculitis, molluscum contagiosum, photosensitivity reaction, psoriasis, seborrhoea, urticaria, vesiculobullous rash.
Musculoskeletal, connective tissue and bone disorders	Frequent	Myalgia. Arthralgia, arthrosis, back pain, facial pain, joint disorder, muscle cramps, muscle weakness, myositis, neck pain, neck rigidity, twitching.
Renal and urinary disorders	Frequent	Dysuria, haematuria, kidney calculus, kidney failure, kidney pain, nocturia, polyuria, pyelonephritis, urethritis, urinary frequency, urinary retention.
Reproductive system and breast disorders	Less frequent	Impotence, penis disorder.

General disorders and administration site conditions	Frequent Less frequent	Asthenia. Fever, pain. Abnormal gait, chest pain, chills, flu syndrome, malaise, substernal chest pain.
Investigations	Frequent Less frequent	Abnormal liver function tests. Abnormal electro-oculogram, abnormal electroretinogram, altered hormone level.
Injury and poisoning	Less frequent	Accidental injury, hypothermia.
Surgical and medical procedures	Frequent	Vasodilation.

Post-marketing experience with ritonavir:

Nervous system disorders:

There have been post-marketing reports of seizure. Cause and effect relationship has not been established.

Metabolism and nutrition disorders:

Dehydration, usually associated with gastrointestinal symptoms, and sometimes resulting in hypotension, syncope or renal insufficiency has been reported. Syncope, orthostatic hypotension and renal insufficiency have also been reported without known dehydration.

Cardiac disorders:

Myocardial infarction has been reported.

Reproductive system and breast disorders:

Menorrhagia has been reported.

Laboratory determinations:

Data below was obtained from Phase II/III combined studies for clinical chemistry and haematology variables in adult patients who exceeded extreme limit criteria. The variables are listed below in order of highest to lowest frequency within each category.

Chemistry:

Liver Function tests:

Increased gamma-glutamyl transpeptidase (GGT) (>300 IU/L) in 102 (12 %) patients;

Increased aspartate aminotransferase (AST) (> 180 IU/L) and alanine aminotransferase (ALT) (> 215 IU/L) in 37 (4%) and 53 (6 %) of patients, respectively;

Increased total bilirubin (> 3,6 mg/dL in 11 (1 %) patients;

Increased alkaline phosphate (> 550 IU/L) in 10 (1%) patients;

Decreased albumin (< 2 g/dL) in 2 (< 1 %) patients.

Other clinical chemistry tests:

Increased creatine phosphokinase (CPK) (> 1 000 IU/L) in 71 (8 %) patients;

Increased triglycerides (> 1 500 mg/dL) in 69 (7 %) patients;

Increased amylase (> 2 x upper limit of normal range) in 20 (2 %) patients;

Increased uric acid (> 12 mg/dL) in 20 (2 %) patients;

Decreased potassium (> 3 mEq/L) in 15 (2 %) patients and increased potassium (> 6 mEq/L) in 5 (> 1 %) patients;

Increased serum magnesium (>2 ,9 mEq/L) in 10 (1 %) patients and decreased serum magnesium (< 1,0 mEq/L) in 5 (< 1 %) patients;

Decreased total serum calcium (< 6,9 mEq/L) in 10 (1 %) patients and increased total serum calcium (> 12,6 mEq/L) in 1 (< 1 %) patient;

Increased glucose level (> 250 mg/dL) in 6 (1 %) patients and decreased glucose level (< 40 mg/dL) in 1 (< 1 %) patient.

Increased lactate dehydrogenase (> 1170 IU/L) in 5 (< 1 %) patients;

Increased serum chloride (> 122 mEq/L) in 4 (< 1 %) patients and decreased serum chloride (< 84 mEq/L) in 1 (< 1 % patient;

Increased serum sodium (>157 mEq/L) and decreased serum sodium (<123 mEq/L) in 2 (<1 %) patients each;

Increased creatinine (> 3,6 mg/dL) in 1 (< 1 %) patient;

Increased inorganic phosphorus (> 7,0 mg/dL) in 1 (< 1 %) patient.

Haematology:

Decreased white blood cell (WBC) count (< 2,5 x 10^9/L) in 146 (16 %) patients and increased WBC count (> 25 x 10^9/L) in 8 (1 %) patients;

Decreased red blood cell (RBC) count (< 3,0 x 10^{12}/L) in 89 (9,5%) patients;

Decreased haematocrit (< 30 %) in 77 (8 %) patients;

Decreased haemoglobin (< 8 g/dL) in 23 (3 %) patients;

Decreased neutrophil count (< 0,5 x 10^9/L) in 25 (3 %) patients and increased neutrophil count (> 20 x 10^9/L) in 9 (1 %) patients;

Increased eosinophil count (> 1,0 x 10^9/L) in 15 (2 %) patients;

Decreased platelet count (< 20 x 10^9/L) in 4 (<1 %) patients;

Increased prothrombin time (> 1,5 x ULN) in 6 (1 %) patients;

Increased activated partial thromboplastin time (> 2,3 x ULN) in 3 (< 1 %) patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose of VITRAVIR, side effects can be precipitated and/or be of increased severity (see Section 4.8).

Ritonavir

One patient in clinical trials took ritonavir 1 500 mg/day for two days and reported paraesthesia's which resolved after dose was decreased. A post-marketing case of renal failure with eosinophilia has been reported with ritonavir overdose.

Management of overdose of VITRAVIR

There is no specific antidote for overdose with darunavir or ritonavir. Treatment of overdose with **VITRAVIR** 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 substances is to be achieved by

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors ATC code: J05AR26

Category and Class

A20.2.8 Antiviral agents

Darunavir:

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

Antiviral activity in vitro

Darunavir exhibited 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 *in vitro* with median EC_{50} values ranging from 1,2 to 8,5 nM (0,7 to 5,0 ng/mL). The EC_{50} value of darunavir increases by a median factor of 5,4 in the presence of human serum. Darunavir showed synergistic antiviral activity when studied in combination with

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

Resistance in vitro

In vitro darunavir-resistant virus isolates from wildtype HIV-1 selected viruses showing decreased susceptibility to darunavir (range: 6-21-fold) harboured 3 to 6 amino acid substitutions in the protease gene. Determinants of decreased susceptibility to darunavir in those viruses have not been identified. *In vitro* selection of darunavir resistant HIV 1 (range: 53 641 fold change in EC_{50} values) from 9 HIV 1 strains harbouring multiple PI (protease inhibitor) resistance-associated mutations (RAMs) resulted in the overall emergence of 22 mutations in the protease, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V and I84V were present in more than 50 % of the 9 darunavir resistant isolates. A minimum of 8 of these darunavir *in vitro* selected mutations, from which at least 2 were already present in the protease prior to selection, were required in the HIV-1 protease to render a virus resistant (fold change [FC] > 10) to darunavir. In 1 113 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir and in 886 baseline isolates from the patients enrolled in clinical trials, only the subgroups with > 10 PI RAMs showed a median FC for darunavir > 10.

Cross-resistance in vitro

Cross-resistance has been observed among HIV protease inhibitors. Darunavir has a < 10-fold decreased susceptibility against 90 % of 3 309 clinical isolates resistant to at least one protease inhibitor. Seven of the nine darunavir resistant viruses selected from PI resistant viruses had phenotypic data for tipranavir. Six of those showed a fold change (FC) < 3 for tipranavir, indicative of cross-resistance between these 2 protease inhibitors.

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

Ritonavir:

Ritonavir is used in this combination as pharmacokinetic enhancer, as it is an inhibitor of CYP3A, thereby increasing the plasma concentrations of darunavir.

Resistance of ritonavir

Ritonavir-resistant isolate of HIV-1 have been selected *in vitro*. The resistant isolates showed reduced susceptibility to ritonavir and genotypic analysis showed that the resistance was attributable primarily to specific amino acid substitutions in the HIV-1 protease at condons V82F, I84V, A71V and M46I. Phenotypic and genotypic changes in HIV isolates from selected patients treated with ritonavir were monitored in Phase I/II trails. Serial genotypic and phenotypic analysis

indicated that susceptibility to ritonavir declined in an ordered and stepwise fashion. Initial mutations occurred at positions 82 (Val to Ala/Phe), 54 (IIe to Val), 71 (Ala to Val/Thr) and 36 (IIe to Leu), followed by combinations of mutations at an additional 5 specific amino acid positions. Viral strains isolated *in vivo* without a change in codon 82 did not have decreased susceptibility to ritonavir. The 82 mutation appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a greater than or equal to five fold decrease in viral sensitivity *in vitro* from baseline. The clinical relevance of phenotypic and genotypic changes associated with ritonavir therapy has not been established. The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Therefore it is unknown what effect ritonavir therapy will have on the activity of concordantly or subsequently administered protease inhibitors. Serial HIV isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility *in vitro* but did not demonstrate a concordant decrease in susceptibility to saquinavir *in vitro* when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decreased susceptibility to indinavir *in vitro* (8-fold). Isolates from five patients were also tested for cross-resistance to amprenavir and nelfinavir; isolates from two patients had a decrease in susceptibility to nelfinavir (12 to 14-fold), and none to amprenavir. Cross-resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. One ZDV-resistant HIV isolate tested *in vitro* retained its full susceptibility to ritonavir.

5.2 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 alpha-1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG and, therefore, higher plasma concentrations. Darunavir is primarily metabolised by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

Absorption

Darunavir was well absorbed following oral administration in the presence of low-dose ritonavir. Maximum plasma concentration of darunavir in the presence of low-dose ritonavir is generally achieved within 2,5 to 4,0 hours. The absolute oral bioavailability of a single 600 mg dose of darunavir alone was approximately 37 % and increased to approximately 82 % in the presence of 100 mg twice daily ritonavir.

The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily (see Section 4.4). When administered without food, the relative bioavailability of darunavir in the presence of low-dose ritonavir is 30 % lower as compared to intake with food. Therefore, darunavir tablets should be taken with ritonavir and with food. The type of food does not affect exposure to darunavir.

Distribution

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

Metabolism

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

Elimination

After a 400/100 mg ^{14}C - darunavir/rtv dose, approximately 79,5 % and 13,9 % of the administered dose of ^{14}C - darunavir could be retrieved in faeces and urine, respectively. Unchanged darunavir accounted for approximately 41,2 % and 7,7 % of the administered dose in faeces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir. The intravenous clearance of darunavir alone (150 mg) and in the presence of low-dose ritonavir was 32,8 ℓ/h and 5,9 ℓ/h, respectively.

Special populations

Paediatrics

There is no information on the use of darunavir in combination with ritonavir in the paediatric population for the once daily dose.

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 (see Section 4.4).

Gender

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

Renal impairment

Results from a mass balance study with ^{14}C -darunavir/rtv showed that approximately 7,7 % of the administered dose of darunavir is excreted in the urine as unchanged substance. Darunavir has not been studied in patients with renal impairment (see Section 4.2 and 4.4).

Hepatic impairment

Darunavir is primarily metabolised and eliminated by the liver. In a multiple dose study with darunavir co-administered with ritonavir (600/100 mg) twice daily, it was demonstrated that the steady-state pharmacokinetic parameters of darunavir in subjects with mild (Child-Pugh Class A, n=8) and moderate (Child Pugh Class B,

n=8) hepatic impairment were comparable with those in healthy subjects. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see Sections 4.2, 4.3 and 4.4).

Ritonavir:

In a single-dose pharmacokinetic study in HIV positive fasting male subjects, high levels of ritonavir were achieved and maintained for several hours after oral administration of 100 mg, 200 mg, 400 mg, 600 mg, 800 mg or 1 000 mg or ritonavir. Area under the concentration-time curve (AUC) ranged from 3,92 to 123 µg,h/mℓ, respectively and the maximal concentration (C_{max}) ranged from 0,416 to 12,7 µg/mℓ. The pharmacokinetics of ritonavir was dose-dependent; with more than proportional increases in the AUC and C_{max} occurring with increasing dose. The time to maximum concentration (T_{max}) remained constant at approximately 2-4 hours with increasing dose. Renal clearance averaged less than 0,1ℓ/h and was relatively constant throughout the dosage range. There is no parenteral formulation of ritonavir, therefore, the absolute bioavailability has not been determined.

After administration of a single 100 mg dose tablet, the area under concentration-time curve (AUC) is 3,7 µg.h/mℓ, maximal concentration (C_{max}) is 0,44 ± 0,29 µg/mℓ, T_{max} is 4,4 ± 1,2 h.

Relative to fasting conditions, the extent of absorption of ritonavir from the soft gelatin capsule formulation was 12 % higher when administered with high fat meal. When the liquid formulation was given under fasting conditions, peak ritonavir

concentrations increased 28 %, relative to non-fasting conditions. The clinical implications of these differences are not known.

The pharmacokinetics of ritonavir during multiple dose regimens were studied in non-fasting HIV positive adult volunteers. Upon multiple dosing, ritonavir accumulation is less than predicted from single dose due to a time and dose related increase in apparent clearance (CI/F). Trough concentrations of ritonavir were observed to decrease over time, possibly due to enzyme induction, but appeared to stabilise by the end of 2 weeks. At steady state with a 600 mg twice day dose, C_{max} and C_{trough} values of 141,2 and 3,7 µg/mL were observed, respectively.

The $t_{½}$ of ritonavir was approximately 3 to 5 hours. The steady-state apparent clearance in patients treated with 6600 mg twice a day has averaged 8,8 ± 3,2 L/h. No clinically significant differences in AUC or C_{max} were noted between males and females. Ritonavir pharmacokinetic parameters were not significantly associated with body weight or lean body mass. The apparent volume if distribution (VD/F) of ritonavir is approximately 0,41 ± 0,25 L/kg after a single dose. The protein binding of ritonavir in human plasma was noted to be approximately 98 to 99 %. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities. Total plasma protein binding is constant over the concentration range 1 to 100 µ/mL.

Tissue distribution studies with ^{14}C-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 one measured in rat lymph nodes suggests that ritonavir distributes into lymphatic tissue. Ritonavir penetrates minimally into the brain.

Ritonavir was noted to be extensively metabolised by the hepatic cytochrome P450 system, primarily isozyme CYP3A and to a lesser extent CYP2D6. Animal studies as well as *in vitro* experiments with human hepatic microsomes indicated that ritonavir primarily underwent oxidative metabolism. Five 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 ritonavir. However the AUC of the M-2 metabolite was approximately 3 % of the AUC of ritonavir.

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86 % of radiolabel was recovered in the stool. In these studies renal elimination was not found to be major route of elimination of ritonavir.

Effects on electrocardiogram:

QTcF interval was evaluated in 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) msec 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 experiences 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. Maximum PR interval was 252 msec and no second- or third-degree heart block was observed.

Renal impairment:

Currently there is no data specific to this patient population. However, because ritonavir is highly protein bound it is unlikely that ritonavir will be significantly removed by haemodialysis or peritoneal dialysis (see Section 4.2 and 4.4).

Hepatic impairment:

In six HIV-infected adult subjects with mild hepatic insufficiency dosed with ritonavir 400 mg twice a day, ritonavir exposures were similar to control subjects dosed with 500 mg twice a day. Results indicated that dose adjustment is not required in patients with mild hepatic impairment. Adequate pharmacokinetic data are not available for patients with moderate hepatic impairment. Protein binding ritonavir was not statistically significant affected by mild or moderately impaired hepatic function (see Section 4.2, 4.3 and 4.4).

5.3 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. A variable but limited decrease in red blood cell-related parameters was observed, together with increases in activated partial thromboplastin time.

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

In a study conducted in rats, the number of corpora lutea and implantations were decreased in the presence of maternal toxicity. Otherwise, there were no effects on mating or fertility with darunavir treatment up to 1 000 mg/kg/day and exposure levels below (AUC-0,5 fold) of that in human at the clinically recommended dose. Up to same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. The exposure levels were lower than those with the recommended clinical dose in humans. In a pre- and postnatal development assessment in rats, darunavir with and without ritonavir, caused a transient reduction in body weight gain of the offspring pre-weaning and there was a slight delay in the opening of eyes and ears. Darunavir in combination with ritonavir caused a reduction in the number of pups that exhibited the startle response on day 15 of lactation and a reduced pup survival during lactation. These effects may be secondary to pup exposure to the active substance via the milk and/or maternal toxicity. No post weaning functions were affected with darunavir alone or in combination with ritonavir. In juvenile rats receiving darunavir up to days 23-26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher than in adult rats after comparable doses in mg/kg between

days 5 and 11 of age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals. No treatment related mortalities were noted in juvenile rats dosed at 1 000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats. Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, darunavir with low dose ritonavir should not be used in paediatric patients below 3 years of age. (**VITRAVIR** is not indicated for children under the age of 18 years – see Section 4.2).

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1 000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumours in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0,4 - and 0,7-fold (mice) and 0,7 - and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

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

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

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

The other ingredients of **VITRAVIR** Film-coated tablets are:

Colloidal silicon dioxide.

Copovidone.

Crospovidone.

Microcrystalline cellulose.

Ferric oxide yellow.

Sodium chloride.

Sodium stearyl fumarate.

Sorbitan monolaurate.

Coating: Opadry Yellow 20C520058.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ºC. Protect from light. Store in the original container. Do not remove from the carton until required for use. Keep the bottle tightly closed.

6.5 Nature and contents of container

HDPE bottle pack comprises of opaque HDPE bottle with opaque polypropylene closure and desiccant. HDPE container may be packed in a carton. Pack size 60's.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mylan (Pty) Ltd

Building 6, Greenstone Hill Office Park

Emerald Boulevard

Modderfontein, 1645

Republic of South Africa

8 REGISTRATION NUMBER

56/20.2.8/0672

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date on the registration certificate of the medicine.

10 DATE OF REVISION OF THE TEXT