WARNING:

CO-ADMINISTRATION OF **NORVIR** 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 **NORVIR** ON THE HEPATIC METABOLISM OF THESE MEDICINES. SEE **Section 4.3 and Section 4.4.**

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

NORVIR 100 mg TABLET

NORVIR® Oral Powder 100 mg -Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NORVIR 100 mg Film-coated Tablet:

Each film-coated-tablet contains ritonavir 100 mg (SSSS enantiomer) . Sugar free

Excipients: For the full list of excipients, see section 6.1.

NORVIR® Oral Powder:

Each sachet of oral powder contains 100mg of ritonavir. Sugar free

Excipients: For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

NORVIR 100 mg Tablet: White, ovaloid film-coated tablet debossed with “NK” on one side, providing 100 mg ritonavir.

NORVIR oral powder: The powder is beige to slightly yellow to yellow in colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NORVIR is used as a pharmacokinetic enhancer of certain other antiretroviral protease inhibitors.

4.2 Posology and method of administration

NORVIR oral powder and tablets are administered orally and should preferably be given with food.

Norvir Oral Powder when reconstituted with water, the colour may range from white to yellow.

NORVIR should be initiated by medical practitioners /physicians who are experienced in the treatment of HIV Infection.

ADULTS

When **NORVIR** is used as a pharmacokinetic enhancer for another antiretroviral protease inhibitor, the professional information of the particular protease inhibitor should be consulted.

Paediatric Patients

NORVIR should be used in combination with other antiretroviral medicines. The recommended dosage of **NORVIR** is 400 mg/m^2 of body surface area twice daily by mouth and should not exceed 600 mg twice daily.

NORVIR should be started at 250 mg/m^2 and increased at two to three day intervals by 50 mg/m^2 twice daily. If patients do not tolerate the maximum daily dose due to adverse events, the highest tolerated dose should be used for maintenance therapy in combination with other antiretroviral medicines.

When possible, dose should be administered using a calibrated dosing syringe.

Paediatric Dosage Guidelines for NORVIR Oral Powder (prepared as 100 mg/10 mL)*†			
Body Surface Area (m^2)*	**Twice daily dose 250 mg/m^2**	**Twice daily dose 300 mg/m^2**	**Twice daily dose 350 mg/m^2**
0,25	6,4 mL (62,5 mg)	7,6 mL (76 mg)	8,8 mL (88 mg)
0,50	12,6 mL (126 mg)	15 mL (150 mg)	17,6 mL (176 mg)
0,75	18,8 mL (188 mg)	22,6 mL (226 mg)	26,4 mL (262,5 mg)
1,00	25,0 mL (250 mg)	30,0 mL (300 mg)	35,0 mL (350 mg)
1,25	31,4 mL (312,5 mg)	37,6 mL (376 mg)	43,8 mL (438 mg)
1,50	37,6 mL (376 mg)	45,0 mL (450 mg)	52,6 mL (526 mg)

*When mixed with 9,4 mL of liquid the concentration of the suspension is 10 mg/mL.

†In some instances, the volumes and/or doses have been adjusted to ensure the recommended final dose and dosing volume.

Body Surface Area can be calculated with the following equations:

$\text{BSA } (m^2) = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$	OR	$\text{BSA } (m^2) = \left[\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}\right]^{½}$

To calculate the volume to be administered (in mL) for intermediate body surface areas not included in the above table, the body surface area should be multiplied by a factor of: 25 for a dose of 250 mg/m²; 30 for 300 mg/m²; and 35 for 350 mg/m².

Method of administration

The recommended dose of **NORVIR** oral powder by mouth should either be sprinkled on soft food such as apple sauce or dessert pudding or mixed with a suitable liquid such as water, chocolate milk, or infant formula.

For doses of 100, 200, 300, 400, 500, 600 mg:

• Either sprinkle entire contents of each packet/sachet over soft food (such as apple sauce or vanilla pudding) or mix with small amount of liquid (such as water , chocolate milk, or infant formula) and consume entire contents.

• Once the powder is mixed, the dosage must be consumed within 2 hours.

Doses less than 100 mg or partial doses between 100 mg increments:

• Mix 1 packet/sachet of oral powder (100 mg) with 9,4 mL of liquid (such as water, chocolate milk, or infant formula) in a mixing cup.

• Once mixed, use an oral dosing syringe to measure and administer the prescribed volume

• Once the powder is mixed, the dosage must be consumed within 2 hours.

• Discard any mixture remaining in the mixing cup.

4.3 Contraindications

1**. NORVIR** is contraindicated in patients with known hypersensitivity to ritonavir or any of its formulation excipients listed in section 6.1.

2. When **NORVIR** is used as a pharmacokinetic enhancer of other protease inhibitors, consult the professional information of the co-administered protease inhibitor for contraindications.

3.Severe liver disease.

4. Antituberculosis regimens containing rifampicin.

NORVIR is principally metabolised and eliminated **b**y the liver. Therefore, caution should be exercised when administering **NORVIR** to patients with impaired hepatic function.

In vitro studies have demonstrated that ritonavir is a potent inhibitor of many cytochrome P450 mediated biotransformations. Ritonavir is expected or has been shown to produce large increases in the plasma concentration of the medicines metabolised by cytochrome P450.

Medicines that are contra-indicated with NORVIR

Medicine Class	***Medicines within the Class that are contraindicated with NORVIR***	***Clinical Comments***
Alpha1-adrenoreceptor antagonist	alfuzosin HCL	Potential for hypotension.
Analgesics	Pethidine	Increased plasma concentrations of norpethidine. Thereby increasing the risk of serious respiratory depression or haematologic abnormalities or other serious adverse effects.
Antianginal	Ranolazine	Potential for serious and/or life-threatening reactions.
Antibiotic	Fusidic acid	Potential of increased fusidic acid-associated adverse events such as hepatitis or bone marrow suppression.
Anticancer medicines	Apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of ritonavir and potential loss of virologic response. In addition, exposure of apalutamide may increase with co-administration of ritonavir that may lead to serious adverse events including seizure.

	Neratinib	Potential for serious and/or life-threatening reactions including hepatotoxicity (see section 4.5).
	Venetoclax	Increased plasma concentrations of venetoclax. Increased risk of tumor lysis syndrome at the dose initiation and during the dose titration phase (see section 4.5).
Antidysrhythmics	amiodarone, bepridil, dronedarone, flecainide, propafenone, quinidine, encainide, digoxin	Potential for cardiac dysrhythmias.
Antifungal	Voriconazole	Significant decreases in voriconazole plasma concentrations may lead to loss of antifungal response.
Antigout	colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antihistamines	astemizole,	Increased plasma concentrations of astemizole and, thereby, increasing the risk of serious dysrhythmias from these medicines.
Antipsychotic	Blonanserin	May result in potential increase in frequency or intensity of known neurological or other toxicities associated with blonanserin.

	Lurasidone	Potential for serious and/or life-threatening reactions.
	Pimozide	Potential for cardiac arrthmias.
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated (see section 4.3).
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine	Post-marketing reports of acute ergot toxicity characterized by vasospasm and tissue ischaemia have been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
GI Motility medicines	Cisapride	Potential for cardiac dysrhythmias.
Herbal Products	St Johns wort (hypericum perforatum)	Co-administration may lead to a decrease in ritonavir levels, and to loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors
Lipid Modifying medicines		
HMG-CoA Reductase Inhibitors:	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Microsomal triglyceride	Lomitapide	Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors

transfer protein (MTTP) Inhibitor		increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated (see prescribing information for lomitapide).
Long acting beta-adrenoceptor agonist	salmeterol	May result in potential increased risk of cardiovascular adverse events associated with salmeterol.
PDE5 inhibitor	Avanafil	Increased plasma concentrations of avanafil (see **Section** 4.4. and 4.5).
	sildenafil* only when used for the treatment of pulmonary arterial hypertension (PAH)	Increased potential for sildenafil-associated adverse events (which include hypotension and syncope).
	Vardenafil	Increased plasma concentrations of vardenafil (see **Section** 4.4. and 4.5).
Sedative/hypnotics	Midazolam, triazolam	**NORVIR** is likely to produce large increases in these highly metabolized sedatives and hypnotics resulting in the potential for prolonged or increased sedation or respiratory depression.
**see Special warnings and precautions for use and Medicine Interactions for co-administration of sildenafil in patients with erectile dysfunction.*		

4.4 Special warnings and precautions for use

When **NORVIR** is used as a pharmacokinetic enhancer of other protease inhibitors, full details on the warnings relevant to that particular protease inhibitor should be considered and the professional information for the particular protease inhibitor must be consulted.

Allergic Reactions

Allergic reactions including urticaria, skin eruptions, bronchospasm, and angioedema have been reported. Rare cases of anaphylaxis and Stevens-Johnson syndrome have also been reported.

Hepatic Reactions

Hepatic transaminase elevations exceeding five times the upper limit of normal, clinical hepatitis and jaundice have occurred in patients receiving **NORVIR** alone or in combination with other antiretroviral medicines. There may be an increased risk for transaminase elevations in patients with underlying hepatitis B or C. Therefore, caution should be exercised when administering **NORVIR** 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 **NORVIR** treatment. There have been reports of hepatic dysfunction, including fatalities, particularly in patients taking multiple concomitant medicines and/or with advanced AIDS. **NORVIR** is contraindicated in patients with severe hepatic insufficiency (see **Section 4.3**).

Pancreatitis

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who

developed hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis. Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur.

Patients who exhibit these signs or symptoms should be evaluated and ritonavir therapy should be discontinued if a diagnosis of pancreatitis is made.

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 **NORVIR**. Some patients required either initiation or dose adjustment of insulin or oral hypoglycaemic medicines for treatment of these events. In some cases, diabetic ketoacidosis has occurred. Patients who discontinued protease inhibitor therapy, the hyperglycaemia persisted in some cases.

Antigout medicines

Life-threatening and fatal medicine interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like **NORVIR** (see **Section 4.3 and Section 4.5).**

Corticosteroids

Concomitant use of **NORVIR** and inhaled, injectable, or intranasal fluticasone, budesonide, triamcinolone, or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.

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 **NORVIR** has been co-administered with inhaled or intranasally administered fluticasone propionate or budesonide or injectactable triamcinolone.

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 **NORVIR.** Co-administration of **NORVIR** 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 **NORVIR** is contraindicated in pulmonary arterial hypertension patients (see **Section 4.3**).

Herbal Products

Patients on **NORVIR** 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 warnings and Special precautions for use and (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 **NORVIR** with simvastatin or lovastatin is contraindicated due to an increased risk of myopathy including rhabdomyolysis.

Caution must be exercised, and reduced doses should be considered if **NORVIR** 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 exposure has been reported with NORVIR co-administration. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see TABLE 2).

Antimycobacterials

Bedaquiline: Co-administration of bedaquiline with strong CYP3A4 inhibitors may increase the systemic exposure of bedaquiline, which may potentially increase the risk of bedaquiline-related adverse reactions (including QT prolongation) (see **section 4.5**).

Bedaquiline must be used cautiously with ritonavir, only if the benefit of co-administration outweighs the risk. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see **section 4.5**).

Delamanid: Co-administration of delamanid with a strong inhibitor of CYP3A (ritonavir) may slightly increase exposure to delamanid metabolite, which has been associated with QTc prolongation.

Therefore, if co-administration of delamanid with ritonavir is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (see **section 4.5**).

Resistance/Cross-Resistance

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of **NORVIR** therapy following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors.

The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Therefore, it is unknown what effect **NORVIR** therapy will have on the activity of concordantly or subsequently administered protease inhibitors.

Laboratory Tests

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

Haemophilia

There have been reports of increased bleeding, including spontaneous skin haematomas and

haemoarthroses, in patients with haemophilia type A and B treated with protease inhibitors. In some patient's 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 the 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 **NORVIR**. **NORVIR** should be used with caution in such patients.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution accumulation of body fat including central obesity, dorso-cervical fat, 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 Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment when the immune system responds, patients may develop an inflammatory response to asymptomatic or residual opportunistic infections (such as Mycobacterium avium infection,

cytomegalovirus, Pneumocystis jiroveci (carinii) pneumonia or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain- Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

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 NORVIR 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.

The risk of HIV transmission to others

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

Lipid Disorders

Treatment with **NORVIR** therapy in combination with saquinavir has resulted in substantial increases in the concentration of total triglycerides 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 medicine interactions with NORVIR and HMG-CoA Reductase Inhibitors (hypolipidemics).

Geriatric Use

Safety and efficacy has not been established in the elderly.

4.5 Interaction with other medicines and other forms of interaction

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

NORVIR 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 N**ORVIR** may induce glucuronosyl transferase, CYP1A2, CYP2C9 and CYP2C19 enzymes.

Decreased plasma concentrations of the other medicine and loss of therapeutic effects during **NORVIR** co-administration may signify the need for dosage alteration of these medicines. In addition to the medicines listed in the **contraindications** section 4.3 **TABLE 2** summarises

some commonly prescribed medicines separated by the type of metabolism and expected magnitude of interaction when co-administered with **NORVIR**.

Co**-** administration of **NORVIR** 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 medicines extensively metabolised by CYP3A.

Cardiac and neurologic events have been reported when **NORVIR** 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 NORVIR

(Contraindicated Medications are listed in Column 1)

Medicine Category	**Representative Medicines by Potential Interaction Category**					
	Contra-indicated Medication	**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] (glucu-ronidation)**
Analgesics, narcotics		Alfentanil Fentanyl	Hydrocodone Oxycodone Tramadol		Levamethadyl (LAAM)	Codeine Hydromorphone Meperidine* Methadone* Morphine

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Analgesics, non-steroidal				Diclofenac Flurbiprofen Ibuprofen Indomethacin	Nabumetone Sulindac	Ketoprofen Ketorolac Naproxen
Antidysrhythmic	Amiodarone Dronedarone Encainide Flecainide Propafenone Quinidine Digoxin	Lidocaine	Disopyramide Mexiletine		Tocainide [11]	
Antiasthmatic						Theophylline *****
Antibiotic, macrolide		Erythromycin	Clarithromycin *			
Antibiotic, steroidal		Fusidic acid				
Anticonvulsant		Carbamazepine	Clonazepan Ethosuximide		Phenobarbitone	Divalproex Lamotrigine Phenytoin

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Antidepressant tricyclic			Amitriptyline Clomipramine Desipramine* Imipramine Maprotiline Nortriptyline Trimipramine		Doxepin[11]	
Antidepressant SSRIs and non-tricyclics		Nefazodone Sertraline	Fluoxetine Paroxetine Trazodone* Venlafaxine		Fluvoxamine	Bupropion
Antidiarrhoeal						Diphenoxylate Loperamide
Antiemetics Prokinetics	Cisapride		Ondansetron		Prochlorperazine [11] Promethazine	Metaclopramide
Antifungal medicines	voriconazole	Itraconazole Ketoconazole* Miconazole				
Antigout	Colchicine					
Antihistamines	Astemizole	Loratadine				
Antihyper-tensive	Alfuzosin	Bosentan		Losartan	Doxazosin [11] Prazosin [11] Terazosin [11]	

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Antimyco-bacterial		Rifabutin*			Ethionamide Rifampicin	
Antiparasitics		Quinine		Proguanil	Albendazole Chloroquine Metronidazole Primaquine Pyrimethamine	Atovaquone
Antipsychotics	Blonanserin					
Protein pump inhibitors				Lansoprazole Omeprazole		
B-blockers			Metoprolol Penbutolol Pindolol Timolol	Propranolol	Betaxolol[11]	
β2-agonist (long-acting)	Salmeterol					

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Calcium channel blockers	Bepridil	Amlodipine Diltiazem Felodipine Isradipine Nicardipine Nifedipine Nimodipine Nisoldipine Nitrendipine Verapamil				
Cancer chemo-therapeutic medicines	Apalutamide Neratinib	Abemaciclib Encorafenib Tamoxifen Dasatinib Ivosidenib Nilotinib	Etoposide Fostamatinib's metabolite R406 Paclitaxel Vinblastine Vincristine	Cyclophos-phamide[3] Ifosfamide [3]	Apalutamide Daunorubicin [11] Doxorubicin [11]	
Ergot alkaloids and derivatives	Dihydroer-Gotamine Ergonovine [11] Ergotamine Methylergo-novine [11]	Bromocriptine			Methysergide [11]	

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Gonadotropin releasing hormone (GnRH) receptor antagonist					Elagolix[4]	
Haemorheologic Medicines					Pentoxifylline	
Herbal Products	St. John's Wort					
HCV Antivirals		Glecaprevir/pibrentasvir				
HIV Antivirals		Atazanavir Darunavir (fos) amprenavir Indinavir * Saquinavir * Tipranavir	Maraviroc		Nevirapine [11]	
Hypo-glycaemics				Glimepiride Glipizide Glyburide Tolbutamide		
Hypolipidemics	Lomitapide Lovastatin Simvastatin	Atorvastatin	Rosuvastatin		Gemfibrozil	Clofibrate

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Immuno-suppressants		Ciclosporine Everolimus Tacrolimus Sirolimus (rapamycin)				
Neuroleptics	Pimozide		Chlorpromazine Haloperidol Perphenazine Risperidone			Clozapine
PDE5 inhibitor	Sildenafil indicated for PAH	Avanafil Sildenafil indicated for ED Tadalafil Vardenafil				
Sedative/ hypnotics	Midazolam Triazolam	Buspirone	Clorazepate Diazepam Estazolam Flurazepam Zolpidem			Lorazepam Oxazepam Propofol Temazepam
Steroids		Dexamethasone Fluticasone*	Prednisone			Ethinyl Estradiol*
Stimulants			Dexfenfluramine Methamphetamine		Methylphenidate	

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[1] Large = > 3X; Moderate = 1.5-3X

[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 NORVIR resulted in a 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 **NORVIR.**

Bedaquiline: In a healthy volunteer medicine interaction study of 400 mg single dose bedaquiline and lopinavir/ritonavir 400/100 twice daily for 24 days, bedaquiline exposures (AUC) were increased by 22 %. Bedaquiline must be used cautiously with **NORVIR,** only if the benefit of co-administration outweighs the risk. (**see Section 4.4).**

Bosentan: Co-administration of bosentan and **NORVIR** may increase steady-state bosentan maximum concentrations (C_{max}) and area-under-the-curve (AUC). Refer to the bosentan professional information for prescribing information.

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

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

Clarithromycin: the concomitant administration of **NORVIR** 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 by 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 **NORVIR**.

Colchicine: Concentrations of colchicine are expected to increase when coadministered with **NORVIR**. Life threatening and fatal medicine interactions have been reported in patients treated with colchicine and ritonavir (see **Section 4.3 and Section 4.4).** Refer to the colchicine professional information prescribing information.

Delamanid: No interaction study is available with ritonavir only. In a healthy volunteer medicine interaction study of delamanid 100 mg twice daily and lopinavir/ ritonavir 400/100 mg twice daily

for 14 days, exposures of delamanid and a delamanid metabolite DM-6705, were slightly increased. Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with ritonavir is considered necessary, frequent ECG monitoring throughout the full

delamanid treatment period is recommended.

Delavirdine: Delavirdine is an inhibitor of CYP3A-mediated metabolism. In a published study, concurrent administration of clinical doses of delavirdine 400 mg three times daily with **NORVIR** 600 mg twice daily (n=12 HIV-infected patients) was reported to increase steady-state ritonavir C_{max} AUC by approximately 50 % and C_{min} by about 75 %. Based on comparison to historical data, the pharmacokinetics of delavirdine did not appear to be affected by **NORVIR.** When used in combination with delavirdine, a dose reduction of **NORVIR** should be considered.

Desipramine: Co-administration of **NORVIR** 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 **NORVIR** 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 **NORVIR** pharmacokinetics. Dose alteration of ddl during concomitant **NORVIR** therapy should not 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 coadministration of **NORVIR** (300 mg every 12 hours) and digoxin resulted in significantly increased digoxin levels. Caution should be exercised when coadministration **NORVIR** with digoxin, with appropriate monitoring of serum digoxin levels.

Efavirenz: In healthy volunteers receiving 500 mg **NORVIR** 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 **NORVIR** of 17 % was observed.

Elagolix: Coadministration of elagolix with **NORVIR** could increase elagolix exposure due to inhibition of CYP3A and P-gp known serious adverse events for elagolix include suicidal ideation and hepatic transaminase elevations. In addition, elagolix is a weak/moderate inducer of CYP3A, which may decrease exposure of **NORVIR**. Refer to the elagolix professional information for dosing information with strong CYP 3A4 inhibitors.

Fentanyl: Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral medicine inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir.

Kinase inhibitors (also see anticancer medicines): Fostamatinib: Coadministration of fostamatinib with **NORVIR** could increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia.

Glecaprevir/pibrentasvir: Coadministration with ritonavir is not recommended due to an increased risk of ALT elevations associated with increased GLE exposure.

Inhaled, injectable or itranasal fluticasone propionate, budesonide, triamcinolone: Concomitant use of **NORVIR** and fluticasone propionate may increase concentrations of fluticasone propionate. or other glucocorticoids that are metabolized by CYP3A is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Use with caution. Consider alternatives to fluticasone propionate, budesonide, and injectable triamcinolone particularly for long-term use (see **Section 4.4**)

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

Hypericum perforatum (St. John's Wort): Patients on NORVIR 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 may result in the loss of therapeutic effect and development of resistance (see **section 4.3** and **Section 4.4**).

Indinavir: **NORVIR** inhibits the CYP3A-mediated metabolism of indinavir. In healthy subjects, 200 to 400 mg of NORVIR 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 and 600 mg indinavir given alone. Concomitant administration of 400 mg **NORVIR** 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 underfasting conditions. Co-administration of **NORVIR** with indinavir will result

in increased indinavir serum concentrations. There is 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 **NORVIR**. Adequate hydration and monitoring of the patients is warranted.

Ketoconazole: Concomitant administration of **NORVIR** (500 mg q12h) and ketoconazole (200 mg q6h) resulted in an increase of mean ketoconazole AUC_{24} and C_{max} by 244 % and 55 %,

respectively. The mean half-life of ketoconazole increased from 2.7 to 13.2 h. Mean AUC_{24} and C_{max} of ritonavir increased by 18 and 10 % respectivley. No dosage adjustment of **NORVIR** is necessary; however doses of ketoconazole 200 mg/day or greater should be used with caution in combination with **NORVIR** and a decreased dosage may be considered.

Lomitapide: Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27 fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated.

Maraviroc: Concurrent administration of maraviroc with **NORVIR** will increase plasma levels of maraviroc. The dose of maraviroc should be decreased during co-administration with ritonavir. For further details see the professional information for maraviroc.

Methadone: Coadministration of **NORVIR** with methadone is expected to decrease methadone concentrations. A dosage increase of methadone may be considered.

Nelfinavir: Interactions between **NORVIR** and nelfinavir are likely to involve both cytochrome P450 inhibition and induction. Concurrent **NORVIR** 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 patients nelfinavir 750 mg and **NORVIR** 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 **NORVIR** 500 mg every 12 hours and a fixed combination oral contraceptive resulted in reductions of the ethinyl estradiol mean C_{max} and mean AUC by 32 % and 40 %, respectively. Increased doses of oral contraceptives or patch contraceptives containing ethinyl estradiol, or alternate methods of contraception, should be considered.

Pethidine: Ritonavir co-administration is likely to result in increased plasma concentrations of pethidine and is therefore contraindicated (see **Section 4.3**).

Raltegravir: A pharmacokinetic study showed that co-administration of **NORVIR** 100 mg twice daily and raltegravir 400 mg single dose resulted in a minor reduction in raltegravir $C_{12}h$, $AUC_{0-\infty}$, and C_{max} of 1 %, 16 % and 24 %, respectively.

Rifabutin: A pharmacokinetic study demonstrated that the concomitant administration of **NORVIR** 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-O 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 dosage reduction may be necessary.

Dabigatran etexilate and Edoxaban: Serum concentrations may be increased due to P-gp inhibition by ritonavir. Clinical monitoring and/or dose reduction of the direct oral anticoagulants (DOAC) should be considered when a DOAC transported by P-gp but not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co-administered with **NORVIR**.

Rivaroxaban: Coadministration of **NORVIR** and rivaroxaban resulted in increased exposure of rivaroxaban which may lead to risk of increased bleeding.

Saquinavir: A pharmacokinetic study demonstrated that **NORVIR** 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 **NORVIR** (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 **NORVIR**. When used in combination therapy for up to 24 weeks, doses greater than 400 mg twice a day of either **NORVIR** or saquinavir were associated with an increase in adverse events.

Simeprevir: A pharmacokinetic study demonstrated that concomitant administration of simeprevir 200 mg once daily with **NORVIR** 100 mg b.i.d resulted in an increase in simeprevir concentrations. It is not recommended to co-administer ritonavir with simeprevir.

PDE5 inhibitors

Sildenafil, Tadalafil & Vardenafil: Caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving **NORVIR**. Co administration of **NORVIR** 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 **NORVIR** is contraindicated in pulmonary arterial hypertension patients (see **Section 4.3**).

Tadalafil: Use tadalafil for the treatment of erectile dysfunction with caution at reduced doses of no more than 10 mg every 72hours with increased monitoring for adverse events**.** When tadalafil is used concomitantly with **NORVIR** in patients with pulmonary arterial hypertension, refer to the tadalafil professional information for prescribing information.

Sulfamethoxazole/trimethoprim: A pharmacokinetic study demonstrated that the concomitant administration of **NORVIR** 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 **NORVIR** 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 **NORVIR**.

Trazodone: Concomitant use of **NORVIR** and trazodone may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed. If trazodone is used with a CYP3A4 inhibitor such as **NORVIR**, the combination should be used with caution and a lower dose of trazodone should be considered.

Anticancer medicines

Afatinib: Serum concentrations may be increased due to Breast Cancer Resistance Protein and acute P-gp inhibition by **NORVIR**. The extent of increase in AUC and Cmax depends on the timing of **NORVIR** admnistration. Caution should be exercised in administering afatinib with **NORVIR**.

Abemaciclib: Serum concentrations may be increased due to CYP3A4 inhibition by **NORVIR**. Co-administration of abemaciclib and NORVIR should be avoided. If this co-administration is unavoidable, refer to the abemaciclib professional information for dosage adjustment recommendations. Monitor for adverse events related to abemaciclib.

Apalutamide: Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of **NORVIR** and potential loss of virologic response. In addition, serum concentrations may be increased when co-administered with **NORVIR** resulting in the potential for serious adverse events including seizure. Concomitant use of **NORVIR** with apalutamide is not recommended.

Ceritinib: Serum concentrations may be increased due to CYP3A and P-gp inhibition by **NORVIR**. Caution Should be exercised in administering Ceritinib with **NORVIR**.

Dasatinib, nilotinib Vincristine, Vinblastine: Serum concentrations may be increased when co-administered with **NORVIR** resulting in the potential for increased incidence of adverse events.

Encorafenib, Ivosidenib: Serum concentrations may be increased when co administered with ritonavir which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Co-administration of encorafenib and NORVIR should be avoided. If the benefit is considered to outweigh the risk and NORVIR must be used, patients should be

carefully monitored for safety. If co-admnistration of ivosidenib and ritonavir cannot be avoided , refer to ivosidenib professional information for dosage adjustment recommendations.

Fostamatinib: Co-administration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension, or diarrhoea. Refer to the fostamatinib professional Information for dose reduction recommendations if such events occur.

Ibrutinib: Serum concentrations of ibrutinib may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk for toxicity including risk of tumor lysis syndrome. Co-administration of ibrutinib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.

Neratinib: Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with **NORVIR** is contraindicated due to serious and/or life-threatening potential reactions including hepatotoxicity (see section 4.3).

Venetoclax: Serum concentrations may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase. For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors.

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

Warfarin: Anticoagulant metabolism may be induced, resulting in decreased concentrations of warfarin. International Normalized Ratio(INR) should be measured more frequently , and the dose of warfarin may need to be adjusted.

Zidovudine: A pharmacokinetic study demonstrated that the concomitant administration of **NORVIR** 300 mg every 6 hours and zidovudine (AZT) 200 mg every 8 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 **NORVIR** pharmacokinetics. Dose alteration of AZT during concomitant ritonavir therapy should not be necessary.

TABLE 3

Effect on AUC and C_{max} of Co-administration of NORVIR with Other Medicines

	Effect on Ritonavir			
Medicine	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	←→	←→

TABLE 3

Effect on AUC and C_{max} of Co-administration of NORVIR with Other Medicines

Medicine	Effect on Ritonavir Ritonavir Dosage	n	AUC % (95 CI)	C_{max} % (95 CI)

[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

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

Breastfeeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

When **NORVIR** is used as a pharmacokinetic enhancer with other protease inhibitors, full details on the side effects and special precautions relevant to that particular protease inhibitor should be considered, therefore the professional information for that particular protease inhibitor must be consulted.

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 frequency (very common ≥ 1/10; common ≥ 1/100, < 1/10) in TABLE 4 below. Where frequency data is not available in adverse events occurring in less than 2 % of patients the term “less frequently” is used.

TABLE 4

TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN PATIENTS RECEIVING RITONAVIR AND WITH POSSIBLE, PROBABLE OR UNKOWN RELATIONSHIP TO RITONAVIR IN PHASE II/III COMBINED STUDIES

ORGAN CLASS CLASSIFICATION	**FREQUENCY**	**ADVERSE EVENT**
Infections and infestations	Common	Pharyngitis

TABLE 4

TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN PATIENTS RECEIVING RITONAVIR AND WITH POSSIBLE, PROBABLE OR UNKOWN RELATIONSHIP TO RITONAVIR IN PHASE II/III COMBINED STUDIES

ORGAN CLASS CLASSIFICATION	**FREQUENCY**	**ADVERSE EVENT**
Blood and the lymphatic system disorders	Uncommon	Anaemia, ecchymosis, leukopenia, lymphadenopathy, lymphocytosis, thrombocytopenia
Immune system disorders	Common	Allergic reactions
Endocrine disorders	Uncommon	Diabetes mellitus
Metabolism and nutrition disorders	Very common Common	Anorexia, hyperlipaemia, weight loss Avitaminosis, cachexia, dehydration, oedema, glycosuria, gout, hypercholesterolaemia, peripheral oedema, redistribution/accumulation of body fat (see section 4.4)
Psychiatric disorders	Very common	Anxiety, insomnia

TABLE 4

TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN PATIENTS RECEIVING RITONAVIR AND WITH POSSIBLE, PROBABLE OR UNKOWN RELATIONSHIP TO RITONAVIR IN PHASE II/III COMBINED STUDIES

ORGAN CLASS CLASSIFICATION	**FREQUENCY**	**ADVERSE EVENT**
	Common	Agitation, confusion, depression, emotional lability, euphoria, hallucinations, decreased libido, nervousness, personality disorder, abnormal thinking
Nervous system disorders	Very common	Circumoral paraesthesia, headache, peripheral paraesthesia, taste perversion
	Common	Dizziness, hyperaesthaesia, paraesthesia, somnolence
	Uncommon	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

TABLE 4

TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN PATIENTS RECEIVING RITONAVIR AND WITH POSSIBLE, PROBABLE OR UNKOWN RELATIONSHIP TO RITONAVIR IN PHASE II/III COMBINED STUDIES

ORGAN CLASS CLASSIFICATION	**FREQUENCY**	**ADVERSE EVENT**
Eye disorders	Common	Abnormal vision, amblyopia/blurred vision, blepharitis, diplopia, eye pain, iritis, photophobia, uveitis
Ear and labyrinth disorders	Uncommon	Ear pain, hearing impairment, increased cerumen, tinnitus, vertigo
Cardiac disorders	Uncommon	Palpitation, syncope
Vascular disorders	Common	Haemorrhage, hypotension, migraine, peripheral vascular disorder, postural hypotension, tachycardia
Respiratory, thoracic and mediastinal disorders	Very common	Increased cough
	Uncommon	Asthma, dyspnoea, epistaxis, hiccup, hypoventilation, interstitial pneumonia, lung disorder and rhinitis

TABLE 4

TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN PATIENTS RECEIVING RITONAVIR AND WITH POSSIBLE, PROBABLE OR UNKOWN RELATIONSHIP TO RITONAVIR IN PHASE II/III COMBINED STUDIES

ORGAN CLASS CLASSIFICATION	**FREQUENCY**	**ADVERSE EVENT**
Gastrointestinal disorders	Very Common	Abdominal pain, diarrhoea, nausea, vomiting
	Common	Dry mouth, dyspepsia, eructation, flatulence, local throat irritation, mouth ulcer
	Uncommon	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	Common	Cholangitis, hepatitis, hepatomegaly, liver damage

TABLE 4

TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN PATIENTS RECEIVING RITONAVIR AND WITH POSSIBLE, PROBABLE OR UNKOWN RELATIONSHIP TO RITONAVIR IN PHASE II/III COMBINED STUDIES

ORGAN CLASS CLASSIFICATION	**FREQUENCY**	**ADVERSE EVENT**
Skin and subcutaneous tissue disorders	Very Common	Macropapular rash, pruritus, rash, sweating
	Common	Acne, contact dermatitis, dry skin, eczema, facial oedema, folliculitis, molluscum contagiosum, photosensitivity reaction, psoriasis, seborrhoea, urticaria, vesiculobullous rash
Musculoskeletal, connective tissue and bone disorders	Very Common	Myalgia
	Common	Arthalgia, arthrosis, back pain, facial pain, joint disorder, muscle cramps, muscle weakness, myositis, neck pain, neck rigidity, twitching
Renal and urinary disorders	Common	Dysuria, haematuria, kidney calculus, kidney failure, kidney pain, nocturia, polyuria,

TABLE 4

TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN PATIENTS RECEIVING RITONAVIR AND WITH POSSIBLE, PROBABLE OR UNKOWN RELATIONSHIP TO RITONAVIR IN PHASE II/III COMBINED STUDIES

ORGAN CLASS CLASSIFICATION	FREQUENCY	ADVERSE EVENT
		pyelonephritis, urethritis, urinary frequency, urinary retention
Reproductive system and breast disorders	Uncommon	Impotence, penis disorder
General disorders and administration site conditions	Very common	Asthenia
	Common	Fever, pain
	Uncommon	Abnormal gait, chest pain, chills, flu syndrome, malaise, substernal chest pain
Investigations	Common	Abnormal liver function tests
	Uncommon	Abnormal electro-oculogram, abnormal electroretinogram, altered hormone level

TABLE 4 **TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN PATIENTS RECEIVING RITONAVIR AND WITH POSSIBLE, PROBABLE OR UNKOWN RELATIONSHIP TO RITONAVIR IN PHASE II/III COMBINED STUDIES**		
ORGAN CLASS CLASSIFICATION	**FREQUENCY**	**ADVERSE EVENT**
Injury and poisoning	Uncommon	Accidental injury, hypothermia
Surgical and medical procedures	Common	Vasodilation

Post-Marketing Experience

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.

Renal and urinary disorders: Nephrolithiasis

Reproductive system and breast disorders: Menorrhagia has been reported.

Skin and subcutaneous tissue disorders*:* Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome

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 the 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 phosphatase (> 550 IU/L) in 10 (1 %) patients;

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

Other clinical chemistry tests:

Increased creatine phosphokinase (CPK) (> 1000 IU/L) in 71 (8 %) patients;

Increased triglycerides (> 1500 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 8 (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 (< 40mg/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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare professionals, patients and caregivers are also asked to report any suspected adverse reaction to AbbVie (Pty) Ltd via this e-mail address: MEAPV@abbvie.com

4.9 Overdose

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

Management of Overdosage:

There is no specific antidote for overdose with **NORVIR**. Treatment of overdose with **NORVIR** should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. It is proposed that management of overdose could also entail and administration of activated charcoal. Since **NORVIR** is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A20.2.8 - Antiviral agent

Ritonavir is a peptidomimetic inhibitor of the HIV-1 and HIV-2 aspartyl proteases. Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polyprotein precursor and leads to the production of HIV particles with immature morphology that are unable to initiate new rounds of infection. Ritonavir has selective affinity for the HIV protease and has little inhibitory activity against human aspartyl proteases.

In vitro data indicate that ritonavir is active against all strains of HIV tested in a variety of transformed and primary human cell lines. The concentration of ritonavir that inhibits 50 % and 90 % of viral replication *in vitro* in plasma-free surroundings is approximately 0,02 µm and 0,11 µm, respectively. Similar potencies were found with both AZT-sensitive and AZT-resistant strains of HIV. Studies which measured direct cell toxicity of ritonavir on several cell lines, showed no direct toxicity at concentrations up to 25 µm, with a resulting *in vitro* therapeutic index of at least 1000.

Ritonavir-resistant isolates 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 codons V82F, I84V, A71V and M46I. Phenotypic and genotypic changes in HIV isolates from selected patients treated with ritonavir were monitored in Phase I/II trials. 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 (Ile to Val), 71 (Ala to Val/Thr) and 36 (Ile to Leu), followed by combinations of mutations at an additional 5 specific amino acid positions. Viral strains isolated *in vivo* without a change at 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 full susceptibility to ritonavir.

5.2 Pharmacokinetic properties

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 1000 mg of 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-dependant; 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 0,1 L/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 a single 600 mg dose under non-fasting conditions the 100 mg (n=57) soft gelatin capsule and the oral solution (n=18) formulations yielded mean ± SD AUCs of 121,7 ± 53,8 µg.h/mL and 129,0 ± 39,3 µg.h/mL, respectively. Plasma concentrations of ritonavir after administration of a single 100 mg dose tablet are similar to the 100 mg soft gelatin capsule under fed conditions, as supported by the point estimates located within the 92,8 % CI. Area under the concentration-time curve (AUC) is 3,7 µg,h/mL, maximal concentration (Cmax) is 0,44 ± 0,29 µg/mL, Tmax is 4,4 ± 1,2 h.

After administration of a single 100 mg dose under fed conditions, ritonavir AUC and C_{max} of the oral powder are bioequivalent to the oral solution.

Relative to fasting conditions, the extent of absorption of ritonavir from the soft gelatin capsule formulation was 12 % higher when administered with a meal. When the liquid formulation was given under fasting conditions, peak ritonavir concentrations increased 28 %, relative to non-fasting conditions.

Administration of a single 100 mg dose of ritonavir tablet with a moderate fat meal (857 kcal, 31 % calories from fat) or a high fat meal (907 kcal, 52 % calories from fat) was associated with a mean decrease of 20-23 % in ritonavir AUC and C_{max}.

Administration of ritonavir oral powder with a moderate fat meal (617 kcal, 29 % calories from fat) or a high fat meal (917 kcal, 60 % calories from fat) was associated with a mean decrease of 23-49 % in ritonavir AUC and C_{max} relative to 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 a single dose due to a time and dose-related increase in apparent clearance (Cl/F). Trough concentrations of ritonavir were observed to decrease over time, possibly due to enzyme induction, but appeared to stabilize by the end of two weeks. At steady state with a 600 mg twice a day dose, C_{max} and C_{trough} values of 11,2 and 3,7 µg/mL were observed, respectively.

The $t_{1/2}$ of ritonavir was approximately three to five hours. The steady-state apparent clearance in patients treated with 600 mg twice a day has averaged 8,8 ± 3,2L /h.

No clinically significant differences in AUC or C_{max} were noted between males and females. Ritonavir pharmacokinetic parameters were not statistically significantly associated with body weight or lean body mass.

The apparent volume of distribution (V_B/F) of ritonavir is approximately 0,41 ± 0,25 L-/kg after a single 600 mg 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 of 1 to 100µg/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 tissues. 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 % percent 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 a major route of elimination of ritonavir.

Effects on Electrocardiogram: QTcF interval was evaluated in a randomized, 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 experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec. Modest prolongation of the PR interval was also noted in subjects receiving ritonavir in the same study on Day 3. Maximum PR interval was 252 msec and no second- or third-degree heart block was observed.

The pharmacokinetic profile of ritonavir in paediatric patients below the age of two years has not been established. Steady-state pharmacokinetics were evaluated in 37 HIV-infected patients ages 2 – 14 years receiving doses ranging from 250 mg/m^2 twice a day to 400 mg/m^2 twice a day**.**

Across dose groups, ritonavir steady-state oral clearance was approximately 1,5 times faster in paediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg/m^2 twice daily in paediatric patients were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m^2) twice daily.

Renal Impairment: Currently, there are no data specific to this patient population. However, because ritonavir is highly protein it is unlikely that ritonavir will be significantly removed by haemodialysis or peritoneal dialysis.

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 indicate 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 of ritonavir was not statistically significantly affected by mild or moderately impaired hepatic function.

5.3 Preclinical safety data

Carcinogenesis and Mutagenesis

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

NORVIR 100 mg Film-coated Tablet:

Copovidone

Sorbitan laurate

Colloidal anhydrous silica

Sodium stearyl fumarate

Calcium hydrogen phosphate anhydrous

Hypromellose

Titanium dioxide E171

Macrogols type 400

Hydroxypropyl cellulose

Talc

Macrogols type 3350

Polysorbate 80

NORVIR® Oral Powder:

Copovidone

Sorbitan laurate

Colloidal anhydrous silica

6.3 Shelf life

NORVIR 100 mg TABLET 24 months

NORVIR® Oral Powder 36 months

6.4 Special precautions for storage

NORVIR 100 mg Tablet should be stored at room temperature (below 30 °C). Keep the bottle tightly closed.

NORVIR oral powder should be stored at room temperature (at or below 30 °C).

Avoid exposure to excessive heat. The reconstituted powder must be consumed within 2 hours.

The solution formulations should be stored in their original container and protected from excessive heat and freezing.

The oral dosing syringe and mixing cup should be cleaned immediately with warm water and soap after use. When cleaned immediately, medicine residue is removed. The oral dosing syringe and mixing cup should be dry prior to use.

6.5 Nature and contents of container

NORVIR 100 mg Tablet: The 30 or 60-count film-coated tablets are available in a white high-density polyethylene (HDPE) bottle, closed with a white polypropylene cap consisting of an induction inner seal.

NORVIR oral powder: 30 aluminium foil lacquer-laminate single-use, white sachets per carton. The aluminium foil is laminated with Polyethylene terephthalate to low density polyethylene.

The carton also contains a mixing cup and 10 mL calibrated oral dosing syringe. Syringe Assembly, Oral Dosing, 10 mL (Polypropylene barrel and piston, Silicone sealing ring, and 0, 2 mL printed graduation markings). Mixing Cup with Cap, Molded 20mL (Polypropylene cup with High Density Polyethylene lid).

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

NORVIR 100 mg Tablet 44/20.2.8/0128

Kenya:H2015/CTD257/396 Namibia: 11/202.8/0012(NS2) Zambia: 128/030

NORVIR oral powder 51/20.2.8/0154

Kenya: H2021/CTD7295/14281

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

NORVIR 100 mg Tablet 11 June 2015

NORVIR oral powder 25 September 2018

10. DATE OF REVISION OF THE TEXT

The date of the most recently revised PI as approved by SAHPRA

24 January 2025