AUSTRALIAN PRODUCT INFORMATION – NORVIR®

RITONAVIR

1 NAME OF THE MEDICINE

Ritonavir

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Norvir film coated tablets are available for oral administration in a strength of 100mg ritonavir with the following inactive ingredients: copovidone, calcium hydrogen phosphate, sorbitan monolaurate, colloidal anhydrous silica, and sodium stearylfumarate. The following are the ingredients in the film coating: hypromellose, titanium dioxide, macrogol 400, hydroxypropylcellulose, purified talc, macrogol 3350, colloidal anhydrous silica, and polysorbate 80.

3 PHARMACEUTICAL FORM

White to off-white film coated ovaloid tablets debossed with “NK” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Norvir is indicated for use in combination with appropriate antiretroviral agents or as monotherapy if combination therapy is inappropriate, for the treatment of HIV-1 infection in adults and children aged 12 years and older.

For persons with advanced HIV disease, the indication for ritonavir is based on the results for one study that showed a reduction in both mortality and AIDS defining clinical events for patients who received ritonavir. Median duration of follow-up in this study was 6 months. The clinical benefit from ritonavir for longer periods of treatment is unknown. For persons with less advanced disease, the indication is based on changes in surrogate markers in controlled trials of up to 16 weeks duration (see 5.1 PHARMACODYNAMIC PROPERTIES).

4.2 Dose and method of administration

General Dosing Guidelines

Consult the product information of the particular protease inhibitor (PI) when ritonavir is used as a pharmacokinetic enhancer for another antiretroviral protease inhibitor up to a maximum daily dose of 200 mg.

Ritonavir is no longer recommended in clinical practice at the antiretroviral dose of 1200 mg (600 mg twice daily).

Norvir tablets should be swallowed whole and not chewed, broken or crushed.

4.3 Contraindications

Norvir is contraindicated in patients with known hypersensitivity to it or any of its ingredients.

When co-administering ritonavir with other PIs, see the full product information for that protease inhibitor including contraindication information.

Ritonavir is expected to produce large increases in the plasma concentrations of drugs metabolised by cytochrome P450 (CYP). Co-administration of Norvir is contraindicated with the drugs listed in Table 1.

Table 1: Drugs that are Contraindicated with Ritonavir

Drug Class	Drugs within Class that are Contraindicated with Ritonavir	Clinical comments
Alpha1-adrenoreceptor antagonist	alfuzosin hydrochloride	Potential for hypotension.
Analgesic Sodium channel blocker	suzetrigine	Ritonavir is likely to increase exposure of suzetrigine and its active metabolite M6-SUZ. Concomitant use of strong CYP3A inhibitors with suzetrigine is contraindicated (see prescribing information for suzetrigine).
Antianginal	ranolazine	Potential for serious and/or life-threatening reactions.
Antiarrhythmics	amiodarone, bepridil, dronedarone, flecainide, propafenone, quinidine, encainide	Potential for cardiac arrhythmias.
Antibiotic	fusidic acid	Potential of increased fusidic acid-associated adverse events such as hepatitis or bone marrow suppression.

Drug Class	Drugs within Class that are Contraindicated with Ritonavir	Clinical comments
Anticancer Agents	neratinib	Potential for serious and/or life-threatening reactions including hepatoxicity.
	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.
	venetoclax	Concomitant use of strong CYP3A inhibitors, such as NORVIR, and venetoclax may increase the risk of tumour lysis syndrome at the dose initiation and during the ramp-up phase.
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, terfenadine	Increased plasma concentrations of astemizole and terfenadine, thereby, increasing the risk of serious arrhythmias from these agents.
Antimycobacterial	rifabutin	Concomitant use of ritonavir and rifabutin due to an increase of rifabutin serum concentrations and risk of adverse events including uveitis.

Drug Class	Drugs within Class that are Contraindicated with Ritonavir	Clinical comments
Antipsychotics	blonanserin, clozapine	May result in potential increase in frequency or intensity of known neurological or other toxicities associated with blonanserin and clozapine such as neurological or hematologic toxicities.
	lurasidone	Potential for serious and/or life-threatening reactions.
	pimozide	Potential for cardiac arrhythmias.
Ergot Derivatives	dihydroergotamine, ergometrine, ergotamine, methylergometrine	Post-marketing reports of acute ergot toxicity characterised by peripheral vasospasm and tissue ischemia of the extremities have been associated with coadministration of ritonavir and dihydroergotamine, ergometrine, ergotamine, methylergometrine.
GI Motility Agent	cisapride	Potential for cardiac arrhythmias.
Herbal Products	St John's 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 PIs.
<u>Lipid-modifying agents</u> HMG-CoA Reductase Inhibitors	lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Microsomal triglyceride transfer protein (MTTP) inhibitor	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 (see prescribing information for lomitapide).
Long acting beta-adrenoceptor agonist	salmeterol	May result in potential increased risk of cardiovascular adverse events associated with salmeterol.

Drug Class	Drugs within Class that are Contraindicated with Ritonavir	Clinical comments
PDE5 inhibitor	sildenafil* only when used for the treatment of pulmonary arterial hypertension (PAH)	Increased potential for sildenafil associated adverse events (which include hypotension and syncope).
Opioid analgesic	pethidine, dextropropoxyphene	Increase in plasma concentration resulting in toxicity associated with pethidine and dextropropoxyphene.
Sedative/hypnotics	clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem	Ritonavir is likely to produce large increases in these highly metabolised sedatives and hypnotics resulting in the potential for extreme sedation and respiratory depression.
*see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for coadministration of sildenafil in patients with erectile dysfunction		

4.4 Special warnings and precautions for use

When co-administering ritonavir with other PIs, see the full product information for that protease inhibitor including 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Allergic Reactions

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

Use in hepatic impairment

Ritonavir is principally metabolised by the liver; therefore, caution should be exercised if this drug is administered to patients with impaired hepatic function.

Hepatic transaminase elevations exceeding five times the upper limit of normal, clinical hepatitis and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretroviral drugs (see Table 4). There may be an increased risk of transaminase elevations in patients with underlying hepatitis B or C. Therefore, caution should be exercised when administering ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

There have been post-marketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients taking multiple concomitant medications and/or with advanced AIDS. A definitive causal relationship has not been established.

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. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycaemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made. Consideration should be given to the monitoring of blood glucose.

Retinal Toxicity

Preclinical studies suggested the possibility of retinal toxicity but this has not been proven in an analysis of over 300 patients receiving ritonavir for up to 36 weeks, who underwent detailed ocular examination.

Haemophilia

In haemophiliac patients treated with ritonavir and other PIs there have been several reports of increased bleeding, including spontaneous skin haematomas and haemarthroses. A causal relationship to treatment has not been definitely established.

Resistance/Cross Resistance

The potential for HIV cross-resistance between PIs has not been fully assessed. It is unknown what affect ritonavir will have on the activity of subsequent PIs (see 5.1 PHARMACODYNAMIC PROPERTIES).

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including Norvir. 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 pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre 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.

PR Interval Prolongation

Norvir has been shown to cause modest asymptomatic prolongation of the PR interval in some patients. Rare 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 drugs 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.

Fat Redistribution

Redistribution of body fat (fat loss or fat gain) has been associated with combination antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevation

Marked elevations of triglycerides (> 16.9 mmol/L) was reported in around 10% of ritonavir treated patients. The potential for pancreatitis in association with high triglyceride elevations has not been fully assessed.

Treatment with ritonavir 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 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS: HMG-CoA Reductase Inhibitors for additional information on potential drug interactions with ritonavir and HMG-CoA reductase inhibitors.

Use in the elderly

No data available.

Paediatric use

The safety and effectiveness of ritonavir in children below the age of 12 have not been established.

Effects on laboratory tests

Ritonavir has been associated with alterations in cholesterol, triglycerides, AST, ALT, GGT, CPK and uric acid (see also 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Hepatic Impairment and Lipid Elevation). Appropriate laboratory testing should be performed prior to initiating ritonavir 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, physicians should refer to the complete product information for each of these drugs.

4.5 Interactions with other medicines and other forms of interactions

When co-administering ritonavir with other PIs, see the full product information for that protease inhibitor including information for drug interactions.

These examples are a guide and not considered a comprehensive list of all possible drugs that may interact with ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

Ritonavir has been demonstrated to have the potential for significant drug interactions with a variety of agents, particularly those metabolised by the P450 enzyme system.

Ritonavir has a high affinity for several CYP isoforms with the following rank order: CYP3A > CYP2D6 > CYP2C9, CYP2C19 >> CYP2A6, CYP1A2, CYP2E1. There are some indications that ritonavir may increase the activity of glucuronsyltransferases; thus, loss of therapeutic effects from directly glucuronidated agents during ritonavir therapy may signify the need for dosage alteration of these agents.

Specific drug interaction studies were performed with clarithromycin, zidovudine, didanosine (ddI), trimethoprim/sufamethoxazole, fluconazole, ethinyloestradiol, theophylline, rifabutin, saquinavir and ketoconazole.

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

Anti-HIV Agents

Nucleoside Reverse Transcriptase Inhibitors

Didanosine

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 600 mg q12h and ddI 200 mg q12h resulted in a reduction of the ddI steady-state maximum concentration (C_{max}) and area under the curve (AUC) of 16% and 13%, respectively. In contrast, little if any effect was noted on ritonavir pharmacokinetics. Dose alteration of ddI during concomitant therapy should not be necessary. However, administration of ddI and ritonavir should be separated by 2.5 hours to avoid formulation incompatibility.

Zidovudine

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 300 mg q12h and zidovudine 200 mg q8h 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. Reduction in zidovudine concentration may be of potential clinical significance when lower zidovudine doses (500 to 600 mg/day) are utilised.

Non-Nucleoside Reverse Transcriptase Inhibitors

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 ritonavir 600 mg twice daily (n=12 HIV-infected patients) was reported to substantially increase steady-state ritonavir C_{max}, C_{min} and AUC. Based on comparison to historical data, the pharmacokinetics of delavirdine did not appear to be affected by ritonavir. When used in combination with delavirdine, a dose reduction of ritonavir should be considered.

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.

Protease Inhibitors (PIs)

Saquinavir

Ritonavir extensively inhibits the metabolism of saquinavir resulting in greatly increased saquinavir plasma concentrations. Co-administration of ritonavir 400 mg or 600 mg q12h regimens produced greater than 20-fold increases in steady-state dose-normalised saquinavir concentrations in healthy subjects. The appropriate dosing for this combination has not been established (see also 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Lipid Elevation).

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

Amprenavir

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

Indinavir

Ritonavir inhibits the CYP3A-mediated metabolism of indinavir. 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 ritonavir. Adequate hydration and monitoring of the patient is warranted.

Nelfinavir

Interactions between ritonavir and nelfinavir are likely to involve both CYP 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.

Tipranavir

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

<u>CCR5 antogonists</u>

Maraviroc

Concurrent administration of maraviroc with ritonavir will increase plasma levels of maraviroc. The dose of maraviroc should be decreased during co-administration with ritonavir. For further details see complete maraviroc product information for prescribing information.

Integrase Inhibitors

Raltegravir

A pharmacokinetic study showed that co-administration of ritonavir 100 mg BD and raltegravir 400 mg single dose resulted in a minor reduction in raltegravir $C_{12}h$, $AUC_{0-\infty}$, and C_{max}.

Other Drugs

Alpha$_1$-Adrenoreceptor Antagonist

Alfuzosin hydrochloride

Based on results of a drug interaction study with ketoconazole, another potent inhibitor of CYP3A4, and alfuzosin, a significant increase in alfuszosin exposure is expected in the presence of ritonavir (600 mg twice daily). Therefore alfuzosin should not be co-adminstered with ritonavir.

Analgesics

Fentanyl

Ritonavir 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.

Sodium Channel Blocker (suzetrigine [see 4.3 CONTRAINDICATIONS]): Co-administration of suzetrigine with a strong inhibitor of CYP3A may increase exposure of suzetrigine and its metabolite.

Antiarrhythmics

Digoxin

A literature report has shown that co-administration of ritonavir (300 mg every 12 hours) and digoxin resulted in significantly increased digoxin levels. Caution should be exercised when co-administering ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.

Anticancer agents

Abemaciclib, Apalutamide, Dasatinib, Encorafenib, Ibrutinib, Ivosidenib, Neratinib, Nilotinib, Vincristine, Vinblastine

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

Co-administration of ibrutinib with ritonavir is not recommended due to expected increase in ibrutinib exposure that could potentially result in a serious risk of tumour lysis syndrome.

Co-administration of dasatinib with ritonavir should be avoided due to expected increase in dasatinib exposure. If the co-administration is unavoidable, close monitoring for toxicity and a dasatinib dose reduction should be considered (see dasatinib product information).

Co-administration of nilotinib with ritonavir should be avoided due to expected increase in nilotinib exposure. If the co-administration is unavoidable, close monitoring for the QT interval prolongation is recommended (see nilotinib product information).

Co-administration of encorafenib or ivosidenib with ritonavir could increase encorafenib or ivosidenib exposure, potentially increasing the risk of serious adverse events such as QT interval prolongation.

Concomitant use of ritonavir with apalutamide is contraindicated (see 4.3 CONTRAINDICATIONS).

Kinase inhibitors (also see anticancer agents above)

Fostamatinib

Co-administration of fostamatinib with ritonavir could increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia.

Anticoagulants

Warfarin

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

Rivaroxaban

Co-administration of ritonavir and rivaroxaban resulted in increased exposure of rivaroxaban which may lead to risk of increased bleeding.

Antidepressants

Trazodone

Concomitant use of ritonavir 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 ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Antifungals

Ketoconazole

Concomitant administration of ritonavir (500 mg q12h) and ketoconazole (200 mg every day) 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%, respectively. No dosage adjustment of ritonavir is necessary; however, doses of ketoconazole 200 mg/day or greater should be used with caution in combination with ritonavir and a decreased dosage may be considered.

Voriconazole

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

Fluconazole

In a study of concomitant administration of ritonavir (200mg four times a day) and fluconazole (200 mg/day) increases in mean ritonavir C_{max} and AUC were 14.5% and 12%, respectively. It is not clear if a clinically significant drug interaction would result with higher fluconazole doses.

Anti-infectives

Clarithromycin

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg q8h and clarithromycin 500 mg q12h 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 concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-[R]-hydroxy-clarithromycin was noted. Increases in clarithromycin concentrations may be significant when high doses are used or in patients with impaired renal function. Increases in clarithromycin

concentrations may be significant when high doses are used or in patients with impaired renal function. For patients with renal impairment the following dosage adjustment should be considered: for creatinine clearance (CLCR) of 30-60 mL/min the clarithromycin dose should be reduced by 50%, for CLCR < 30 mL/min the clarithromycin dose should be reduced by 75%. Doses of clarithromycin greater than 1 g/day should not be co-administered with ritonavir.

Sulfamethoxazole/trimethoprim

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 600 mg q12h 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.

Fusidic Acid

Co-administration of PIs, including ritonavir with fusidic acid is expected to increase fusidic acid, as well as the protease inhibitor concentration in plasma (see 4.3 CONTRAINDICATIONS).

Antimycobacterial

Rifabutin

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500mg q12h and rifabutin resulted in an approximate 4-fold and 35-fold increase in the AUC of rifabutin and its active metabolite 25-O-defacetyl rifabutin, respectively. The significance of this interaction has been confirmed in clinical trials. Studies to evaluate the effect of rifabutin on ritonavir levels are currently underway. Therefore concomitant use of ritonavir and rifabutin is contraindicated (see 4.3 CONTRAINDICATIONS).

Bedaquiline

Co-administration of bedaquiline with strong CYP3A4 inhibitors may increase the systemic exposure of bedaquiline, which could potentially increase the risk of bedaquiline-related adverse reactions. Bedaquiline must be used cautiously with ritonavir, only if the benefit of co-administration outweighs the risk.

Delamanid

No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, exposures of delamanid and a delamanid metabolite, DM-6705, were slightly increased. Exposure to the delamanid metabolite has been associated with QTc prolongation.

Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with lopinavir/ritonavir is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended.

Anxiolytic

Buspirone

Buspirone is primarily metabolised by CYP3A4. Concurrent administration of buspirone with drugs that potently inhibit CYP3A, such as ritonavir is expected to substantially elevate buspirone levels. When co-administered with ritonavir, a dose reduction or low dose of buspirone used cautiously is recommended.

Antipsychotics

Quetiapine

Caution should be exercised when ritonavir is co-administered with quetiapine. Due to CYP3A inhibition of ritonavir, concentrations of quetiapine are expected to increase, which may lead to quetiapine-related toxicities. When quetiapine is administered to patients who are receiving ritonavir, refer to the quetiapine product information for prescribing information.

Corticosteroids

Concomitant use of ritonavir and inhaled, injectable, or intranasal fluticasone, budesonide, triamcinolone or other glucocorticoids that are metabolised 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.

Caution should be used when co-administering ritonavir and fluticasone or any of the inhaled or intranasally administered glucocorticoids (e.g. budesonide). Consider alternative to fluticasone propionate or budesonide, particularly for long-term use. Concomitant use of ritonavir can greatly increase fluticasone propionate plasma concentration. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when ritonavir has been co-administered with inhaled or intranasally administered fluticasone propionate, or budesonide or injectable triamcinolone.

Fluticasone propionate

86% decrease in cortisol AUC resulted when fluticasone propionate was co-administered with ritonavir. Fluticasone propionate C_{max} was increased from 10.8-14.1 to 318 picogram/mL (mean) and AUC was increased from 4.2-18.8 picogram.h/mL to 3102.6 picogram.h/mL (mean) after concurrent administration of ritonavir and fluticasone nasal spray for 7 days.

Hepatitis C direct acting antiviral

Simeprevir

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

Glecaprevir/Pibrentasvir

Coadministration with ritonavir is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.

Disulfiram/Metronidazole

Ritonavir formulations contain alcohol, which can produce reactions when co-administered with disulfiram or other drugs that produce disulfiram-like reactions (eg. metronidazole). The effects of chronic alcohol ingestion on ritonavir metabolism have not been studied.

PDE5 inhibitors

Co-administration of ritonavir with avanafil is not recommended. Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction (ED) in patients receiving ritonavir. Co-administration of ritonavir with these drugs is expected to substantially increase their concentrations and may result in increased associated adverse events, such as hypotension, and prolonged erection.

Avanafil

A pharmacokinetic study demonstrated that concomitant administration of avanafil and ritonavir resulted in significant increases in avanafil AUC_{inf} and C_{max}. Co-administration of ritonavir with avanafil is not recommended.

Sildenafil

Use sildenafil for the treatment of ED with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Coadministration of ritonavir with sildenafil is expected to substantially increase sildenafil concentrations (11-fold increase in AUC) and may result in an increase in sildenafil-associated adverse events, including hypotension, syncope, visual changes, and prolonged erection. Concomitant use of sildenafil with ritonavir is contraindicated in PAH patients (see 4.3 CONTRAINDICATIONS).

Tadalafil

Ritonavir (200 mg twice daily) increased tadalafil 20 mg single dose exposure (AUC) by 124% with no change in C_{max}, relative to the values for tadalafil 20 mg alone. Use tadalafil for the treatment of ED with caution. It is recommended not to exceed 10 mg every 72 hour period, when used in combination with ritonavir. Increased monitoring for adverse events is recommended.

When tadalafil is used concomitantly with ritonavir in patients with PAH, refer to the tadalafil product information for prescribing information.

Vardenafil

Ritonavir (600 mg twice daily) co-administered with vardenafil 5 mg resulted in a 49-fold increase in vardenafil AUC and a 13-fold increase in C_{max}. Consequently, it is recommended not to exceed a single 2.5 mg vardenafil dose in a 72 hour period when used in combination with ritonavir.

Herbal Products

Patients on ritonavir should not use concomitantly 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 an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see 4.3 CONTRAINDICATIONS).

HMG-CoA Reductase Inhibitors

Concomitant use of ritonavir with simvastatin and lovastatin is contraindicated (see 4.3 CONTRAINDICATIONS). Caution should be exercised if HIV PIs, including ritonavir, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolised by the CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy including rhabdomyolysis may be increased when HIV PIs, including ritonavir, are used in combination with these drugs. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir coadministration. Consideration should be given both to the benefit of lipid lowering by the use of rosuvastatin in patients receiving ritonavir and the potential risks of this increased exposure to rosuvastatin when initiating and up titrating rosuvastatin treatment.

Microsomal triglyceride transfer protein (MTTP) inhibitor

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.

Bosentan

Co-administration of bosentan and ritonavir may increase steady-state bosentan C_{max} and AUC. Refer to the bosentan product information for prescribing information.

Hypnotics

Alprazolam

Coadministration of alprazolam with ritonavir resulted in a statistically significant decrease in mean alprazolam C_{max} values (16%) but not in mean AUC values (12%). Prolongation of the observed and self-related levels of sedation were noted with alprazolam and ritonavir co-administered compared to alprazolam alone, however, there was no statistically significant change in the extent of sedation (maximum score). Mild psychomotor impairment was confounded by a learning effect. These pharmacokinetic and pharmacodynamic results are inconsistent when considering the pharmacologic effect of alprazolam. These results were not considered clinically significant (see also 4.3 CONTRAINDICATIONS).

Oral Contraceptives or Patch Contraceptives

Concomitant administration of oral contraceptives and ritonavir markedly reduces the AUC and C_{max} of the oestradiol component. The AUC of ethinyloestradiol was reduced 40% and the C_{max} reduced 32% during concomitant dosing with ritonavir 600 mg q12h. Similarly, ritonavir may exert an effect on patch contraceptive. Dosage increase or alternate contraceptive measures should be considered.

Smoking Cessation Medications

Bupropion

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

Colchicine

Concentrations of colchicine are expected to increase when co-administered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir (see 4.3 CONTRAINDICATIONS). Refer to the colchicine product information for prescribing information.

Theophylline

The AUC of theophylline was reduced by 43% when co-administered with ritonavir. Increased dosage of theophylline may be required. Ritonavir C_{max} and AUC were reduced by 25% and 37% respectively after concurrent administration of theophylline for a two-week period.

Gonadotropin releasing hormone (GnRH) receptor antagonist

Elagolix

Co-administration of elagolix with ritonavir 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 ritonavir. Refer to the elagolix product information for dosing information with strong CYP3A4 inhibitors.

A systematic review of over 200 medications prescribed to HIV-infected patients was performed to identify potential drug interactions with ritonavir. Large dosage reductions (>50% reduction) may be required for some of these agents extensively metabolised by CYP3A.

These potential drug interactions are summarised in Tables 2 and 3.

Table 2: Effect on AUC and C_{max} of Co-administration of Ritonavir with Other Drugs

Effect on Ritonavir				
Drug	**Ritonavir dosage**	**n**	**AUC% (95→%CI)**	**C_{max} %(95→% CI)**
Didanosine 200 mg q.12h. 4 days	600 mg q.12h. 4 days	12	↔	↔
Fluconazole 400 mg day 1, then 200 mg daily 4 days	200 mg q.6h. 4 days	8	↑ 12% (5, 20%)	↑ 15% (7, 22%)
Zidovudine 200 mg	300 mg q.6h. 4 days	10	↔	↔

Effect on Ritonavir				
Drug	**Ritonavir dosage**	**n**	**AUC% (95→%CI)**	**C_{max} %(95→% CI)**
q.8h. 4 days				

↑ Indicates increase

↓ Indicates decrease

↔ Indicates no change

Table 3: Potential effects on Drugs Co-administered with ritonavir

Drug Category	**Representative Drugs by Potential Interaction Category**					
	Contraindicated Medications	**Large[1] ↑AUC[2] (CYP3A)**	**Moderate ↑AUC (CYP2D6)**	**Moderate ↑ or ↓AUC (CYP2C19)**	**Possible ↑AUC (unknown CYP or Non CYP Interactions)**	**Possible ↓AUC (glucuronidation)**
Analgesics, Narcotics	dextropropoxy-phene pethidine	alfentanil fentanyl methadone	hydrocodone oxycodone tramadol			codeine heroin hydromorphone morphine naloxone naltrexone
Analgesics, Nonsteroidal anti-inflammatory drugs				diclofenac flurbiprofen ibuprofen indomethacin	sulindac	ketoprofen ketorolac naproxen paracetamol
Antianginal	ranolazine					
Antiarrhythmics	amiodarone dronedarone encainide flecainide propafenone quinidine	lignocaine	disopyramide mexiletine		digoxin	
Antiasthmatic						theophylline*

Drug Category	Representative Drugs by Potential Interaction Category					
	Contraindicated Medications	**Large[1] ↑AUC[2] (CYP3A)**	**Moderate ↑AUC (CYP2D6)**	**Moderate ↑ or ↓AUC (CYP2C19)**	**Possible ↑AUC (unknown CYP or Non CYP Interactions)**	**Possible ↓AUC (glucuronidation)**
Antibiotic macrolide		erythromycin*	clarithromycin		clindamycin tinidazole	
Antibiotic Steroidal	fusidic acid					
Anticoagulants			warfarin			
Anticonvulsants		carbamazepine	clonazepam ethosuximide	phenytoin	phenobarbitone	sodium valproate lamotrigine
Antihistamine	astemizole terfenadine	loratadine			azatadine brom-pheniramine chlorpheniramine diphenhydramine mepyramine triprolidine	cyprohepatine
Antidepressants, tricyclic			amitriptyline clomipramine imipramine nortriptyline trimipramine		doxepin[4]	
Antidepressants, other		nefazodone sertraline	fluoxetine paroxetine venlafaxine	moclobemide	fluvoxamine	
Antidiarrhoeal						diphenoxylate loperamide
Antiemetics	cisapride		ondansetron		prochlorperazine[4] promethazine[4]	metoclopramide
Antifungals	voriconazole		itraconazole ketoconazole* miconazole			

Drug Category	Representative Drugs by Potential Interaction Category					
	Contraindicated Medications	**Large[1] ↑AUC[2] (CYP3A)**	**Moderate ↑AUC (CYP2D6)**	**Moderate ↑ or ↓AUC (CYP2C19)**	**Possible ↑AUC (unknown CYP or Non CYP Interactions)**	**Possible ↓AUC (glucuronidation)**
Antigout	colchicine					
Antihypertensives	alfuzosin	bosentan	triamterene	losartan	prazosin[4] terazosin[4]	
Antimycobacterial	rifabutin	rifampicin[3]				
Antipsycotics	blonanserin clozapine lurasidone pimozide					
Antiparasitics		quinine		proguanil	albendazole chloroquine mebendazole mefloquine metronidazole pentamidine praziquantel primaquine pyrimethamine thiabendazole	atovaquone
Antiulcer agents				lansoprazole omeprazole	cimetidine	
$Beta_2$ agonists (long acting)	salmeterol					
Beta-blockers			metoprolol pindolol timolol	propranolol	betaxolol[4]	labetalol
Calcium channel blockers	bepridil	amlodipine diltiazem felodipine nifedipine nimodipine verapamil				

Drug Category	Representative Drugs by Potential Interaction Category					
	Contraindicated Medications	**Large[1] ↑AUC[2] (CYP3A)**	**Moderate ↑AUC (CYP2D6)**	**Moderate ↑ or ↓AUC (CYP2C19)**	**Possible ↑AUC (unknown CYP or Non CYP Interactions)**	**Possible ↓AUC (glucuronidation)**
Cancer chemotherapy agents	apalutamide neratinib	abemaciclib encorafenib tamoxifen dasatinib ivoosidenib nilotinib	etoposide fostamatinib's metabolite R406 paclitaxel vinblastine vincristine	cyclo-phosphamide[3] ifosfamide[3]	apalutamide[4] daunorubicin[4] doxorubicin[4]	
Ergot alkaloids and derivatives	dihydro-ergotamine ergotamine ergometrine methyl-ergometrine	bromocriptine			ergonovine methysergide[4]	
GnRH receptor antagonist					elagolix[4]	
Corticosteroids/ steroid hormones		dexamethasone finasteride flutamide prednisone fluticasone*	anabolic steroids levonorgestrel medroxy-progesterone norethinderone prednisone testosterone			ethinyloestradiol*
Herbal products	St. John's Wort					
HCV Antivirals		glecaprevir/ pibrentasvir				

Drug Category	Representative Drugs by Potential Interaction Category					
	Contraindicated Medications	**Large[1] ↑AUC[2] (CYP3A)**	**Moderate ↑AUC (CYP2D6)**	**Moderate ↑ or ↓AUC (CYP2C19)**	**Possible ↑AUC (unknown CYP or Non CYP Interactions)**	**Possible ↓AUC (glucuronidation)**
HIV Antivirals		atazanavir darunavir fosamprenavir indinavir* saquinavir* tipranavir	maraviroc		nevirapine	didanosine zidovudine
Hypoglycaemics				glimepiride glipizide glibenclamide glyburide tolbutamide		
Hypolipidaemics	lomitapide simvastatin lovastatin	fluvastatin atorvastatin	pravastatin rosuvastatin		gemfibrozil	
Immuno-supressants		cyclosporin everolimus[4] tacrolimus sirolimus				
Neuroleptics			chlorpromazine haloperidol risperidone thioridazine		other phenothiazines	
PDE5 inhibitors	sildenafil (indicated for PAH)	sildenafil (indicated for ED) tadalafil varadenafil				

Drug Category	Representative Drugs by Potential Interaction Category					
	Contraindicated Medications	**Large[1] ↑AUC[2] (CYP3A)**	**Moderate ↑AUC (CYP2D6)**	**Moderate ↑ or ↓AUC (CYP2C19)**	**Possible ↑AUC (unknown CYP or Non CYP Interactions)**	**Possible ↓AUC (glucuronidation)**
Sedative/hypnotic	Clorazepate diazepam estazolam flurazepam midazolam triazolam zolpidem	clonazepam buspirone			other benzodiazepines zopiclone	lorazepam oxazepam propofol temazepam
Smoking cessation						bupropion
Stimulants/ Decongestants/ Antitussives			dextro-methorphan		methylphenidate	caffeine

1. Large = > 3x; Moderate = 1.5-3x
2. AUC = area under the plasma concentration time curve, a measure of drug exposure.
3. Undefined AUC increase
4. A possible increase in concentration is more likely when combined with ritonavir

* Clinical drug interaction study has been performed

Information for Patients

Patients should be informed that Norvir is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections.

Patients should be told that the long-term effects of ritonavir are unknown at this time. They should be informed that ritonavir therapy has not been shown to reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be informed to take Norvir every day as prescribed. Patients should not alter the dose or discontinue ritonavir without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the dose.

Since ritonavir interacts with some drugs when taken together, patients should be advised to report to their doctor the use of any other medications, including prescription and non- prescription drugs.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Oral treatment of male rats for 28 days prior to mating and of female rats for 14 days prior to mating had no effect on fertility; doses used achieved mean plasma AUC values of up to 61 (male) and 91 microgram.h/mL (female), approximately 23% (male) and 35% (female) of daily human exposure based on AUC.

Use in pregnancy

Pregnancy Category B3

No treatment-related malformations were observed when ritonavir was administered orally to pregnant rats or rabbits. Developmental toxicity observed in rats (early resorptions, decreased foetal body weight and ossification delays and developmental variations) occurred at a maternally toxic dosage of 75 mg/kg/day (approximately 17% of daily human exposure based on AUC). A slight increase in the incidence of cryptorchidism was also noted in rats given 35 mg/kg/day (approximately 13% of daily human exposure based on AUC). Developmental toxicity observed in rabbits (resorptions, decreased litter size and decreased foetal weights) also occurred at a maternally toxic dosage of 110 mg/kg/day (approximately 32% of daily human exposure based on AUC). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Antiretroviral (ART) Pregnancy Registry

The objective of this US based Registry is to detect any major birth defect on exposure to ART during pregnancy. Enrolment is voluntary, prospective (prior to outcome) and ongoing. Each year the Registry has enrolled approximately 1,300 pregnant women in the US (about 15% of HIV positive women who give birth to live infants annually) and approximately 200 pregnant women from other countries.

Based on the review of data through 31 July 2016, among women exposed to ritonavir-containing ART during first trimester the prevalence rate of birth defects per 100 live births (65 cases in 2983 enrolled) was 2.2% (95% CI 1.7, 2.8%). The prevalence rate of birth defects for exposure to ritonavir-containing ART during second/third trimester (97 cases in 3330 enrolled) was 2.9% (95% CI 2.4%, 3.5%). In a reference population in the US CDC's birth defects surveillance system (MACDP) the reported background rate of birth defects is 2.7%.

Use in lactation

Limited published data reports that ritonavir is present in human milk.

There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving ritonavir.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (Undesirable effects)

When co-administering ritonavir with other PIs, see the full product information for that protease inhibitor including adverse reactions.

Treatment-emergent adverse events that were related to study drug (possibly, probably or of unknown relationship) and were rated as moderate, severe or life-threatening intensity and occurred in > 2% of patients in a ritonavir treatment group are summarised in Table 4 for Study 245 and Table 5 for Study 247. Similar adverse events were reported in other trials for ritonavir.

Table 4: Percentage of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Occurring in > 2% of Patients Receiving Ritonavir in Study 245

Adverse Events	RTV + ZDV N = 116	RTV N = 117	ZDV N = 119
Body as a Whole			
Abdominal Pain	4.3	3.4	4.2
Asthenia	27.6	9.4	10.1
Headache	7.8	5.1	7.6
Malaise	4.3	1.7	3.4
Cardiovascular			
Vasodilation	2.6	1.7	0.8
Digestive			
Anorexia	7.8	0.9	3.4
Constipation	2.6	0.0	0.8
Diarrhoea	21.6	12.8	0.0
Flatulence	2.6	0.9	0.8

Nausea	46.6	23.1	24.4
Vomiting	22.4	12.8	12.6
Nervous			
Circumoral Paraesthesia	5.2	2.6	0.0
Dizziness	5.2	2.6	1.7
Insomnia	3.4	2.6	0.8
Paraesthesia	5.2	2.6	0.0
Peripheral Paraesthesia	0.0	6.0	0.0
Somnolence	2.6	2.6	0.0
Abnormal Thinking	2.6	0.0	0.8
Respiratory			
Pharyngitis	0.9	2.6	0.0
Skin and Appendages			
Sweating	3.4	2.6	1.7
Special Senses			
Taste Perversion	15.5	10.3	7.6

[1] Includes those adverse events at least possibly related to study drug or of unknown relationship and excludes concurrent conditions.

Table 5: Percentage of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Occurring in ≥ 2% of Patients Receiving Ritonavir in Study 247

Adverse Events	**RTV N = 541**	**Placebo N = 545**
Body as a Whole		
Abdominal Pain	7.0	3.1
Asthenia	14.2	5.3
Fever	4.4	2.2
Headache	6.3	4
Digestive		
Anorexia	6.1	2.0
Diarrhoea	18.3	6.1
Dyspepsia	4.8	0.7
Local Throat Irritation	2.6	0.2
Nausea	26.2	5.7
Vomiting	15.2	2.6

Adverse Events	RTV N = 541	Placebo N = 545
Musculoskeletal		
Myalgia	2.2	0.9
Nervous		
Circumoral Paraesthesia	5.9	0.2
Dizziness	3.3	1.1
Paraesthesia	2.0	0.2
Peripheral Paraesthesia	5.0	0.7
Somnolence	2.0	0.2
Skin and Appendages		
Rash	2.6	0.9
Special Senses		
Taste Perversion	5.4	1.7

[1] Includes those events at least possibly related to study drug or of unknown relationship and excludes concurrent conditions.

Adverse events occurring in less than 2% of patients receiving ritonavir in all phase II/phase III studies and considered at least possibly related or unknown relationship to treatment and of at least moderate intensity are listed below by body system.

Body as a Whole: Abdomen enlarged, accidental injury, allergic reaction, back pain, cachexia, chest pain, chills, facial oedema, facial pain, flu syndrome, hormone level altered, hypothermia, kidney pain, neck pain, neck rigidity, pain (unspecified), substernal chest pain and photosensitivity reaction.

Cardiovascular System: Haemorrhage, hypotension, migraine, palpitation, peripheral vascular disorder, postural hypotension, syncope and tachycardia.

Digestive System: Abnormal stools, bloody diarrhoea, cheilitis, cholangitis, colitis, dry mouth, dysphagia, eructation, oesophagitis, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal haemorrhage, gingivitis, hepatitis, hepatomegaly, ileitis, liver damage, liver function tests abnormal, mouth ulcer, oral moniliasis, pancreatitis, periodontal abscess, rectal disorder, tenesmus and thirst.

Endocrine System: Diabetes mellitus

Haemic and Lymphatic System: Anaemia, ecchymosis, leucopenia, lymphadenopathy, lymphocytosis and thrombocytopenia.

Metabolic and Nutritional Disorders: Avitaminosis, dehydration, oedema, glycosuria, gout, hypercholesteraemia, peripheral oedema and weight loss.

Musculoskeletal System: Arthralgia, arthrosis, joint disorder, muscle cramps, muscle weakness, myositis and twitching.

Nervous System: Abnormal dreams, abnormal gait, agitation, amnesia, anxiety, aphasia, ataxia, confusion, convulsion, depression, diplopia, emotional lability, euphoria, grand mal convulsion, hallucinations, hyperaesthesia, incoordination, libido decreased, nervousness, neuralgia, neuropathy, paralysis, peripheral neuropathy, personality disorder, tremor, urinary retention and vertigo.

Respiratory System: Asthma, dyspnoea, epistaxis, hiccup, hypoventilation, increased cough, interstitial pneumonia, lung disorder and rhinitis.

Skin and Appendages: Acne, contact dermatitis, dry skin, eczema, folliculitis, maculopapular rash, molluscum contagiosum, pruritus, psoriasis, seborrhoea, urticaria and vesiculobullous rash.

Special Senses: Abnormal electro-oculogram, abnormal electroretinogram, abnormal vision, amblyopia/blurred vision, blepharitis, ear pain, eye pain, hearing impairment, increased cerumen, iritis, parosmia, photophobia, taste loss, tinnitus, uveitis and visual field defect.

Urogenital System: Dysuria, haematuria, kidney calculus, kidney failure, nocturia, penis disorder, polyuria, pyelonephritis, urethritis and urinary frequency.

Marked Laboratory Determinations

The incidence of extreme laboratory changes from baseline to the most extreme value during treatment (from ACTG grade 0 to grade 3 or 4; or from ACTG grade 1 to grade 4) is summarised in Table 6 for Study 245 and Study 247. ACTG toxicology grades were used except for triglycerides (grade 0 < 4.51 mmol/L, grade 1 = 4.51 - 11.29 mmol/L, grade 2 = 11.3 - 16.93 mmol/L, grade 3 = 16.94 - 22.58 mmol/L, grade 4 > 22.58 mmol/L).

Table 6: Percentage of Patients, by Treatment Group, with Marked[1] Chemistry and Haematology Laboratory Value Abnormalities

		Study 245 Naive Patients			Study 247 Advanced Patients	
Variable	**Limit**	**RTV+ ZDV**	**RTV**	**ZDV**	**RTV**	**Placebo**
CHEMISTRY	**HIGH**					
Glucose	>13.8 mmol/L	2.0	-	-	0.4	1.1

		Study 245 Naive Patients			Study 247 Advanced Patients	
Variable	**Limit**	**RTV+ ZDV**	**RTV**	**ZDV**	**RTV**	**Placebo**
Uric Acid	>0.7 mmol/L	-	-	-	3.6	0.2
Creatinine	>0.3 mmol/L	-	-	-	0.2	0.2
Potassium	>6.0 mmol/L	-	-	-	0.4	0.2
Chloride	>122 mmol/L	-	0.9	-	-	-
Total Bilirubin	>61 µmol/L	-	-	-	1.2	0.2
Alkaline Phosphatase	>550 U/L	-	0.9	-	1.4	1.7
AST	>180 U/L	2.9	6.5	1.7	3.8	4.3
ALT	>215 U/L	3.9	5.6	2.6	6.1	2.6
GGT	>300 U/L	2.0	2.8	0.9	14.7	6.7
LDH	>1170 U/L	-	-	-	1.0	0.2
Triglycerides	>16.9 mmol/L	1.0	2.8	-	10.1	0.2
Triglycerides Fasting	>16.9 mmol/L	2.1	1.4	-	7.9	0.4
CPK	>1000 U/L	7.0	7.5	7.1	8.6	4.5
Amylase	>2 x ULN[1]	-	0.9	-	0.2	-
Cholesterol	12.93mmol/L	-	-	-	-	-
Cholesterol Fasting	12.93mmol/L	-	-	-	-	-
CHEMISTRY	**LOW**					
Albumin	<20 g/L	-	-	-	0.2	0.6
Sodium	<123 mmol/L	-	-	-	0.2	-
Potassium	<3.0 mmol/L	-	0.9	-	2.0	1.1
Chloride	<84 mmol/L	-	0.9	-	-	0.4
Magnesium	<1.0 mmol/L	-	-	-	0.4	0.4
Calcium	<3.45 mmol/L	-	-	-	1.2	0.9
HAEMATOLOGY	**LOW**					
Haemoglobin	<80 g/L	-	-	-	2.8	2.4
Haematocrit	<0.3	2.0	-	-	11.7	16
RBC	$<3.0x10^{12}$/L	1.0	-	1.7	14.9	19.7
WBC	$<2.5x10^{9}$/L	-	-	3.5	25.1	51.4
Platelet Count	$<2.0x10^{9}$/L	-	-	-	0.4	0.6
Neutrophils	$<0.5x10^{9}$/L	-	-	-	4	6.9
HAEMATOLOGY	**HIGH**					

		Study 245 Naive Patients			Study 247 Advanced Patients	
Variable	**Limit**	**RTV+ ZDV**	**RTV**	**ZDV**	**RTV**	**Placebo**
WBC	>25x10^9/L	-	-	-	1.6	0.7
Neutrophils	>20x10^9/L	-	-	-	1.8	0.9
Eosinophils	>1.0x10^9/L	-	1.9	0.9	1.8	2.6
Prothrombin Time	>1.5xULN[1]	1.0	-	-	1.0	1.3

[1] ULN = upper limit of the normal range

- Indicates no events reported

Post-Marketing Experience

Nervous system disorders: There have been post-marketing reports of seizure. A cause and effect relationship has not been established.

Endocrine disorders: Hyperglycaemia has been reported in individuals with and without a known history of diabetes. A 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.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis.

Renal and urinary disorders: Nephrolithiasis

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems

4.9 Overdose

Acute Overdosage

Human Overdose Experience: Human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg/day for two days. The patient reported paraesthesias which resolved after the dose was decreased.

A post-marketing case of renal failure with eosinophilia has been reported with ritonavir overdose.

Management of Overdosage

Treatment of overdose with ritonavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with ritonavir. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Since ritonavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Ritonavir is an orally active peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. Inhibition of HIV protease renders the enzyme incapable of processing the gag-pol polyprotein precursor which 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 some inhibitory activity against human aspartyl proteases. Studies of ritonavir in animals to date have not used doses which resulted in systemic ritonavir exposures significantly greater than those expected in humans treated at the oral dose.

Studies which measured direct cell toxicity of ritonavir on several cell lines showed no direct toxicity at concentrations up to 25 microM, with a resulting in-vitro therapeutic index of at least 1000.

Antiviral activity *in-vitro*

The activity of ritonavir was assessed *in-vitro* in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes. EC_{50} values (50% inhibitory concentrations of HIV-1 strains) were generally uniform but ranged from 4 to 153 nM in peripheral blood lymphocytes. The average EC_{50} value was 22 nM. In HIV-1 infected MT4 cells, ritonavir in combination with either zidovudine or didanosine had at least additive activity.

Resistance

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 82 and 84.

Some patients receiving ritonavir monotherapy developed HIV strains with decreased susceptibility to drug. Serial genotypic and phenotypic analysis indicated that susceptibility to ritonavir declined in an ordered and stepwise fashion. Initial mutations occurred at position 82 from wildtype valine to usually alanine or phenylalanine (V82A/F). Viral strains isolated in-vitro without a change at codon 82 did not have decreased susceptibility to ritonavir. Subsequent mutations occurred, in descending order, at position 54 (wildtype isoleucine to valine, I54V), position 71 (wildtype alanine to valine or threonine, A71V/T), and position 36 (wildtype isoleucine to leucine, I36L).

Of 18 patients for which both phenotypic and genotypic analysis were performed on free HIV-1 virus isolated from plasma, 12 showed reduced susceptibility *in-vitro*. All 18 patients possessed one or more mutations in the viral protease gene.

Cross-Resistance

Cross-resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. Zidovudine-resistant HIV isolates retain full susceptibility to ritonavir. Viral clones containing mutations conferring decreased susceptibility to ritonavir (V82A/F, I54V, A71V/T and I36L) retained susceptibility to saquinavir. Similarly, viral clones containing mutations with reduced susceptibility to saquinavir (L90M or G48V) retained susceptibility to ritonavir. The concomitant use of saquinavir or other PIs with ritonavir has not been fully assessed in humans. The effect of ritonavir therapy on the activity of subsequently administered PIs is unknown. 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 5 patients were also tested for cross-resistance to VX-478 and nelfinavir; isolates from 2 patients had a decrease in susceptibility to nelfinavir (12 -14 fold) and none to VX-478.

Effects on Electrocardiogram

QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 45 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) difference in QTcF from placebo was 5.5 (7.6) 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 (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Clinical trials

The activity of ritonavir as monotherapy or in combination with other antiretroviral agents has been evaluated in two double-blind, randomised trials in a total of 1446 patients. Ritonavir therapy in combination with zidovudine and zalcitabine was also evaluated in a single group study in 32 patients. The clinical studies reported here were all conducted using ritonavir liquid.

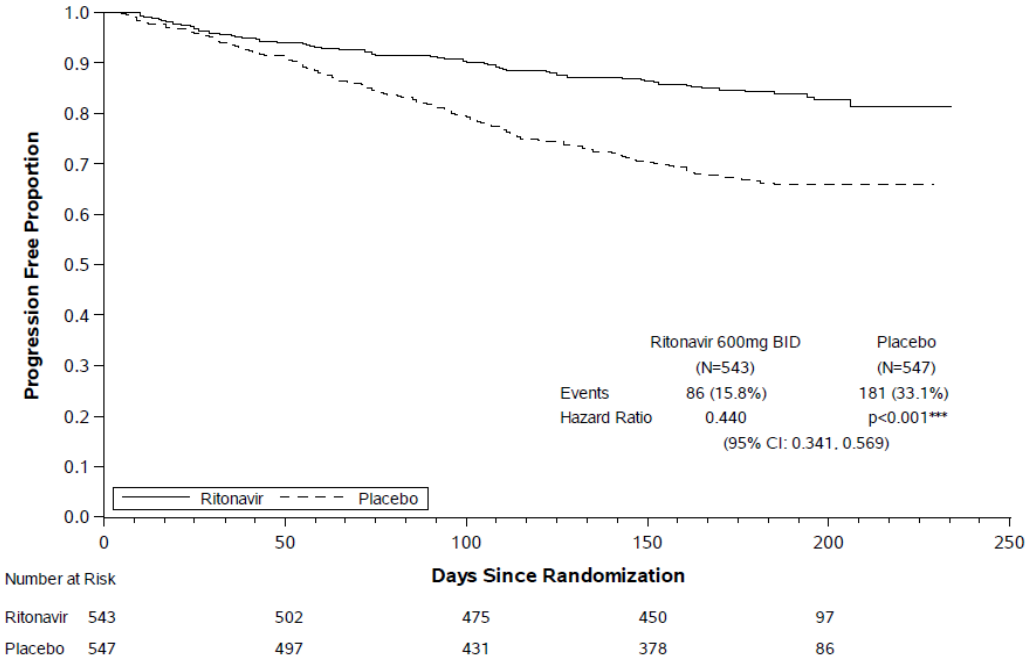
Advanced Patients with Prior Antiretroviral Therapy

Study 247 is a randomised, double-blind trial conducted in patients with at least nine months of prior nucleoside analogue antiretroviral therapy and baseline CD4 cell counts < 100 cells/microlitre. Ritonavir 600 mg twice daily or placebo was added to each patient's baseline antiretroviral therapy regimen, which could have consisted of up to two approved antiretroviral agents. The study accrued 1090 patients, with mean baseline CD4 cell count at study entry of 32 cells/microlitre. Median duration of follow-up was 6 months. A preliminary analysis demonstrated a statistical and clinically significant reduction in mortality and clinical progression of HIV disease (defined as a new AIDS-defining illness, according to WHO classification, or selected disease recurrences - pneumocystis pneumonia, oesophageal candidiasis and chronic herpetic ulcer (Table 7 and Figure 1).

Table 7: Disease Progression or Death

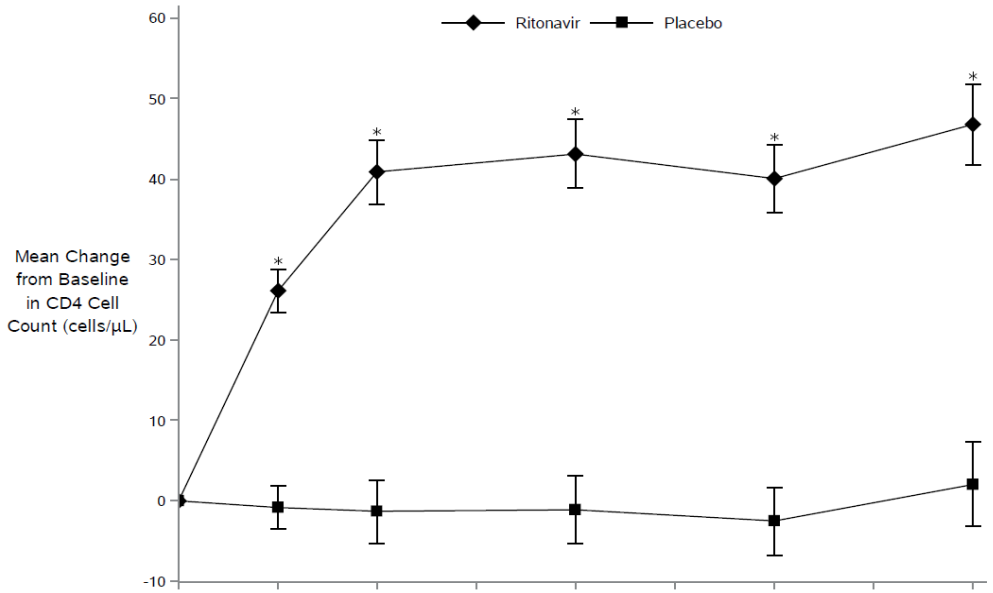
All Events Postrandomisation			
Ritonavir	86 events/543 patients	15.8%	p < 0.001
Placebo	181 events/547 patients	33.1%	
All Deaths Postrandomisation			
Ritonavir	26 deaths/543 patients	4.8%	p = 0.021
Placebo	46 deaths/ 547 patients	8.4%	

Figure 1: Time to Disease Progression or Death in Study 247



In addition, analysis of mean CD4 cell count changes from baseline over the first 16 weeks of study for the first 211 patients enrolled (mean baseline CD4 cell count = 29 cells/microlitre) showed that ritonavir was associated with larger increases in CD4 cell counts than was placebo (see Figure 2).

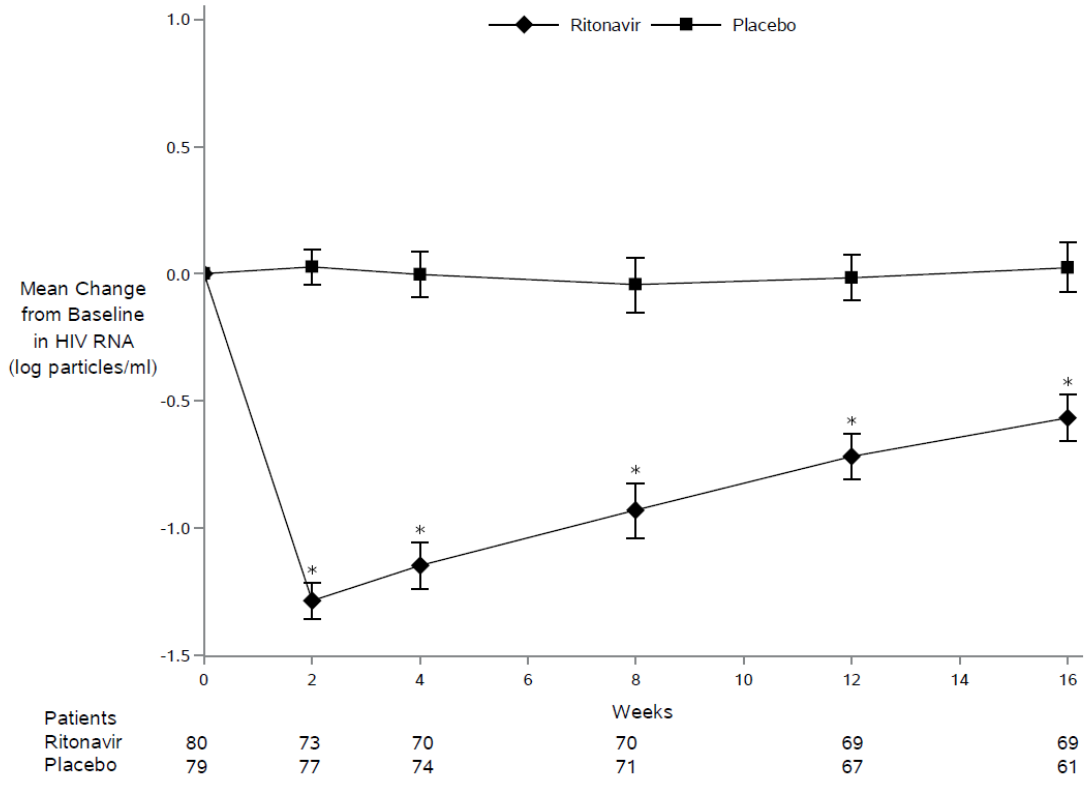
Figure 2: Mean CD4 Count Changes (cells/microL) From Baseline in Study 247



* Statistically significantly superior to the placebo group ($p \leq 0.001$).

Figure 3 summarises the mean changes from baseline in log HIV RNA levels for Study 247.

Figure 3: Mean change from Baseline in Log HIV RNA levels[1] in Study 247



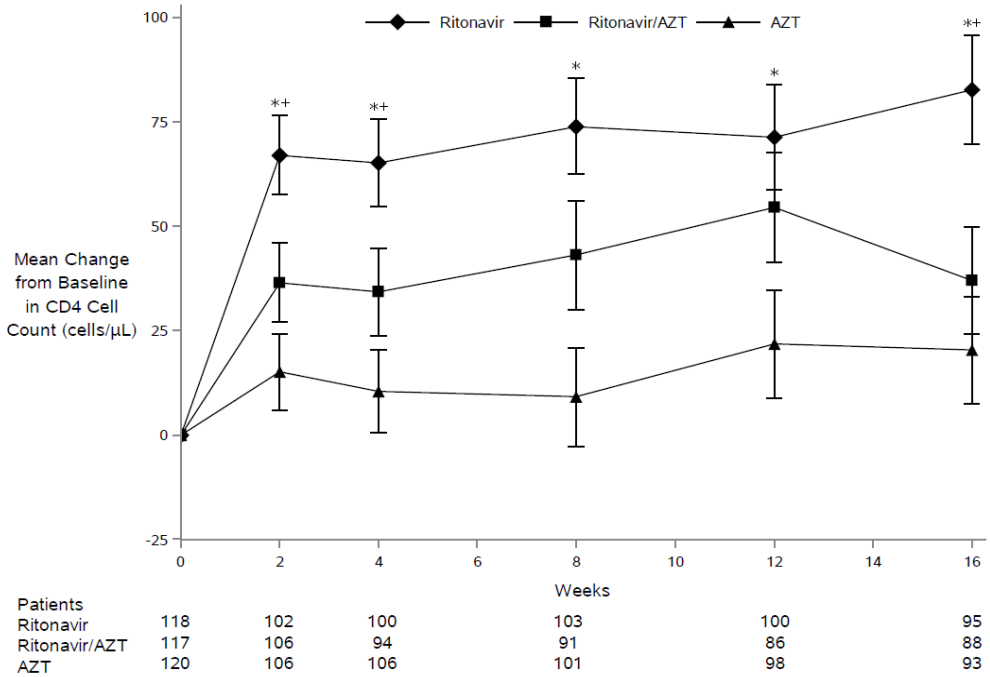
* Statistically significantly superior to the placebo group ($p \leq 0.001$).

[1] The clinical significance of changes in HIV RNA measurement has not been established.

Patients Without Prior Antiretroviral Therapy

In ongoing Study 245, 356 antiretroviral-naive patients (mean baseline CD4 = 364) were randomised to receive either ritonavir 600 mg twice daily, zidovudine 200 mg three times a day or a combination of these regimens. In analyses of average CD4 cell count changes over 16 weeks, both ritonavir monotherapy and combination therapy produced greater increases in CD4 cell count than did zidovudine monotherapy (see Figure 4). The CD4 cell count increases for ritonavir monotherapy were larger than the increases for combination therapy.

Figure 4: Mean CD4 Count Changes (cells/mm^3) From Baseline in Study

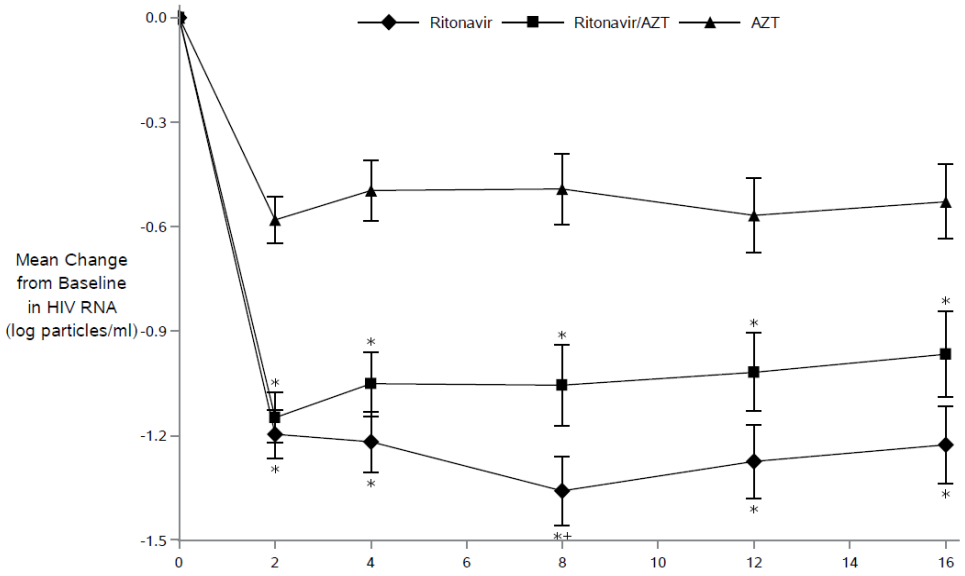


Patients						
Ritonavir	118	102	100	103	100	95
Ritonavir/AZT	117	106	94	91	86	88
AZT	120	106	106	101	98	93

* Statistically significantly superior to the AZT group ($p \leq 0.05$).
\+ Statistically significantly superior to the combination group ($p \leq 0.05$).

Figure 5 summarises the mean changes from baseline in log HIV RNA levels for Study 245.

Figure 5: Mean change from Baseline in Log HIV RNA Levels in Study



Patients						
Ritonavir	118	106	101	93	90	78
Ritonavir/AZT	116	102	91	71	70	58
AZT	121	110	102	93	92	81

* Statistically significantly superior to the AZT group ($p \leq 0.05$).
\+ Statistically significantly superior to the combination group ($p \leq 0.05$).

Combination Therapy with Norvir®, Zidovudine and Zalcitabine in Antiretroviral-Naive Patients

In Study 208, 32 antiretroviral-naive patients initially received ritonavir 600 mg twice daily monotherapy. Zidovudine 200 mg three times a day and zalcitabine 0.75 mg three times a day were added after 14 days of ritonavir monotherapy. Results of combination therapy for the first 20 weeks of this study show median increases in CD4 cell counts from baseline levels of 83 to 106 cells/microlitre over the treatment period. Mean decreases from baseline in HIV RNA particle levels ranged from 1.69 to 1.92 logs.

5.2 Pharmacokinetic properties

A single dose pharmacokinetic study in HIV positive fasting male subjects was conducted with oral administration of 100 mg, 200 mg, 400 mg, 600 mg, 800 mg or 1000 mg of ritonavir. AUC ranged from 3.92 to 123 microgram.h/mL. The pharmacokinetics of ritonavir were dose-dependent; more than proportional increases in the AUC and C_{max} were reported with increasing dose. The time to maximum concentration (T_{max}) remained constant at approximately 3 hours with increasing dose. Renal clearance averaged less than 0.1 L/h and was relatively constant, throughout the dosage range.

The pharmacokinetics of ritonavir during multiple dose regimens were studied in non-fasting HIV positive adult volunteers. Upon multiple dosing, ritonavir accumulation is slightly less than predicted from a single dose possibly 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 stabilise by the end of 2 weeks. At steady state with a 600 mg twice daily dose, C_{max} and C_{trough} values of 11.2 and 3.7 microgram/mL were observed, respectively. The $t_{1/2}$ of ritonavir was approximately 3 to 5 hours. The steady-state apparent clearance in patients treated with 600 mg BD averaged 8.8 ± 3.2 L/h (Table 8). Dosing individualisation is not required.

Ritonavir pharmacokinetic parameters were not significantly associated with body weight or lean body mass.

With multiple dosing under non-fasting conditions, there is a diurnal effect on the pharmacokinetics of ritonavir with later and lower peak concentrations occurring after evening doses. This diurnal variation may be related to absorption differences but is not considered to be clinically significant.

Absorption

After oral administration, peak concentrations of ritonavir are achieved approximately 2 hours and 4 hours after dosing under fasting and non-fasting conditions, respectively. There is no parenteral formulation of ritonavir and therefore the absolute bioavailability has not been determined in man. Peak concentration and extent of absorption of ritonavir from the soft capsule formulation are not significantly affected by a low fat meal. The affect of a high fat meal on absorption of ritonavir from the soft capsule has not been assessed. When the liquid formulation was given under fasting conditions, peak ritonavir concentrations increased 28%, but the extent of absorption was not significantly affected relative to non-fasting conditions (light meal). Dilution of the liquid formulation with 240 mL of chocolate milk or ENSURE® does not significantly affect the extent and rate of ritonavir absorption. Grapefruit juice would not be expected to affect the plasma concentration of ritonavir. The effects of antacids on the absorption of ritonavir have not been studied (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.2 DOSE AND METHOD OF ADMINISTRATION).

Plasma concentrations of ritonavir after administration of a single 100 mg dose were not significantly different to the 100 mg soft gelatin capsule in healthy adults under fed conditions. Food slightly decreases the bioavailability of the Norvir tablet. Mean decreases of 20-23 % in ritonavir AUC and C_{max} were seen when a single 100 mg dose of Norvir tablet was administered with a moderate fat meal (857 kcal, 31 % calories from fat) or a high fat meal (907 kcal, 52 % calories from fat).

Distribution

The apparent volume of distribution (V_β/F) of ritonavir is approximately 0.41 ± 0.25 L/kg after a single 600 mg dose. Ritonavir is 98-99 % bound to plasma proteins, primarily to albumin and α1-acid glycoprotein. Plasma protein binding is constant over the concentration range of 1-100 microgram/mL. Ritonavir penetrates poorly into red blood cells with a blood/plasma ratio of 0.14. In the rat, concentrations of ritonavir in lymphatic tissue and plasma are comparable. Ritonavir

penetrates minimally into the rat brain and is not expected to be excreted in human milk due to its low free fraction.

Metabolism

Nearly all of the plasma radiolabel after a single oral 600 mg dose of radiolabeled ritonavir was attributed to unchanged ritonavir. Four ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent drug; however, the concentration of the metabolite in plasma are low. The AUC of the M-2 metabolite was approximately 3 % of the AUC of parent drug. Studies utilising human liver microsomes have demonstrated that CYP3A4 is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formulation of M-2. The metabolites are principally eliminated in the faeces.

Excretion

Studies with radiolabeled drug have demonstrated that 11.3 % and 86.4 % of the radiolabel are recovered in urine and faeces, respectively. Less than 4 % of the ritonavir dose is excreted unchanged in the urine, with 11.3 % of the dose excreted into the urine as parent drug plus metabolites.

Special Populations

Geriatric

No age related pharmacokinetic differences have been observed in adult patients (18 to 63 years). Ritonavir pharmacokinetics have not been studied in older patients.

Paediatric

Ritonavir has not been studied in patients below the age of 12 years.

Gender

A study of ritonavir pharmacokinetics in healthy males and females showed no statistically significant differences in the pharmacokinetics of ritonavir.

Ethnicity

Pharmacokinetic differences due to ethnic background have not been identified.

Renal Impairment

Ritonavir pharmacokinetics have not been studied in patients with renal insufficiency however since renal clearance is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency. Ritonavir is highly protein bound (98-99 %) and will not be significantly removed from the blood in patients undergoing haemodialysis or peritoneal dialysis.

Hepatic Impairment

Ritonavir pharmacokinetics have not been studied in subjects with hepatic insufficiency; therefore, caution should be exercised if this drug is administered to patients with impaired hepatic function (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Drug-Drug Interactions

Agents which increase CYP3A activity (e.g., phenobarbital, carbamazepine, phenytoin, dexamethasone, rifampicin and rifabutin) would be expected to increase the clearance of ritonavir. Tobacco use is associated with an 18 % decrease in the AUC of ritonavir (See 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Table 8: Ritonavir Pharmacokinetic Characteristics

Parameter	n	Values (Mean ± SD)
C_{max} SS†	10	11.2 ± 3.6 microgram/mL
C_{trough} SS†	10	3.7 ± 2.6 microgram/mL
$V_\beta/F_§$	91	0.41 ± 0.25 L/kg
$t_{1/2}$		3 - 5 h
CL/F§	10	8.8 ± 3.2 L/h
CL/F§	91	4.6 ± 1.6 L/h
CL_r	62	< 0.1 L/h
RBC/Plasma Ratio		0.14
Percent Bound‡		98 % to 99 %

† SS = steady state: patients taking ritonavir 600 mg q12h.

§ Single ritonavir 600 mg dose.

‡ Primarily bound to human serum albumin and alpha-1 acid glycoprotein over the ritonavir concentration range of 0.01 to 30 microgram/mL.

5.3 Preclinical safety data

Genotoxicity

Ritonavir showed no mutagenic potential in a series of assays for gene mutations *(S. typhimurium, E. coli* and mouse lymphoma cells) and chromosomal damage (mouse micronucleus assay *in-vivo* and human lymphocytes *in-vitro*).

Carcinogenicity

Two-year carcinogenicity studies have been conducted in rodents, at ritonavir dietary levels of 50, 100 and 200 mg/kg/day in mice, and 7, 15 and 30 mg/kg/day in rats. In male mice there was a dose-dependent increase in the incidence of hepatocellular adenomas, and adenomas and carcinomas combined, both reaching statistical significance only at the high-dose. In female mice there were small, statistically significant increases in these tumour incidences only at the high-dose. In rats, there were no tumourigenic effects. Ritonavir exposures at the high-doses were, in mice, approximately 15 % (males) or 32 % (females), and, in rats, approximately 2 % (males) or 3 % (females) of daily (fasted) human exposure based on AUC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Refer to 2 QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store Norvir film-coated tablets at below 30°C. Store in the original bottle in order to protect from moisture.

6.5 Nature and contents of container

Available in 30 tablet bottle.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

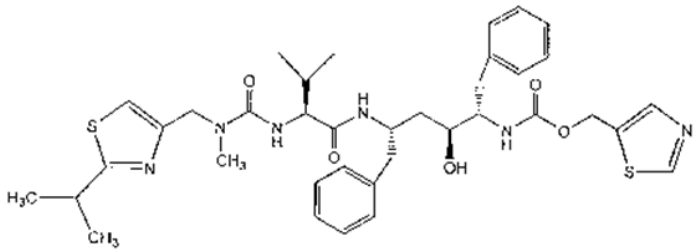
6.7 Physicochemical properties

Ritonavir is a white to light tan powder. Ritonavir has a bitter metallic taste. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

Chemical structure

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl) -1-[2-(1-methylethyl)-4-thiazolyl]-3, 6-dioxo-8, 11-bis (phenylmethyl)-2, 4, 7, 12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)].

Ritonavir has the following structural formula:



CAS number

155213-67-5

Molecular Weight

720.95

Molecular Formula

$C_{37}H_{48}N_6O_5S_2$

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

15 February 2010

10 DATE OF REVISION

13 March 2026

Summary table of changes

Section Changed	Summary of new information
4.3	Addition of Suzetrigine for concomitant use of ritonavir
4.5	Addition of suzetrigine drug-drug interaction with ritonavir.
10	Copyright statement and other minor editorial updates

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