NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Norvir® 100 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg ritonavir. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White film-coated oval tablets debossed with the corporate Abbott "A" logo and the Abbott-Code “NK”.

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 section 5.1 Pharmacodynamic properties).

4.2 Dose and method of administration

General Dosing Guidelines

Prescribers should consult the full product information and clinical study information of protease inhibitors if they are co-administered with a reduced dose of ritonavir.

The recommended dose of NORVIR is 600 mg (six tablets) twice daily by mouth, and should be given with food.

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

Paediatric population

Ritonavir has not been studied in patients below the age of 12 years; hence the safety and efficacy of ritonavir in children below the age of 12 have not been established.

4.3 Contraindications

NORVIR is contraindicated in patients with known hypersensitivity to ritonavir or any of the excipients listed in section 6.1.

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

In vitro studies have demonstrated that ritonavir is a potent inhibitor of many cytochrome P450-mediated biotransformations. Based primarily on literature review, ritonavir is expected to produce large increases in the plasma concentrations of medicines metabolised by cytochrome P450. Co-administration of NORVIR is contraindicated with the medicines 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	Potential for hypotension.
Antianginal	ranolazine	Potential for serious and/or life-threatening reactions.
Antiarrhythmics	amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine	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 hepatotoxicity.
	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.
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 co-administration of ritonavir and dihydroergotamine, ergometrine, ergotamine, methylergometrine.
GI Motility Agent	cisapride	Potential for cardiac arrhythmias.
Herbal Product	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 protease inhibitors.

Drug Class	Drugs within Class that are Contraindicated with Ritonavir	Clinical comments
Lipid-modifying agents 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.
NSAIDs	piroxicam	Increased plasma concentrations of piroxicam thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from this agent.
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 analgesics	pethidine, dextropropoxyphene	Increase in plasma concentration resulting in toxicity associated with pethidine and dextropropoxyphene.

Drug Class	Drugs within Class that are Contraindicated with Ritonavir	Clinical comments
Sedative/hypnotics	clorazepate, diazepam, estazolam, flurazepam, oral 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 section 4.5 Interaction with other medicines for co-administration of sildenafil in patients with erectile dysfunction		

4.4 Special warnings and precautions for use

When co-administering ritonavir with other protease inhibitors, see the full product information for that protease inhibitor including special warnings and precautions for use.

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 Impairment

Ritonavir is principally metabolised and eliminated by the liver. Therefore, caution should be exercised if it is administered to patients with moderate to severe hepatic impairment.

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 5). 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 and a causal relationship between protease inhibitor therapy and those events has not been established. 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 patients with haemophilia type A and B treated with ritonavir and other protease inhibitors, there have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has been postulated, although a mechanism of action has not been established.

Resistance/Cross Resistance

The potential for HIV cross-resistance between protease inhibitors has not been fully assessed. It is unknown what effect ritonavir will have on the activity of concordant or subsequent protease inhibitors (see section 5 Pharmacological 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-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.

PR Interval Prolongation

Ritonavir 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 medicines known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving ritonavir. NORVIR should be used with caution in such patients.

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 alone or 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 section 4.5 Interaction with other medicines and other forms of interaction: HMG-CoA Reductase Inhibitors for additional information on potential drug interactions with ritonavir and HMG CoA reductase inhibitors.

Effect on Laboratory Tests

Ritonavir has been associated with alterations in cholesterol, triglycerides, AST, ALT, GGT, CPK and uric acid (see also Hepatic Impairment and Lipid Elevation, above). 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 Interaction with other medicines and other forms of interaction

When co-administering ritonavir with other protease inhibitors, 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 medicines that may interact with Norvir. The healthcare provider should consult appropriate references for comprehensive information.

Since NORVIR 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.

Effects on ritonavir

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

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

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 cytochrome P450 (CYP) isoforms with the following rank order: CYP3A4 > CYP2D6 > CYP2C9 > CYP2C19 >> CYP2A6, CYP1A2, CYP2E1. There is evidence that ritonavir may induce glucuronosyl transferase, CYP1A2, CYP2C9 and CYP2C19 enzymes; thus, decreased plasma concentrations of the other drug and loss of therapeutic effects during ritonavir co-administration may signify the need for dosage alteration of these agents.

In addition to the drugs listed in section 4.3 Contraindications, Table 3 summarises some commonly prescribed drugs, categorised by the predicted magnitude of interaction that could result if co-

administered with ritonavir. Co-administration of ritonavir and drugs primarily metabolised by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects. Careful monitoring of therapeutic and adverse effects is recommended when these drugs are concomitantly administered with ritonavir. Dosage reductions may be required for those agents extensively metabolised by CYP3A.

Cardiac and neurologic events have been reported when ritonavir has been co-administered with disopyramide, mexiletine, nefazodone or fluoxetine (see also Table 2). The possibility of a drug interaction cannot be excluded.

Anti-HIV Agents

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Didanosine

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 600 mg every 12 hours and didanosine (ddI) 200 mg every 12 hours resulted in a reduction of the ddI steady-state C_{max} and 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. (See also Table 2.)

Zidovudine

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 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 ritonavir pharmacokinetics. Dose alteration of AZT during concomitant ritonavir therapy should not be necessary. (See also Table 2.)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

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 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 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 (PI's)

Saquinavir

A pharmacokinetic study demonstrated that ritonavir extensively inhibits the metabolism of saquinavir, resulting in greatly increased saquinavir plasma concentrations. Following approximately four weeks of a combination regimen of saquinavir hard gel capsules (400 or 600 mg twice daily) and ritonavir (400 or 600 mg twice daily) 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 daily without ritonavir. When used in combination therapy for up to 24 weeks, doses greater than 400 mg twice daily of either ritonavir or saquinavir were associated with an increase in adverse

events. Plasma exposures achieved with saquinavir mesylate hard gel capsules (400 mg twice daily) and ritonavir (400 mg twice daily) are similar to those achieved with saquinavir soft gel capsules (400 mg twice daily) and ritonavir (400 mg twice daily). See also section 4.4 Special warnings and precautions for use: Lipid Elevation.

Saquinavir and ritonavir should not be given together with rifampicin due to the risk of severe hepatotoxicity (presenting as increased transaminases) if the three drugs are given together. (See also Table 2.)

Simeprevir

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

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. In healthy subjects, 200 mg to 400 mg of ritonavir twice daily given with a single 400 mg to 600 mg indinavir dose increased the indinavir AUC by 185% to 475%, C_{max} 21% to 110%, and C_{min} 11- to 33-fold, relative to 400 mg to 600 mg indinavir given alone. Concomitant administration of 400 mg ritonavir and 400 mg indinavir twice daily with a meal yielded a similar indinavir AUC, a 4-fold increase in C_{min} and a 50% to 60% decrease in C_{max} as compared to those resulting from administration of indinavir 800 mg three times daily under fasting conditions. Co-administration of ritonavir with indinavir will result in increased indinavir serum concentrations. There are limited safety or efficacy data available on the use of this combination in patients. The risk of nephrolithiasis may be increased when doses of indinavir equal to or greater than 800 mg twice daily are given with ritonavir. Adequate hydration and monitoring of the patients is warranted.

Nelfinavir

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

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.

CCR5 Antagonists

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 prescribing information for maraviroc.

Integrase Inhibitors

Raltegravir

A pharmacokinetic study showed that co-administration of ritonavir 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.

Other Drugs

$Alpha_1$-Adrenoreceptor Antagonist

Alfuzosin

Based on results of a drug interaction study with ketoconazole, another potent inhibitor of CYP3A4, and alfuzosin, a significant increase in alfuzosin exposure is expected in the presence of ritonavir (600 mg twice daily). Concomitant use of Norvir with alfuzosin is contraindicated (see section 4.3).

Analgesic:

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.

Methadone

Co-administration of ritonavir with methadone is expected to decrease methadone concentrations. A dosage increase of methadone may be considered.

Antiarrhythmic

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, Venetoclax, 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 venetoclax or ibrutinib with ritonavir could increase venetoclax or ibrutinib exposure, potentially resulting in a serious risk of tumor lysis syndrome. 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 Norvir with apalutamide or neratinib is contraindicated (see section 4.3).

Anticoagulants

Warfarin

In a pharmacokinetic study, multiple-dose ritonavir (400 mg twice daily) differentially affected the single-dose pharmacokinetics of warfarin enantiomers. S-warfarin AUC was not statistically significantly, but variably affected by ritonavir. The less potent R-warfarin AUC was decreased by a

mean of 33% during ritonavir co-administration. The net effect of ritonavir co-administration on the anticoagulant effect of warfarin is difficult to predict based upon these pharmacokinetic results. Anticoagulant metabolism may be induced, resulting in decreased concentrations of warfarin. Initial frequent monitoring of the international normalised ratio (INR) during ritonavir and warfarin co-administration is indicated.

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.

Desipramine

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg every 12 hours and a single dose of desipramine 100 mg resulted in a 145% mean increase in the AUC of desipramine. Dosage reduction of desipramine should be considered in patients taking the combination.

Antifungals

Fluconazole

In a study of concomitant administration of ritonavir (200 mg four times a day) and fluconazole (200mg/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. (See also Table 2.)

Ketoconazole

Concomitant administration of ritonavir (500 mg every 12 hours) 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 co-administration of ritonavir 400 mg every 12 hours decreased voriconazole steady-state AUC by an average of 82%. Concomitant use of Norvir with voriconazole is contraindicated (see section 4.3).

Anti-infectives

Clarithromycin

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg q8h 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 concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-[R]-hydroxy-clarithromycin was noted. Because of the large therapeutic window

for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with creatinine clearance (CL_{CR}) of 30-60 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 reduced by 75%. Doses of clarithromycin greater than 1 g/day should not be co-administered with ritonavir. (See also Table 2.)

Sulfamethoxazole/Trimethoprim

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

Fusidic Acid

Co-administration of protease inhibitors, including ritonavir with fusidic acid is expected to increase fusidic acid, as well as the protease inhibitor concentration in Concomitant use of Norvir with fusidic acid is contraindicated (see section 4.3).

Anti-mycobacterials

Rifabutin

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg every 12 hours and rifabutin resulted in an approximate 4-fold and 35-fold increase in the AUC of rifabutin and its active metabolite 25-O-deacetyl rifabutin, respectively. The significance of this interaction has been confirmed in clinical trials. Concomitant use of Norvir with rifabutin is contraindicated (see section 4.3).

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. In a healthy volunteer drug interaction study of 400 mg single dose bedaquiline and lopinavir/ritonavir 400/100 mg twice daily for 24 days, bedaquiline exposures (AUC) were increased by 22%. 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 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.

Anti-psychotic

Quetiapine

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

Consider alternatives to fluticasone propionate, budesonide and injectable triamcinolone, particularly for long-term use. Concomitant use of ritonavir and fluticasone proprionate 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 ritonavir has been co-administered with inhaled or intranasally administered fluticasone propionate or budesonide, or injectable triamcinolone.

Fluticasone propionate

An 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 pg/mL (mean) and AUC was increased from 4.2-18.8 pg.h/mL to 3102.6 pg.h/mL (mean) after concurrent administration of ritonavir and fluticasone nasal spray for 7 days.

Glecaprevir/Pibrentasvir

Co-administration with ritonavir is not recommended due to an increased risk of ALT elevations associated with increased GLE exposure.

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 50 mg with ritonavir 600 mg every 12 hours resulted in an approximate 13-fold and 2.4-fold increase in avanafil AUC_{inf} and C_{max}, respectively. Co-administration of ritonavir with avanafil is not recommended.

Sildenafil

Use sildenafil for the treatment of erectile dysfunction with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Co-administration 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 ritonavir with sildenafil 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 72 hours, with increased monitoring for adverse events.

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

Vardenafil

Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72hours, with increased monitoring for adverse events.

Gonadotrophin releasing hormone (GnRH) Receptor Antagonists

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 label for dosing information with strong CYP-3A4 inhibitors.

Kinase Inhibitors (see also 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.

Herbal Products

Patients on ritonavir should not concomitantly 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. Concomitant use of Norvir with St John's wort is contraindicated (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 ritonavir with simvastatin or lovastatin is contraindicated due to an increased risk of myopathy, including rhabdomyolysis (see section 4.3 Contraindications). Caution must also be exercised and reduced doses should be considered if ritonavir 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 ritonavir co-administration. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see Table 3).

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 Norvir with lomitapide is contraindicated (see section 4.3).

Hypnotic

Alprazolam

Co-administration of alprazolam with ritonavir resulted in a statistically significant decrease in mean alprazolam C_{max} values (16%) but not in mean AUC values (12%). Similarly, a statistically significant effect on the sedation effect curve was observed, but not on the extent of sedation. 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.

Oral Contraceptives or Patch Contraceptives

Concomitant administration of oral contraceptives and ritonavir markedly reduces the AUC and C_{max} of the oestradiol component. A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg every 12 hours and a fixed-combination oral contraceptive resulted in reductions of the ethinyloestradiol mean AUC and C_{max} and by 40% and 32%, respectively. Increased doses of oral contraceptives or patch contraceptives containing ethinyloestradiol, or alternate methods of contraception, should be considered.

Smoking Cessation Medication

Bupropion

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

Bosentan

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

Antigout Agents

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 ritonavir. Concomitant use of Norvir with colchicine is contraindicated (see section 4.3).

Theophylline

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

Dosage reductions may be required for those agents extensively metabolised by CYP3A.

Potential drug interactions are summarised below 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)**
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, then 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	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	↔	↔

↑ Indicates increase
↓ Indicates decrease
↔ Indicates no change
* parallel group design; entries are subjects receiving combination and control regimens, respectively

Table 3: Potential Effects on Drugs Co-administered with Ritonavir

Drug Category	**Representative Drugs by Potential Interaction Category**					
	Contraindicated Medications	**Large [1] ↑AUC [2]**	**Moderate [1] ↑AUC [2]**	**Moderate [1] ↑ or ↓AUC [2]**	**Unknown**	**Possible ↓AUC [2]**
Analgesics, Narcotics	dextropropoxy-phene pethidine	alfentanil fentanyl	hydrocodone oxycodone tramadol		levamethadyl (LAAM)	codeine heroin hydromorphone meperidine * methadone * morphine naloxone naltrexone
Analgesics, NSAID	piroxicam			diclofenac flurbiprofen ibuprofen indomethacin	nabumetone sulindac	ketoprofen ketorolac naproxen paracetamol
Antianginal	ranolazine					

Drug Category	Representative Drugs by Potential Interaction Category					
	Contraindicated Medications	**Large [1] ↑AUC [2]**	**Moderate [1] ↑AUC [2]**	**Moderate [1] ↑ or ↓AUC [2]**	**Unknown**	**Possible ↓AUC [2]**
Antiarrhythmics	amiodarone dronedarone encainide flecainide propafenone quinidine	lignocaine	disopyramide mexiletine		digoxin tocainide[4]	
Anti-asthmatic						theophylline *
Antibiotic macrolides		erythromycin	clarithromycin *		clindamycin tinidazole	
Antibiotic steroidal	fusidic acid					
Anticoagulant					warfarin	
Anticonvulsants		carbamazepine	clonazepam ethosuximide		phenobarbitone	divalproex sodium valproate lamotrigine phenytoin
Antidepressants, tricyclic			amitriptyline clomipramine desipramine * imipramine maprotiline nortriptyline trimipramine		Doxepin [4]	
Antidepressants, SSRIs and non-tricyclics		nefazodone sertraline	fluoxetine paroxetine trazodone * venlafaxine	moclobemide	fluvoxamine	bupropion
Antidiarrhoeal						diphenoxylate loperamide
Antiemetics, prokinetics	cisapride		dronabinol ondansetron		prochlorperaz-ine [4] promethazine [4]	metoclopramide
Antifungals	voriconazole	itraconazole ketoconazole * miconazole				
Antigout	colchicine					

Drug Category	Representative Drugs by Potential Interaction Category					
	Contraindicated Medications	**Large [1] ↑AUC [2]**	**Moderate [1] ↑AUC [2]**	**Moderate [1] ↑ or ↓AUC [2]**	**Unknown**	**Possible ↓AUC [2]**
Antihistamines	astemizole terfenadine	loratadine			azatadine brompheniramine chlorpheniramine diphenhydramine mepyramine triprolidine	cyproheptadine
Antihypertensives	alfuzosin	bosentan	triamterene	losartan	doxazosin [4] prazosin [4] terazosin [4]	
Anti-mycobacterials	rifabutin *	rifampicin *				
Antipsychotics	blonanserin, clozapine lurasidone pimozide					
Antiparasitics		quinine		proguanil	albendazole chloroquine mebendazole mefloquine metronidazole pentamidine praziquantel primaquine pyrimethamine thiabendazole trimetrexate	atovaquone
Antiulcer agents				lansoprazole omeprazole	cimetidine	
$Beta_2$ agonist (long acting)	salmeterol					
Beta-blockers			metoprolol penbutolol pindolol timolol	propranolol	betaxolol [4]	labetalol

Drug Category	Representative Drugs by Potential Interaction Category					
	Contraindicated Medications	**Large [1] ↑AUC [2]**	**Moderate [1] ↑AUC [2]**	**Moderate [1] ↑ or ↓AUC [2]**	**Unknown**	**Possible ↓AUC [2]**
Calcium channel blockers	bepridil	amlodipine diltiazem felodipine isradipine nicardipine nifedipine nimodipine nisoldipine nitrendipine verapamil				
Cancer chemotherapy agents	apalutamide neratinib	abemaciclib dasatinib encorafenib ivosidenib nilotinib tamoxifen	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 [4] methyl-ergometrine [4]	bromocriptine			methysergide [4]	
GnRH receptor antagonists					elagolix [4]	
Corticosteroids/ steroid hormones		dexamethasone finasteride flutamide fluticasone * prednisone	anabolic steroids levonorgestrel medroxyprogest-erone norethinderone prednisone testosterone			ethinyloestradiol *
Haemorheologic agent					pentoxifylline	
Herbal product	St. John's wort					
HCV antivirals		glecaprevir/pib-rentasvir				
HIV antivirals		atazanavir darunavir (fos)amprenavir indinavir * saquinavir * tipranavir	maraviroc		nevirapine [4]	didanosine * zidovudine *

Drug Category	Representative Drugs by Potential Interaction Category					
	Contraindicated Medications	**Large [1] ↑AUC [2]**	**Moderate [1] ↑AUC [2]**	**Moderate [1] ↑ or ↓AUC [2]**	**Unknown**	**Possible ↓AUC [2]**
Hypoglycaemics				glibenclamide glimepiride glipizide glyburide tolbutamide		
Hypolipidaemics	lomitapide, lovastatin simvastatin	atorvastatin fluvastatin	pravastatin rosuvastatin		gemfibrozil	clofibrate
Immuno-suppressants		cyclosporin everolimus [4] (rapamycin) sirolimus tacrolimus				
Neuroleptics	pimozide		chlorpromazine haloperidol perphenazine risperidone thioridazine		other phenothiazines	
PDE5 inhibitor	sildenafil (indicated for PAH)	avanafil sildenafil (indicated for ED) tadalafil * vardenafil *				
Sedative/ hypnotics	clorazepate diazepam estazolam flurazepam oral midazolam triazolam zolpidem	buspirone clonazepam			other benzodiazepines zopiclone	lorazepam oxazepam propofol temazepam
Smoking cessation						bupropion
Stimulants/ Decongestants/ Antitussives			dexfenfluramine dextro-methorphan methamphetamine		methylphenidate	caffeine

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

* Clinical drug interaction study has been performed

4.6 Fertility, pregnancy and lactation

Fertility

Ritonavir produced no effects on fertility in rats at oral dosage levels up to 125 mg/kg/day for males (a mean plasma exposure of 61 mcg.hr/mL), and 75 mg/kg/day for females (91 mcg.hr/mL). Higher doses were not feasible due to hepatic toxicity.

Pregnancy

Pregnancy Category: B3

There are no adequate and well-controlled studies in pregnant women.

Based on prospective reports to the Antiretroviral Pregnancy Registry (APR) of approximately 6100 live births following exposure to ritonavir-containing regimens (including over 2800 live births exposed in the first trimester and over 3200 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The prevalence of birth defects in live births was 2.3% (95% CI: 1.7%-2.9%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.3%-3.5%) following second and third trimester exposure to ritonavir-containing regimens.

No treatment-related malformations were observed with ritonavir in either 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 (mean plasma exposure of 45 mcg.hr/mL). A slight increase in the incidence of cryptorchidism was also noted in rats given 35 mg/kg/day (34 mcg.hr/mL). Developmental toxicity expressed in rabbits (resorptions, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage of 110 mg/kg/day. Because animal reproduction studies are not always predictive of human response, NORVIR should be used during pregnancy only if the potential benefits clearly outweigh the potential risks.

Breast-feeding

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 its effects 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, mothers should be instructed not to breastfeed if they are receiving ritonavir.

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. Dizziness is a known undesirable effect that should be taken into account when driving or using machinery.

4.8 Undesirable effects

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

Adults

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

Table 4: Treatment-Emergent Adverse Reactions (With Possible or Probable Relationship to Study Drug) Occurring in ≥ 1% of Adult Patients Receiving Ritonavir in Combined Phase II/IV Studies (N = 1,755)	
Adverse Reactions	**%**
Eye disorders	
Blurred vision	6.4
Gastrointestinal disorders	
Abdominal Pain (upper and lower)*	26.4
Diarrhoea including severe with electrolyte imbalance*	67.9
Dyspepsia	11.5
Flatulence	8.1
Gastrointestinal haemorrhage*	2.3
Gastroesophageal Reflux Disease (GORD)	1.1
Nausea	57.4
Vomiting*	31.9
General disorders and administration site conditions	
Fatigue including asthenia*	46.2
Hepatobiliary disorders	
Blood bilirubin increased (including jaundice)*	1.4
Hepatitis (including increased AST, ALT, GGT)*	8.7
Immune system disorders	
Hypersensitivity including urticaria and face oedema*	8.2
Metabolism and nutrition disorders	
Oedema and peripheral oedema*	6.3
Gout*	1.4
Hypercholesterolemia*	3.0
Hypertriglyceridemia*	9.0
Musculoskeletal and connective tissue disorders	
Arthralgia and back pain*	18.6
Myopathy/creatine phosphokinase increased*	3.8
Myalgia	8.9
Nervous system disorders	
Dizziness*	15.6
Dysgeusia*	16.2
Paraesthesia (including oral paraesthesia)*	50.7

Peripheral neuropathy	10.1
Syncope*	3.3
Psychiatric disorders	
Confusion*	3.0
Disturbance in attention	2.5
Renal and urinary disorders	
Increased urination*	4.2
Respiratory, thoracic and mediastinal disorders	
Coughing*	21.7
Oropharyngeal Pain*	15.9
Skin and subcutaneous tissue disorders	
Acne*	3.8
Pruritus*	12.2
Rash (includes erythematous and maculopapular)*	27.1
Vascular disorders	
Flushing, feeling hot*	13.2
Hypertension*	3.3
Hypotension including orthostatic hypotension*	1.7
Peripheral coldness*	1.2
* Represents a medical concept including several similar MedDRA PTs	

Paediatric

Treatment-Emergent Adverse Events

The adverse event profile observed during paediatric clinical trials was similar to that for adult patients.

Vomiting, diarrhea, and skin rash/allergy were the only drug-related clinical adverse events of moderate-to-severe intensity observed in ≥ 2% of paediatric patients enrolled in ritonavir clinical trials.

Laboratory Abnormalities

The following Grade 3-4 laboratory abnormalities occurred in ≥ 3% of paediatric patients who received treatment with ritonavir either alone or in combination with reverse transcriptase inhibitors: neutropenia (9%), hyperamylasemia (7%), thrombocytopenia (5%), anaemia (4%), and elevated AST (3%).

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.

Reproductive system and breast disorders: Menorrhagia has been reported.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis (TEN).

Renal and urinary disorders: Nephrolithiasis.

Laboratory determinations

Table 5: Adult Patients Exceeding Extreme Limit Criteria for Clinical Chemistry and Haematology Variables in Phase II/III Combined Studies

Variable		%
CHEMISTRY		
Glucose	(high) > 250 mg/dL	1
Glucose	(low) < 40 mg/dL	<1
BUN	(high) > 120 mg/dL	0
Creatinine	(high) > 3.6 mg/dL	<1
Uric Acid	(high) > 12 mg/dL	2
Sodium	(high) > 157 mEq/L	<1
Sodium	(low) < 123 mEq/L	<1
Potassium	(high) > 6 mEq/L	<1
Potassium	(low) < 3 mEq/L	2
Chloride	(high) > 122 mEq/L	<1
Chloride	(low) < 84 mEq/L	<1
Calcium, total	(high) > 12.6 mEq/L	<1
Calcium, total	(low) < 6.9 mEq/L	1
Inorganic Phosphorus	(high) > 7.0 mg/dL	<1
Inorganic Phosphorus	(low) < 1.4 mg/dL	0
Magnesium	(high) > 2.9 mEq/L	1
Magnesium	(low) < 1.0 mEq/L	<1
Albumin	(high) > 6.7 g/dL	0
Albumin	(low) < 2 g/dL	<1
Total Bilirubin	(high) > 3.6 mg/dL	1
Alkaline Phosphatase	(high) > 550 IU/L	1
SGOT (AST)	(high) > 180 IU/L	4
SGPT (ALT)	(high) > 215 IU/L	6
LDH	(high) > 1170 IU/L	<1
GGT	(high) > 300 IU/L	12
Cholesterol	(high) > 5 x ULN[1]	0
Triglycerides	(high) > 1500 mg/dL	7

Amylase	(high) > 2 x ULN1	2
CPK	(high) > 1000 IU/L	8
HAEMATOLOGY		
Haemoglobin	(high) > 21 g/dL	0
Haemoglobin	(low) < 8 g/dL	3
Haematocrit	(low) < 30%	8
RBC	(low) < 3.0 x 10^{12}/L	9.5
WBC	(high) > 25 X 10^9/L	1
WBC	(low) < 2.5 X 10^9/L	16
Platelet count	(low) < 20 X 10^9/L	<1
Neutrophils	(high) > 20 X 10^9/L	1
Neutrophils	(low) $\leq$ 0.5 X 10^9/L	3
Eosinophils	(high) > 1.0 X 10^9/L	2
Prothrombin Time	(high) > 1.5 x ULN[1]	1
Activated Partial Thromboplastin Time	(high) > 2.3 x ULN[1]	<1
[1] ULN = upper limit of the normal range		

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 professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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.

Ritonavir has a low order of acute toxicity when administered orally. The ALD (approximate lethal dose) or median lethal dose (LD_{50}) was found to be greater than 2500 mg/kg in both mice and rats. The no-effect-level was 200 mg/kg in mice and 250 mg/kg in rats. Clinical signs observed during toxicity studies in laboratory animals are noted in section 5.3 Preclinical safety data.

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. It is proposed that management of overdosage could also entail gastric lavage and administration of activated charcoal. 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, Direct acting antivirals, Protease inhibitors; ATC code J05AE03.

Pharmacodynamic effects

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. ZDV-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 protease inhibitors with ritonavir has not been fully assessed in humans. The effect of ritonavir therapy on the activity of subsequently administered protease inhibitors 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.

Clinical efficacy and safety

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.

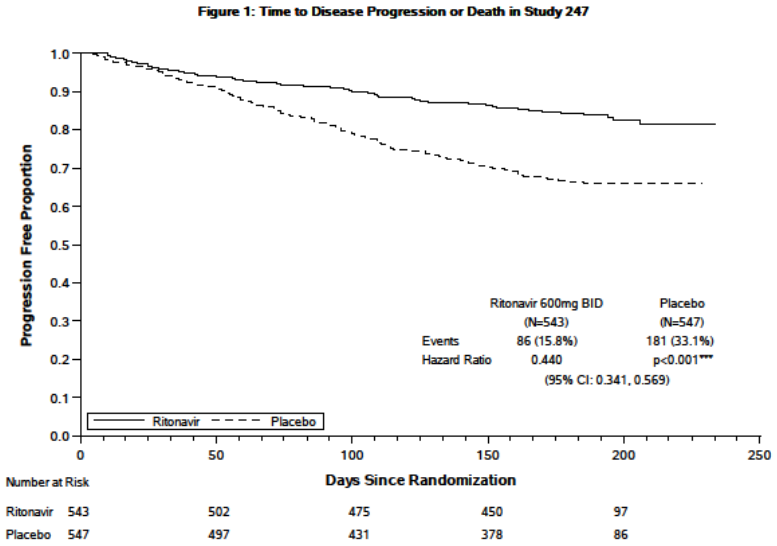
Advanced Patients with Prior Antiretroviral Therapy

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 statistically 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 6 and Figure 1).

Table 6: Disease Progression or Death

All Events Postrandomisation			
Ritonavir	86 events/543 patients	15.8%	p < 0.001
Placebo	181events/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/µL) From Baseline in Study 247

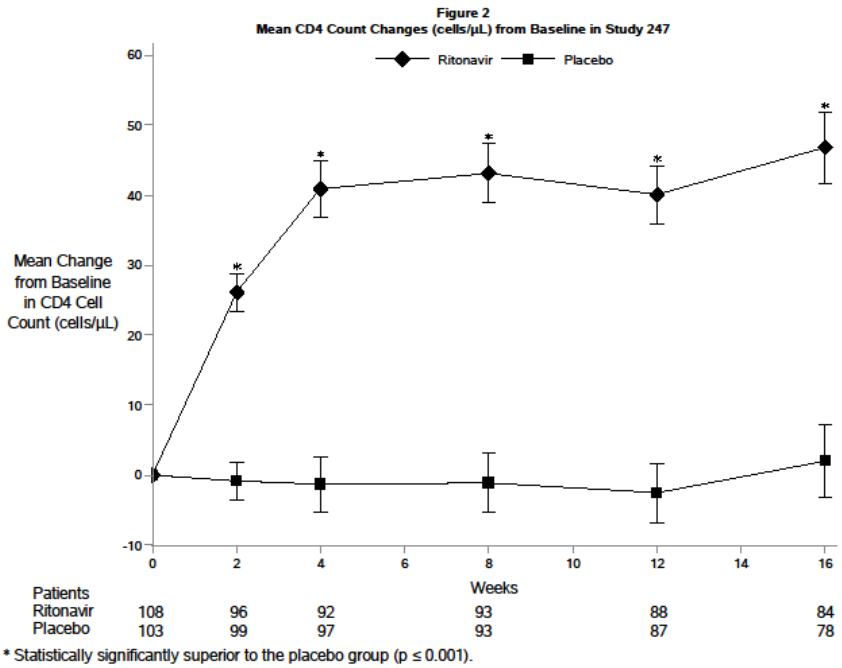
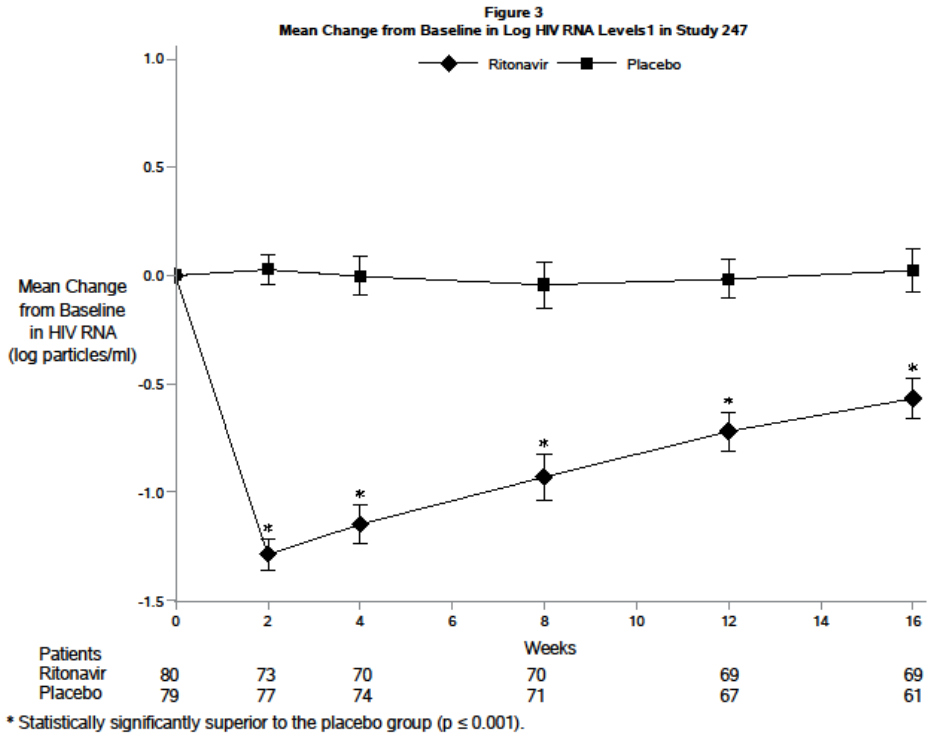


Figure 3 summarises the mean changes from baseline in log HIV RNA levels for Study 247.

Figure 3: Mean change from Baseline in Log HIV RNA levels1 in Study 247



[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-naïve 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 245

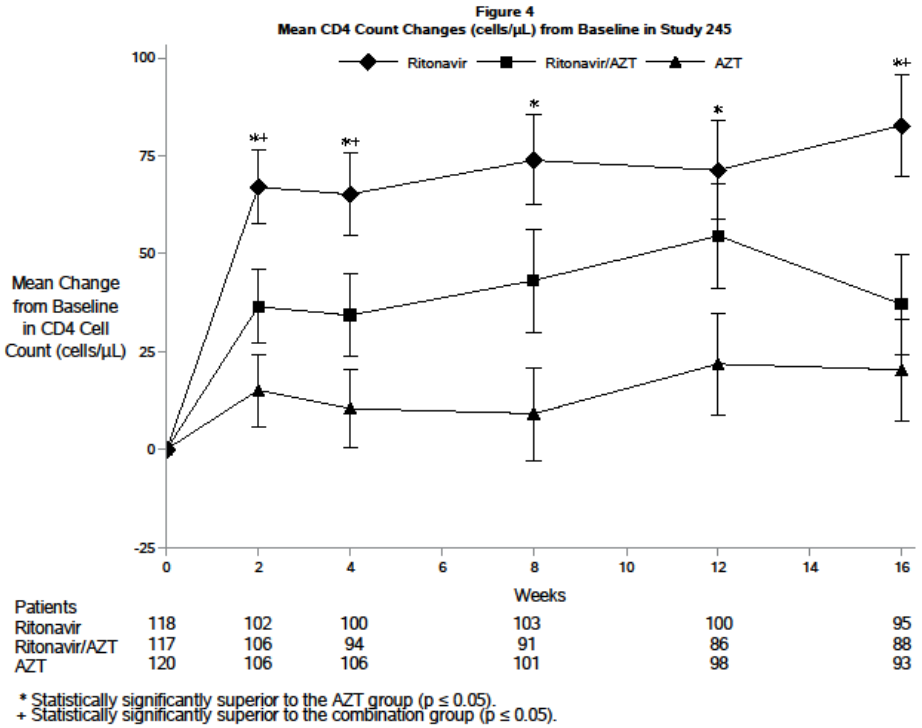
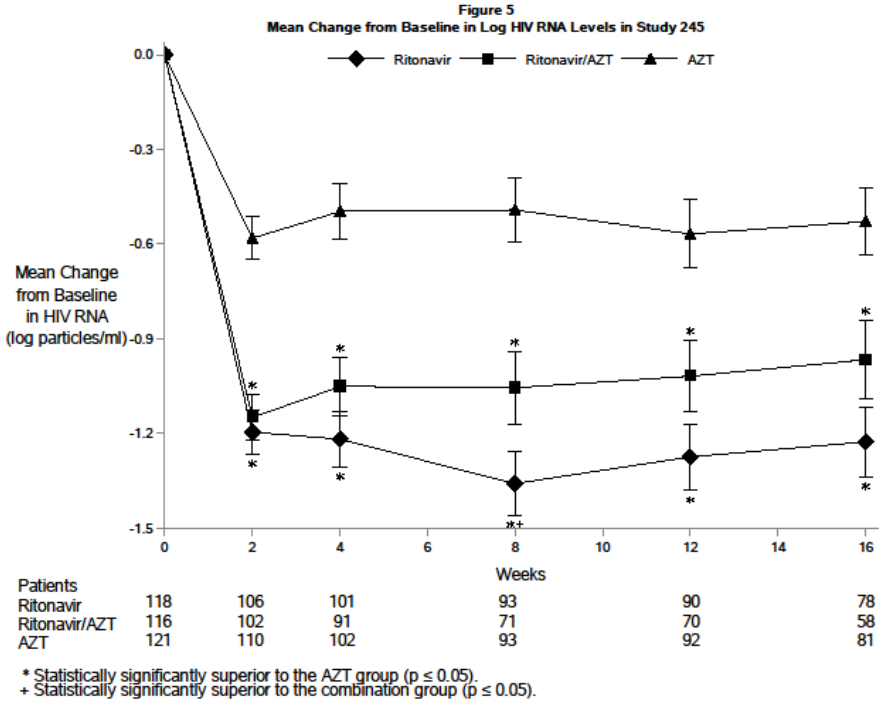


Figure 5 summarises the mean changes from baseline in log HIV RNA levels for Study 245.

Figure 5: Mean change from Baseline in Log HIV RNA Levels in Study 245



Combination Therapy with NORVIR, Zidovudine and Zalcitabine in Antiretroviral-Naïve Patients

In Study 208, 32 antiretroviral-naïve 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.

Paediatric population

Ritonavir has not been studied in patients below the age of 12 years; hence the safety and efficacy of ritonavir in children below the age of 12 have not been established.

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 advised to take NORVIR with food, if possible.

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.

5.2 Pharmacokinetic properties

Table 7: 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 every 12 hours.
§ 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.

A single dose pharmacokinetic study in HIV-positive fasting male subjects was conducted with oral administration of 100 mg, 200 mg, 400mg, 600 mg, 800 mg or 1000 mg of ritonavir. Area under the concentration-time curve (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 0.1L/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 7). 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 effect of a high fat meal on absorption of ritonavir from the soft capsule has not been assessed. 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 section 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 α_1-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.

Biotransformation

Nearly all of the plasma radio-label after a single oral 600 mg dose of radio-labelled ritonavir was attributed to unchanged ritonavir. 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 parent drug; however, the concentration of the metabolite in plasma is 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 cytochrome P450 3A4 (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.

Elimination

Studies with radio-labelled drug have demonstrated that 11.3% and 86.4% of the radio-label 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.

Effects on Electrocardiogram

QT_cF 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 QT_cF 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 QT_cF of ≥ 60 msec from baseline or a QT_cF 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 section 4.4 Special warnings and precautions for use).

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 it is administered to patients with impaired hepatic function (see section 4.4 Special warnings and precautions for use).

5.3 Preclinical safety data

Acute, Subacute and Chronic Toxicity

Ritonavir has a low order of acute toxicity when administered orally. The LD_{50} was found to be greater than 2500 mg/kg in both mice and rats. The signs of toxicity at higher doses in both species included decreased activity, ataxia, dyspnoea and tremors. Signs of toxicity were generally apparent for one to three days after dosing. No gross morphological changes were seen among rats necropsied following a two-week observation period.

Repeated dose toxicity studies in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hypertrophy of the retinal pigment epithelium and retinal degeneration were noted in rodent studies conducted with ritonavir but were not noted in dogs. Ultrastructural evidence suggests that these retinal changes in rodents may be secondary to phospholipidosis. However, three phase II clinical trials revealed no clear evidence of drug-induced retinal changes in humans. Changes relating to the thyroid gland included hypertrophy of follicular cells, decreased serum thyroxine (T4) and/or increased serum TSH levels. All thyroid changes were reversible upon discontinuation of drug. Clinical investigation in humans revealed no clinically significant alteration in thyroid function tests. Renal changes including tubular degeneration, chronic inflammation and proteinuria were noted in rats and were felt to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Ritonavir was not mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes. In addition, carcinogenicity studies in rats and mice indicated that ritonavir was not a direct-acting carcinogen at the dosages tested. An increased incidence of hepatocellular adenomas occurred in male mice that received the high dosage of 200 mg/kg/day. Such tumour responses in mouse liver associated with non-genotoxic compounds, are considered to have little relevance to the response of the human liver.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Copovidone
Sorbitan laurate
Calcium hydrogen phosphate, anhydrous
Silica, colloidal anhydrous
Sodium stearyl fumarate

Film-coating:
Hypromellose
Titanium dioxide (E171)
Macrogols
Hydroxypropyl cellulose
Talc
Silica, colloidal anhydrous
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months, stored at or below 30°C.

6.4 Special precautions for storage

Store in the original bottle in order to protect from moisture.

6.5 Nature and contents of container

Available in a 30-tablet bottle.

6.6 Special precautions for disposal and other handling

Not applicable.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

AbbVie Limited
6th Floor, 156-158 Victoria Street
Wellington 6011
New Zealand

Telephone number: (0800) 900 030

9. DATE OF FIRST APPROVAL

20 January 2000

10. DATE OF REVISION OF THE TEXT

29 April 2020

Version 35

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.3 Contraindications	Clarification re. ritonavir as a potent inhibitor of cytochrome P450-mediated biotransformations included.
4.4 Special warnings and precautions for use	Text under 'Hepatic Impairment', 'Diabetes Mellitus/Hyperglycaemia', and 'Lipid Elevation' updated, in line with the current Company Core Data Sheet (CCDS).
4.5 Interaction with other medicines and other forms of interaction	Text and Tables 2 and 3 significantly updated, in line with the current CCDS.
4.6 Fertility, pregnancy and lactation	Text under 'Fertility' and 'Pregnancy' updated, in line with the current CCDS.
4.8 Undesirable effects	Nephrolithiasis added under new 'Renal and urinary disorders' heading, in line with the current CCDS.
4.9 Overdosage	Text under 'Acute Overdosage' updated, in line with the current CCDS.
5.2 Pharmacokinetic properties	Text under 'Biotransformation' updated, in line with the current CCDS.
5.3 Preclinical safety data	Text updated, in line with the current CCDS.