

PRODUCT INFORMATION

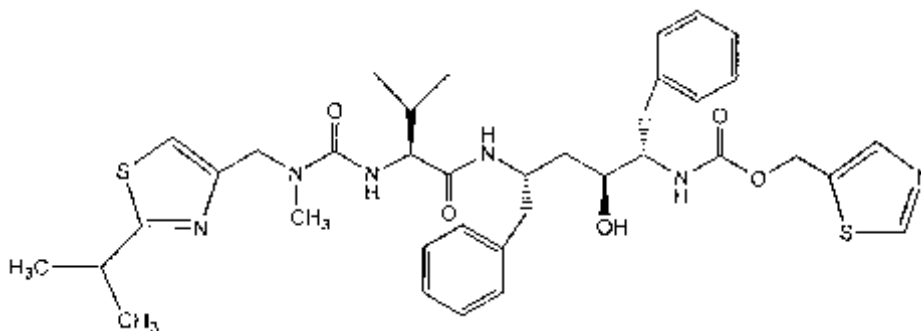
NORVIR[®] CAPSULES AND ORAL SOLUTION

NAME OF THE MEDICINE

Ritonavir 100 mg soft capsules

Ritonavir 80 mg/mL oral solution

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:



Molecular Weight: 720.95

Molecular Formula: C₃₇H₄₈N₆O₅S₂

CAS Number: 155213-67-5

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.

DESCRIPTION

Norvir soft capsules are available for oral administration in a strength of 100 mg ritonavir in a soft capsule. The ritonavir is dissolved in ethanol, oleic acid, butylated hydroxytoluene and PEG 35 castor oil. Other ingredients include: gelatin, sorbitol special, glycerol, titanium dioxide (white colour), coconut oil, lecithin and black ink containing propylene glycol, black iron oxide, polyvinyl acetate phthalate, polyethylene glycol and ammonium hydroxide.

Norvir oral solution is available for oral administration as 80 mg/mL of ritonavir in a peppermint and caramel flavoured vehicle. Each 240 mL bottle contains 7.2 and 19.2 grams of ritonavir, respectively. Norvir oral solution also contains ethanol, water, PEG-35 castor oil, propylene glycol, anhydrous citric acid to adjust pH, saccharin sodium, peppermint oil, creamy caramel flavouring and sunset yellow colour (E110).

PHARMACOLOGY

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 μ M, 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. EC₅₀ values (50% inhibitory concentrations of HIV-1 strains) were generally uniform but ranged from 4 to 153 nM in peripheral blood lymphocytes. The average EC₅₀ 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.

Pharmacokinetics

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 1000mg of ritonavir. Area under the concentration-time curve (AUC) ranged from 3.92 to 123 µg.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 bd dose, C_{max} and C_{trough} values of 11.2 and 3.7 µg/mL were observed, respectively. The t_{1/2} of ritonavir was approximately 3 to 5 hours. The steady-state apparent clearance in patients treated with 600 mg bd averaged 8.8 ± 3.2 L/h (Table 1). 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 **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Distribution

The apparent volume of distribution ($V_{B/F}$) 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 $\mu\text{g/mL}$. 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 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 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.

Effects on Electrocardiogram

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

Modest prolongation of the PR interval was also noted in subjects receiving ritonavir in the same study on Day 3. Maximum PR interval was 252 msec and no second or third degree heart block was observed (see PRECAUTIONS).

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 **PRECAUTIONS**).

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 **PRECAUTIONS: -Interactions with Other Medicines**)

Table 1

Ritonavir Pharmacokinetic Characteristics

Parameter	n	Values (Mean ± SD)
C _{max} SS [†]	10	11.2 ± 3.6 µg/mL
C _{trough} SS [†]	10	3.7 ± 2.6 µg/mL
V _{β/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 µg/mL.

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

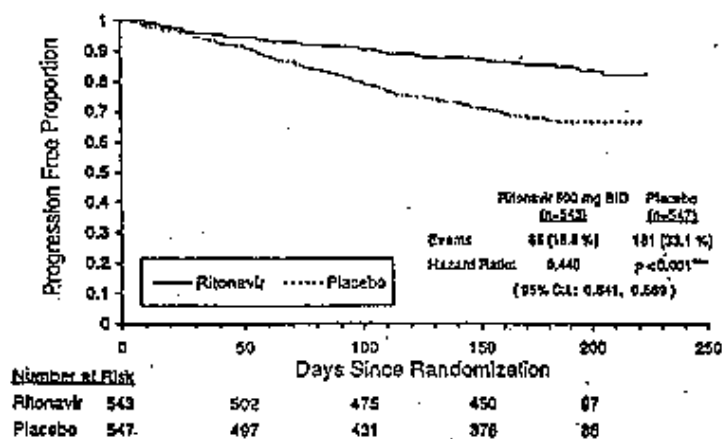
Study 247 is a randomised, double-blind trial conducted in patients with at least nine months of prior nucleoside analogue antiretroviral therapy and baseline CD4 cell counts <100 cells/ μ L. Ritonavir 600 mg bd or placebo was added to each patient's baseline antiretroviral therapy regimen, which could 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/ μ L. 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 2 and Figure 1).

Table 2

Disease progression or Death <u>All Events Postrandomisation</u>			
Ritonavir	86 events/543 patients	15.8%	p < 0.001
Placebo	181 events/547 patients	33.1%	
<u>All Deaths Postrandomisation</u>			
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/ μ L) 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/ μ L) From Baseline in Study 247

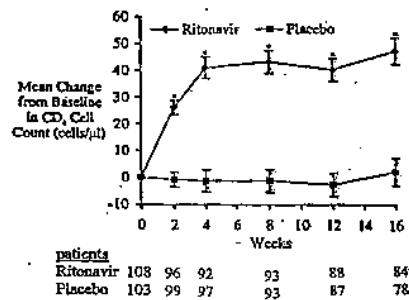
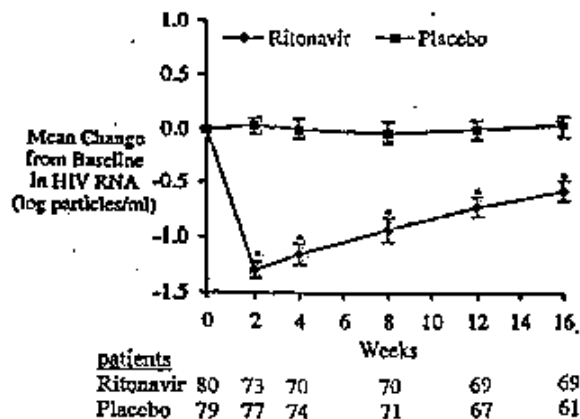


Figure 3 summarises the mean changes from baseline in log HIV RNA levels for Study 247.

Figure 3

Mean change from Baseline in Log HIV RNA levels¹ in Study 247



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

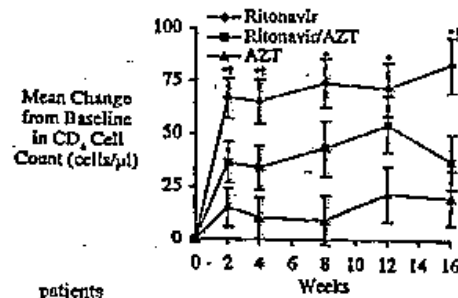
¹ The clinical significance of changes in HIV RNA measurement has not been established.

Patients Without Prior Antiretroviral Therapy

In ongoing Study 245, 356 antiretroviral-naïve patients (mean baseline CD4 = 364) were randomised to receive either ritonavir 600 mg bd, zidovudine 200 mg tid 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/mm³) From Baseline In Study 245



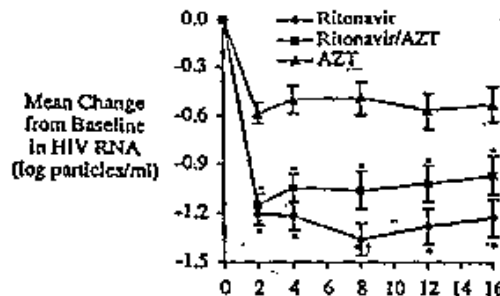
patients	0	2	4	6	8	10	12	14	16
Ritonavir	118	102	100	103	100	95			
Ritonavir/AZT	117	106	94	91	86	88			
AZT	120	106	106	101	98	93			

*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 245



patients	0	2	4	6	8	10	12	14	16
Ritonavir	118	106	101	93	90	70			
Ritonavir/AZT	116	102	91	70	70	50			
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 bd monotherapy. Zidovudine 200 mg tid and zalcitabine 0.75 mg tid 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/ μ L over the treatment period. Mean decreases from baseline in HIV RNA particle levels ranged from 1.69 to 1.92 logs.

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 **CLINICAL TRIALS**).

CONTRAINDICATIONS

Norvir is contraindicated in patients with known hypersensitivity to it or any of its ingredients. Ritonavir is expected to produce large increases in the plasma concentrations of drugs metabolized by cytochrome P450. Co-administration of Norvir is contraindicated with the drugs listed in Table 3:

Table 3 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.
Antiarrhythmics	amiodarone, bepridil, flecainide, propafenone, quinidine, encainide	Potential for cardiac arrhythmias.
Antifungal	voriconazole	Significant decreases in voriconazole plasma concentrations may lead to loss of antifungal response.
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
Antipsychotic	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

Drug Class	Drugs within Class that are Contraindicated with Ritonavir	Clinical comments
		toxicities.
Ergot Derivatives	dihydroergotamine, ergometrine, ergotamine, methylergometrine	Post-marketing reports of acute ergot toxicity characterized 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 Johns wort (hypericum perforatum)	Co-administration may lead to a decrease in ritonavir levels, and to loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Long acting betaadrenoceptor agonist	salmeterol	May result in potential increased risk of cardiovascular adverse events associated with salmeterol.
Neuroleptic	pimozide	Potential for cardiac arrhythmias.
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 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 metabolized sedatives and hypnotics resulting in the potential for extreme sedation and respiratory depression.
*see PHARMACOLOGY and PRECAUTIONS: Interactions with Other Medicines for coadministration of sildenafil in patients with erectile dysfunction		

PRECAUTIONS

Allergic Reactions

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

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 6). 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.

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 protease inhibitors 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 protease inhibitors has not been fully assessed. It is unknown what affect ritonavir will have on the activity of subsequent protease inhibitors (see **PHARMACOLOGY**).

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.

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 preexisting 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 or accumulation of body fat including central obesity, dorsocervical fat enlargement and breast enlargement and loss of body fat from the face, limbs and upper trunk (peripheral lipodystrophy) have been reported in HIV positive patients taking protease inhibitors. Some of these patients had hyperglyceridaemia and insulin resistance also. The long-term implications of these changes are not known.

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 **PRECAUTIONS: HMG-CoA Reductase Inhibitors** for additional information on potential drug interactions with ritonavir and HMG CoA reductase inhibitors.

Laboratory Tests

Ritonavir has been associated with alterations in cholesterol, triglycerides, AST, ALT, GGT, CPK and uric acid (see also **PRECAUTIONS: 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.

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 µg.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.

Use in Lactation

It is not known whether ritonavir or its metabolites are secreted in animal or human milk. Because many drugs are excreted in human milk, caution should be exercised when ritonavir is administered to a nursing woman.

Paediatric Use

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

Carcinogenicity

Two-year carcinogenicity studies have been conducted in rodents, at ritonavir dietary levels of 50, 100 and 200mg/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.

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*).

Interactions with Other Medicines

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: CYP3A > CYP2D6 > CYP2C9, CYP2C19 >> CYP2A6, CYP1A2, CYP2E1. There are some indications that Ritonavir may increase the activity of glucuronosyltransferases; 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, trimethoprim/sufamethoxazole, fluconazole, ethinyl oestradiol, 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 (NRTIs)

Didanosine

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 600 mg q12h and didanosine (ddI) 200 mg q12h 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. In a study of concomitant administration of ritonavir (200mg qid) 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.

Zidovudine

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 300 mg q12h and zidovudine (AZT) 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 600mg/day) are utilised.

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 400mg three times daily with ritonavir 600mg 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 500mg ritonavir twice daily with efavirenz 600mg 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

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 **PRECAUTIONS: 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 800mg 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 400mg 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 200mg 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.

Other Drugs

Alpha₁-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 (600mg twice daily). Therefore alfuzosin should not be co-administered with ritonavir.

Antiarrhythmics

Digoxin

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

Anticancer agents

Vincristine, Vinblastine

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

Anticoagulants

Warfarin

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

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.

Bupropion

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

Antifungals

Ketoconazole

Concomitant administration of ritonavir (500 mg q12h) and ketoconazole (200 mg qd) resulted in an increase of mean ketoconazole AUC₂₄ and C_{max} by 244% and 55%, respectively. The mean half-life of ketoconazole increased from 2.7 to 13.2 h. Mean AUC₂₄ 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 400mg every 12 hours decreased voriconazole steady-state AUC by an average of 82%; therefore, coadministration of these drugs is contraindicated (see **CONTRAINDICATIONS**).

Anti-infectives

Clarithromycin

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg q8h and clarithromycin 500mg 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

(CL_{CR}) of 30-60 mL/min the clarithromycin dose should be reduced by 50%, for CL_{CR} < 30 mL/min the clarithromycin dose should be reduced by 75%. Doses of clarithromycin greater than 1 g/day should not be coadministered 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 protease inhibitors, including ritonavir with fusidic acid is expected to increase fusidic acid, as well as the protease inhibitor concentration in plasma.

Anti-mycobacterial

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 **CONTRAINDICATIONS**).

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.

Corticosteroids

Caution should be used when coadministering ritonavir and fluticasone or any of the inhaled or intranasally administered glucocorticoids. Consider alternative to fluticasone propionate, particularly for long-term use. Concomitant use of ritonavir can greatly increase fluticasone propionate plasma concentration leading to systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.

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 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.

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.

Erectile Dysfunction Agents (PDE5 inhibitors)

Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving ritonavir. Co-administration of ritonavir with these drugs is expected to substantially increase their concentrations and may result in increased associated adverse events, such as hypotension, and prolonged erection.

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 sildenafil with ritonavir is contraindicated in pulmonary arterial hypertension patients (see **CONTRAINDICATIONS**)

Tadalafil

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

Vardenafil

Ritonavir (600mg twice daily) coadministered with vardenafil 5mg 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 2.5mg 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 **CONTRAINDICATIONS**).

HMG-CoA Reductase Inhibitors

Concomitant use of ritonavir with simvastatin and lovastatin is contraindicated (see **CONTRAINDICATIONS**). Caution should be exercised if HIV protease inhibitors, including ritonavir, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy including rhabdomyolysis may be increased when HIV protease inhibitors, 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.

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 **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 ethinylloestradiol 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.

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.

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 below in Tables 4 and 5.

Table 4

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 200mg q.12h. 4 days	600mg q.12h. 4 days	12	↔	↔
Fluconazole 400mg day 1, then 200mg daily 4 days	200mg q.6h. 4 days	8	↑ 12% (5, 20%)	↑ 15% (7, 22%)
Zidovudine 200mg q.8h. 4 days	300mg q.6h. 4 days	10	↔	↔

↑ Indicates increase

↓ Indicates decrease

↔ Indicates no change

Table 5

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	dextropropoxyphene, pethidine	alfentanil fentanyl methadone	hydrocodone oxycodone tramadol			codeine heroin hydro-morphone morphine naloxone naltrexone
Analgesics, NSAID	piroxicam			diclofenac flurbiprofen ibuprofen indomethacin	sulindac	ketoprofen ketorolac naproxen paracetamol
Antiarrhythmics	amiodarone flecainide quinidine	lignocaine	disopyramide mexiletine		digoxin	
Antiasthmatic						theophylline
Antibiotic macrolide		erythromycin	clarithromycin		clindamycin tinidazole	
Antibiotic Steroidal		Fusidic Acid				
Anticoagulents			warfarin			
Anticonvulsants		carbamazepine	clonazepam ethosuximide	phenytoin	phenobarbitone	sodium valproate lamotrigine
Antihistamine		loratadine			azatadine brompheniramine chlorpheniramine diphenhydramine mepyramine triprolidine	cyprohepatine
Antidepressants, tricyclic			amitriptyline clomipramine imipramine nortriptyline trimipramine		doxepin	
Antidepressants, other		nefazodone sertraline	fluoxetine paroxetine venlafaxine	moclobemide	fluvoxamine	bupropion
Antidiarrhoeal						diphenoxylate loperamide
Antiemetics	cisapride		ondansetron		prochlorperazine promethazine	metoclopramide
Antifungals	voriconazole		itraconazole ketoconazole miconazole			
Antihypertensives	alfuzosin		triamterene	losartan	prazosin terazosin	
Antimycobacterial	rifabutin	rifampicin ³				
Antipsychotics	blonanserin, clozapine					

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)
Antiparasitics		quinine		proguanil	albendazole chloroquine mebendazole mefloquine metronidazole pentamidine praziquantel primaquine pyrimethamine thiabendazole	atovaquone
Antiulcer agents				lansoprazole omeprazole	cimetidine	
Beta₂ agonists (long acting)	salmeterol					
Beta-blockers			metoprolol pindolol timolol	propranolol	betaxolol	labetalol
Calcium channel blockers		amlodipine diltiazem felodipine nifedipine nimodipine verapamil				
Cancer chemotherapy agents		tamoxifen	etoposide paclitaxel vinblastine vincristine	cyclophosphamide ifosfamide	daunorubicin doxorubicin	
Ergot alkaloids and derivatives	Dihydroergotamine ergotamine ergometrine methylethergometrine	bromocriptine			ergonovine methysergide	
Corticosteroids/steroid hormones		dexamethasone finasteride flutamide prednisone fluticasone*	anabolic steroids levonorgestrel medroxyprogesterone norethindrone prednisone testosterone			ethinylloestradiol
Herbal products	St. John's Wort					
HIV protease inhibitors		atazanavir darunavir fosamprenavir indinavir saquinavir tipranavir	maraviroc		nevirapine	didanosine zidovudine
Hypoglycaemics				glimepiride glipizide glibenclamide glyburide tolbutamide		
Hypolipidaemics	simvastatin, lovastatin	fluvastatin atorvastatin	pravastatin rosuvastatin		gemfibrozil	
Immunosuppressants		cyclosporin everolimus tacrolimus sirolimus				
Neuroleptics	pimozide		chlorpromazine haloperidol risperidone thioridazine		other phenothiazines	

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)
PDE5 inhibitors	sildenafil indicated for PAH	sildenafil indicated for ED tadalafil vardenafil				
Sedative/hypnotic	clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem	clonazepam buspirone			other benzodiazepines zopiclone	lorazepam oxazepam propofol temazepam
Stimulants/ Decongestants/ Antitussives			dextromethorphan		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
- * Clinical drug interaction study has been performed

Information for Patients

Patients should be informed that Norvir (ritonavir) 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 (ritonavir) with food, if possible.

Patients should be informed to take Norvir (ritonavir) 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 Norvir (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.

ADVERSE EFFECTS

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 $\geq 2\%$ of patients in a ritonavir treatment group are summarised in Table 6 for Study 245 and Table 6 for Study 247. Similar adverse events were reported in other trials for ritonavir.

Table 6

Percentage of Patients with Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Occurring in $\geq 2\%$ of Patients Receiving Ritonavir in Study 245

Adverse Events	RIT + ZDV N = 116	RIT 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 7

Percentage of Patients with Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Occurring in $\geq 2\%$ of Patients Receiving Ritonavir in Study 247

Adverse Events	RIT 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
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, photosensitivity reaction and redistribution/accumulation of body fat. (see **PRECAUTIONS**).

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 8 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 8**Percentage of Patients, by Treatment Group, with Marked¹ Chemistry and Haematology Laboratory Value Abnormalities**

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

There have been post-marketing reports of seizure. Hyperglycaemia has been reported in individuals with and without a known history of diabetes. A cause and effect relationship has not been established.

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.

Myocardial infarction has been reported.

Menorrhagia has been reported.

DOSAGE AND ADMINISTRATION

Norvir is administered orally. Ritonavir soft capsules should preferably be taken with meals. Patients may improve the taste of Norvir oral solution by mixing with chocolate milk or ENSURE®. The effects of antacids on the absorption of ritonavir have not been studied.

The recommended dosage of Norvir is 600 mg (7.5 mL or 6 soft capsules) twice daily by mouth.

The ritonavir solution dosage cup should be cleaned immediately with hot soapy water after use. When cleaned immediately, drug residue is removed. The dosage cup **must** be dry prior to use. Shake bottle well before use.

OVERDOSAGE

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.

PRESENTATION AND STORAGE CONDITIONS

Norvir soft capsules

White capsules imprinted with the Abbott logo, “DS” and “100” containing a liquid essentially free of particles. Available in bottles containing 84 or 120* capsules.

Store under refrigeration between 2-8°C until dispensed. Do not freeze. After dispensed: If used within 30 days, may be stored below 25°C. However refrigeration by the patient is recommended whenever possible.

Norvir oral liquid

Orange-coloured liquid containing 600 mg ritonavir per 7.5 mL marked dosage cup (80 mg/mL). Available in 90mL, 255mL* and 240mL* bottles.

Do not refrigerate. Store at room temperature, between 20°C and 25°C. Shake well before use. Product should be stored in the original container. Avoid exposure to excessive heat. Keep cap tightly closed. Use before expiry date.

* Presentations not currently marketed

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POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

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