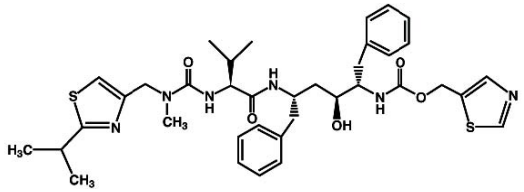
NORVIR®
(ritonavir tablets)

WARNING CO-ADMINISTRATION OF NORVIR WITH CERTAIN NONSEDATING ANTIHISTAMINES, SEDATIVE HYPNOTICS, ANTIARRHYTHMICS, OR ERGOT ALKALOID PREPARATIONS MAY RESULT IN POTENTIALLY SERIOUS AND/OR LIFE-THREATENING ADVERSE EVENTS DUE TO POSSIBLE EFFECTS OF NORVIR ON THE HEPATIC METABOLISM OF CERTAIN DRUGS. SEE CONTRAINDICATIONS AND PRECAUTIONS SECTIONS.

DESCRIPTION
Ritonavir is an inhibitor of HIV protease with activity against the Human Immunodeficiency Virus (HIV). Ritonavir is a white to light tan powder and has a bitter metallic taste. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.
Ritonavir is chemically designated 10-Hydroxy-2-methyl-5-(1-methylethyl)1-[2-(1-methylethyl) -4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$ and molecular weight is 720.95. Ritonavir has the following structure:



Ritonavir is supplied as a film coated tablet.

Ritonavir film coated tablets are available for oral administration in a strength of 100 mg with the following inactive ingredients: copovidone, dibasic calcium phosphate anhydrous / calcium hydrogen phosphate anhydrous, sorbitan monolaurate, colloidal silicon dioxide / colloidal anhydrous silica and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, titanium dioxide E171, polyethylene glycol 400 / macrogol type 400, hydroxylpropyl cellulose, talc, polyethylene glycol 3350 / macrogol type 3350, colloidal silicon dioxide / colloidal silica anhydrous and polysorbate 80.

CLINICAL PHARMACOLOGY

Mechanism of Action
Ritonavir is an orally active peptidomimetic inhibitor of the HIV-1 and HIV-2 aspartyl proteases. Inhibition of HIV protease renders the enzyme incapable of processing the gag-pol polyprotein precursor 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 little inhibitory activity against human aspartyl proteases.

Antiviral Activity in Vitro
In vitro data indicate that ritonavir is active against all strains of HIV tested in a variety of transformed and primary human cell lines. The concentration of drug that inhibits 50% and 90% of viral replication in vitro is approximately 0.02 μM and 0.11 μM, respectively. Similar potencies were found with both AZT-sensitive and AZT-resistant strains of HIV. Studies which measured direct cell toxicity of ritonavir on several cell lines showed no direct toxicity at concentrations up to 25 μM, with a resulting in vitro therapeutic index of at least 1000.

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 84 (lle to Val), 82 (Val to Phe), 71 (Ala to Val), and 46 (Met to Ile). Phenotypic and genotypic changes in HIV isolates from selected patients treated with ritonavir were monitored in Phase I/II trials. Serial genotypic and phenotypic analysis indicated that susceptibility to ritonavir declined in an ordered and stepwise fashion. Initial mutations occurred at position 82 (Val to Ala/Phe), 54 (Ile to Val), 71 (Ala to Val/Thr), and 36 (Ile to Leu), followed by combinations of mutations at an additional

five specific amino acid positions. Viral strains isolated in vitro without a change at codon 82 did not have decreased susceptibility to ritonavir. The 82 mutation appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a greater than or equal to five fold decrease in viral sensitivity *in vitro* from baseline. The clinical relevance of phenotypic and genotypic changes associated with ritonavir therapy has not been established.

Cross-Resistance to Other Antiretrovirals

The potential for HIVcross-resistance between protease inhibitors has not been fully explored. Therefore, it is unknown what effect ritonavir therapy will have on the activity of concordantly or subsequently administered protease inhibitors. Serial HIV isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility in vitro but did not demonstrate a concordant decrease in susceptibility to saquinavir in vitro when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decreased susceptibility to indinavir in vitro (8-fold). Isolates from five patients were also tested for cross-resistance to amprenavir and nelfinavir; isolates from two patients had a decrease in susceptibility to nelfinavir (12- 14-fold), and none to amprenavir. Cross-resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. One ZDV-resistant HIV isolate tested in vitro retained full susceptibility to ritonavir.

Pharmacokinetics

In a single-dose pharmacokinetic study in HIV positive fasting male subjects, high levels of drug were achieved and maintained for several hours after oral administration of 100 mg, 200 mg, 400 mg, 600 mg, 800 mg or 1000 mg of ritonavir. Area under the concentration-time curve (AUC) ranged from 3.92 to 123 mcg•hr/mL, respectively and the maximal concentration (C_{max}) ranged from 0.416 to 12.7 mcg/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 three hours with increasing dose. Renal clearance averaged less than 0.1 L/h and was relatively constant throughout the dosage range. There is no parenteral formulation of ritonavir, therefore, the absolute bioavailability has not been determined.

A food effect is observed for NORVIR tablets. Food decreased the bioavailability of the ritonavir tablets when a single 100 mg dose of NORVIR was administered. Under high fat conditions (907 kcal; 52% fat, 15% protein, 33% carbohydrates), a 23% decrease in mean AUC(0-∞) [90% confidence intervals: ↓30%-↓15%], and a 23% decrease in mean Cmax [90% confidence intervals: ↓34%-↓11%]) was observed relative to fasting conditions. Under moderate fat conditions, a 21% decrease in mean AUC(0-∞) [90% confidence intervals: ↓28%-↓13%], and a 22% decrease in mean Cmax [90% confidence intervals: ↓33%-↓9%]) was observed relative to fasting conditions.

However, the type of meal administered did not change ritonavir tablet bioavailability when high fat was compared to moderate fat meals.

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 due to a time and dose-related increase in apparent clearance (Cl/F). Trough concentrations of ritonavir were observed to decrease over time, possibly due to enzyme induction, but appeared to stabilize by the end of two weeks. At steady state with a 600 mg bid dose, C_{max} and C_{trough} values of 11.2 and 3.7 mcg/mL were observed, respectively. The $t_{1/2}$ of ritonavir was approximately three to five hours. The steady-state apparent clearance in patients treated with 600 mg bid has averaged 8.8 ± 3.2 L/h.

No clinically significant differences in AUC or C_{max} were noted between males and females. Ritonavir pharmacokinetic parameters were not statistically significantly associated with body weight or lean body mass. The apparent volume of distribution (V_B/F) of ritonavir is approximately 0.41 ± 0.25 L/kg after a single 600 mg dose. The protein binding of ritonavir in human plasma was noted to be approximately 98 to 99%. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities. Total plasma protein binding is constant over the concentration range of 1 to 100 mcg/mL.

Tissue distribution studies with ^{14}C-labeled ritonavir in rats showed the liver, adrenals, pancreas, kidneys and thyroid to have the highest concentrations of drug. Tissue to plasma ratios of approximately one measured in rat lymph nodes suggests that ritonavir distributes into lymphatic tissues. Ritonavir penetrates minimally into the brain.

Ritonavir was noted to be extensively metabolized by the hepatic cytochrome P450 system, primarily isozyme CYP3A and to a lesser extent CYP2D6. Animal studies as well as in vitro experiments with human hepatic microsomes indicated that ritonavir primarily underwent oxidative metabolism. Five ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent drug. However, the AUC of the M-2 metabolite was approximately three percent of the AUC of parent drug.

Human studies with radiolabeled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered in the stool. In these studies renal elimination was not found to be a major route of elimination of ritonavir.
The pharmacokinetic profile of ritonavir in pediatric patients below the age of two years has not been established. Steady-state pharmacokinetics were evaluated in 37 HIV infected patients ages 2 to 14 years receiving doses ranging from 250 mg/m^2 bid to 400 mg/m^2 bid. Across dose groups, ritonavir steady-state oral clearance was approximately 1.5 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg/m^2 twice daily in pediatric patients were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m^2) twice daily.

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 **WARNINGS AND PRECAUTIONS**).

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

Hepatic Impairment
In six HIV-infected adult subjects with mild hepatic insufficiency dosed with ritonavir 400 mg bid, ritonavir exposures were similar to control subjects dosed with 500 mg bid. Results indicate that dose adjustment is not required in patients with mild hepatic impairment. Adequate pharmacokinetic data are not available for patients with moderate hepatic impairment. Protein binding of ritonavir was not statistically significantly affected by mild or moderately impaired hepatic function.

PRE-CLINICAL SAFETY DATA
Acute, Subacute and Chronic Toxicity
Ritonavir has a low order of acute toxicity when administered orally. The median lethal dose (LD50) 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, dyspnea 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 (RPE) 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 and Mutagenesis
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 tumor

responses in mouse liver associated with non-genotoxic compounds, are considered to have little relevance to the response of the human liver.

INDICATIONS AND USAGE

Ritonavir is indicated in combination with other antiretroviral agents for the treatment of patients with HIV-1 infection when therapy is warranted based on clinical and/or immunological evidence of disease progression.

CONTRAINDICATIONS

Ritonavir is contraindicated in patients with known hypersensitivity to ritonavir or any of its formulation excipients.

When co-administering ritonavir with other protease inhibitors, see the full prescribing 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 the drugs metabolized by cytochrome P450. Co-administration of ritonavir is contraindicated with the drugs listed in Table 1.

Table 1
Drugs that are Contraindicated with Ritonavir

Drug Class	**Drugs within Class that are Contraindicated with Ritonavir**	**Clinical comments**
$Alpha_1$-adrenoreceptor antagonist	Alfuzosin HCl	Potential for hypotension
Antianginal	Ranolazine	Potential for serious and/or life-threatening reactions
Antiarrhythmics	Amiodarone, bepridil, dronedarone, flecainide, propafenone, quinidine, encainide	Potential for cardiac arrhythmias
Antibiotic	Fusidic acid	Potential of increased fusidic acid-associated adverse events such as hepatitis or bone marrow suppression
Anticancer Agents	Neratinib apalutamide	Potential for serious and/or life-threatening reactions including hepatotoxicity. 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
Antipsychotics	Blonanserin Lurasidone Pimozide	May result in potential increase in frequency or intensity of known neurological or other toxicities associated with blonanserin Potential for serious and/or life-threatening reactions Potential for cardiac arrhythmias
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Post-marketing reports of acute ergot toxicity characterized by vasospasm and tissue ischemia have been associated with co-administration of ritonavir and ergonovine, ergotamine,

		dihydroergotamine or methylergonovine
GI motility agent	Cisapride	Potential for cardiac arrhythmias
Herbal products	St. John's Wort (hypericum perforatum)	Co-administration may lead to a decrease in ritonavir levels, and to loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors
Lipid-modifying agents HMG-CoA reductase inhibitors Microsomal triglyceride transfer protein (MTTP) Inhibitor	 Lovastatin, simvastatin Lomitapide	 Potential for myopathy including rhabdomyolysis 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-adrenoreceptor agonist	Salmeterol	May result in potential increased risk of cardiovascular adverse events associated with salmeterol
PDE5 inhibitor	Sildenafil* (Revatio®) only when used for the treatment of pulmonary arterial hypertension (PAH)	Increase potential for sildenafil-associated adverse events (which include hypotension, visual changes, sustained erection and syncope)
Sedative/hynoptics	Midazolam, triazolam	Ritonavir is likely to produce large increases in these highly metabolized sedatives and hypnotics resulting in the potential for prolonged or increase sedation or respiratory depression
* see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS** for co-administration of sildenafil in patients with erectile dysfunction		

WARNINGS AND PRECAUTIONS

When co-administering ritonavir with other protease inhibitors, see the full prescribing information for that protease inhibitor including Warnings and Precautions.

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

Hepatic Reactions
Ritonavir is principally metabolized and eliminated by the liver. Therefore caution should be exercised when administering this drug to patients with moderate to severe impaired hepatic function (see **CLINICAL PHARMACOLOGY**: 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 3). There may be an increased risk for 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/Hyperglycemia
New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia 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 hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In these patients who discontinued protease inhibitor therapy, hyperglycemia 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 these events has not been established.

Consideration should be given to the monitoring of blood glucose.

Drug Interactions

Antigout agents
Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

Antipsychotics
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 serious and life-threatening adverse reactions (see **DRUG INTERACTIONS**).

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

Concomitant use of ritonavir and fluticasone propionate can significantly increase fluticasone propionate plasma concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when ritonavir has been co-administered with inhaled or intranasally administered fluticasone propionate or budesonide (see **DRUG INTERACTIONS**).

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 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. Concomitant use of sildenafil with ritonavir is contraindicated in pulmonary arterial hypertension patients (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

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

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 **CONTRAINDICATIONS**). Caution must also be exercised and reduced doses should be considered if ritonavir is used concurrently with atorvastatin, which is metabolized to a lesser extent by CYP3A4. While rosuvastatin elimination is not dependant 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).

Alpha$_1$-Adrenoreceptor Antagonist

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

Antimycobacterial
Saquinavir/ritonavir should not be given together with rifampin, due to the risk of severe hepatotoxicity (presenting as increased hepatic transaminases) if the three drugs are given together.

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 (see **DRUG INTERACTIONS**). Bedaquiline must be used cautiously with ritonavir, only if the benefit of co-administration outweighs the risk.

Co-administration of delamanid with a strong inhibitor of CYP3A (ritonavir) may slightly increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with ritonavir is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (see **DRUG INTERACTIONS**).

Protease Inhibitor
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.

Resistance/Cross-Resistance
The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Therefore, it is unknown what effect ritonavir therapy will have on the activity of concordantly or subsequently administered protease inhibitors (see **CLINICAL PHARMACOLOGY**).

Laboratory Tests
Ritonavir has been associated with alterations in triglycerides, cholesterol, SGOT, SGPT, GGT, CPK and uric acid. 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.

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

PR Interval Prolongation
Ritonavir has been shown to cause modest asymptomatic prolongation of 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 ritonavir. Ritonavir should be used with caution in such patients (see CLINICAL PHARMACOLOGY).

Lipid Disorders
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.

Weight and Metabolic Parameters
An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including ritonavir. 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.

DRUG INTERACTIONS

When co-administering ritonavir with other protease inhibitors, see the full prescribing information for that protease inhibitor including information for drug interaction.
These examples are a guide and not considered a comprehensive list of all possible drugs that may interact with ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

Effects On Ritonavir
Agents which increase CYP3A activity (e.g. phenobarbital, carbamazepine, dexamethasone, phenytoin, rifampin and rifabutin) would be expected to increase the clearance of ritonavir resulting in decreased ritonavir plasma concentrations.
Tobacco use is associated with an 18% increase in the AUC of ritonavir.

Effects On Co-administered Drugs
Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms with the following rank order: CYP3A > CYP2D6 > CYP2C9, CYP2C19 >> CYP2A6, CYP1A2, CYP2E1. There is evidence that ritonavir may induce glucuronsyl transferases, CYP1A2, CYP2C9 and CYP2C19 enzymes; thus, decreased plasma concentration 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 the CONTRAINDICATIONS section, Table 3 summarizes some commonly prescribed drugs categorized by the predicted magnitude of interaction that could result if co-administered with ritonavir. Co-administration of ritonavir and drugs primarily metabolized 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 metabolized by CYP3A.

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

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%). 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.

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

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. Coadministration of venetoclax or ibrutinib with ritonavir could increase venetoclax or ibrutinib exposure potentially resulting in a serious risk of tumor lysis syndrome. Coadministration 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 is contraindicated (see CONTRAINDICATIONS).

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

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

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

Buspirone: Buspirone is primarily metabolised by CYP3A4. Concurrent administration of buspirone with drugs that potently inhibit CYP3A4, 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.

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]-hydroxyclarithromycin 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 patients with CL_{CR} 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 co-administered with ritonavir.

Colchicine: Concentrations of colchicine are expected to increase when coadministered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**). Refer to the colchicine prescribing information.

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. 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 (see **WARNINGS AND PRECAUTIONS: Drug Interactions**).

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 increase steady-state ritonavir $C_{max,}$ and AUC by approximately 50% and C_{min} by 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.

Desipramine: A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg q.12h. 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.

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.

Digoxin: A literature report has shown that co-administration of ritonavir (300mg 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.

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.

Elagolix: Coadministration 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.

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.

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

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

Inhaled, injectable, or intranasal fluticasone Propionate, budesonide, triamcinolone: Concomitant use of ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Consider alternatives to fluticasone propionate or budesonide, particularly for long-term use (see **WARNINGS AND PRECAUTIONS**).

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 (see **CONTRAINDICATIONS**).

Hypericum perforatum (St. John's Wort): 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** and **WARNINGS AND PRECAUTIONS**).

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 800mg twice daily are given with ritonavir. Adequate hydration and monitoring of the patients is warranted.

Ketoconazole: Concomitant administration of ritonavir (500 mg q12h) and ketoconazole (200 mg qd) 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.

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

Maraviroc: Concurrent administration of maraviroc with 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.

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

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. 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%. Appropriate doses for this combination, with respect to efficacy and safey, have not been established.

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

Quetiapine: Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Refer to quetiapine prescribing information for dosing instructions (see **WARNINGS AND PRECAUTIONS**).

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

Rifabutin: A pharmacokinetic study demonstrated that the concomitant administration of 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. Dosage reduction of rifabutin by at least three-quarters of the usual dose of 300 mg/day is recommended (e.g., 150 mg every other day or three times a week). Further dosage reduction may be necessary.

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

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 **WARNINGS AND PRECAUTIONS: Lipid Disorders**).
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.

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

PDE5 inhibitors:
Avanafil: A pharmacokinetic study demonstrated that concomitant administration of avanafil 50 mg with ritonavir 600 mg q.12h. 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 (see **WARNINGS AND PRECAUTIONS: Drug Interactions**).

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 sildenfil 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 (PAH) patients (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Tadalafil: Ritonavir (200 mg twice daily) increased tadalafil 20 mg single dose exposure (AUC) by 124% with no change in C_{max}, relative to the values for tadalafil 20 mg alone. Use tadalafil for the treatment of erectile

dysfunction with caution at reduced doses of no more than 10 mg every 72 hour period with increased monitoring for adverse events, when used in combination with ritonavir (see **WARNINGS AND PRECAUTIONS: Drug Interactions**).

Coadministration of ritonavir and tadalafil for the treatment of pulmonary arterial hypertension is not recommended.

Vardenafil: Ritonavir (600 mg twice daily) co-administered with vardenafil 5 mg resulted in a 49-fold increase in vardenafil AUC and a 13-fold increase in C_{max}. Consequently, use vardenafil with caution at reduced doses of no more than a single 2.5mg vardenafil dose in a 72 hour period when used in combination with ritonavir (see **WARNINGS AND PRECAUTIONS: Drug Interactions**).

Sulfamethoxazole/trimethoprim: A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 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.

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.

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.

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

Warfarin: In a pharmacokinetic study, multiple-dose ritonavir (400 mg bid) 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. Initial frequent monitoring of the INR during ritonavir and warfarin co-administration is indicated.

Zidovudine: A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 300 mg q6h 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.

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 2 and 3.

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

Drug	Effect on Ritonavir Ritonavir dosage	n	AUC% (95%CI)	C_{max}% (95%CI)
Clarithromycin 500 mg q.12h. 4 days	200 mg q.8h. 4 days	22	↑ 12% (2, 23%)	↑ 15% (2, 28%)
Didanosine 200 mg q.12h. 4 days	600 mg q.12h. 4 days	12	↔	↔
Fluconazole 400 mg day 1, 200mg daily 4 days	200 mg q.6h. 4 days	8	↑ 12% (5, 20%)	↑ 15% (7, 22%)
Fluoxetine 30 mg q.12h. 8 days	600 mg single dose	16	↑ 19% (7, 34%)	↔

Rifampin 600 mg or 300 mg daily 10 days	500 mg q.12h. 20 days	7,9*	↓ 35% (7, 55%)	↓ 25% (-5, 46%)
Zidovudine 200 mg q.8h. 4 days	300mg q.6h. 4 days	10	↔	↔

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

Table 3
Predicted effects on Drugs Co-administered with ritonavir

Drug Category	**Representative Drugs by Theoretical Prediction of Interaction Category**					
	Contraindicated Medications	**Large[1] ↑ AUC[2]**	**Moderate[1] ↑ AUC[2]**	**Moderate[1] ↑ or ↓ AUC[2]**	**Unknown**	**Possible ↓ AUC[2]**
Analgesics, Narcotics		Alfentanil Fentanyl	Hydrocodone Oxycodone Propoxyphene Tramadol		Levomethadyl (LAAM)	Codeine Hydromorphone Meperidine* Methadone* Morphine Naloxone Naltrexone
Analgesics, NSAID				Diclofenac Flurbiprofen Ibuprofen Indomethacin Piroxicam	Sulindac	Ketoprofen Ketorolac Naproxen Paracetamol
Antiarrhythmics	Amiodarone Dronedarone Encainide Flecainide Propafenone Quinidine	Lignocaine	Disopyramide Mexiletine Digoxin		Tocainide[4]	
Antiasthmatic						Theophylline*
Antibiotic macrolide		Erythromycin	Clarithromycin			
Antibiotic steroidal	Fusidic acid					
Anticoagulants				Warfarin		
Anticonvulsants		Carbamazepine	Clonazepam Ethosuximide		Phenobarbitone	Sodium valproate Lamotrigine Phenytoin
Antidepressants, tricyclic			Amitriptyline Clomipramine Desipramine* Imipramine Nortriptyline Trimipramine		Doxepin[4]	
Antidepressants, other		Nefazodone Sertraline	Fluoxetine Paroxetine Trazodone* Venlafaxine	Moclobemide	Fluvoxamine	Bupropion
Antidiarrhoeal						Diphenoxylate Loperamide
Antiemetics, Prokinetics	Cisapride		Dronabinol Ondansetron		Prochlorperazine[4] Promethazine[4]	Metoclopramide
Antifungals	Voriconazole		Itraconazole Ketoconazole* Miconazole			
Antigout	Colchicine					
Antihistamine	Astemizole Terfenadine	Loratadine				
Antihypertensives	Alfuzosin	Bosentan	Triamterene	Losartan	Doxazosin[4] Prazosin[4] Terazosin[4]	
Antimycobacterial		Rifabutin*				
Antiparasitics		Quinine		Proguanil	Albendazole Chloroquine Metronidazole Primaquine Pyrimethamine	Atovaquone
Antipsychotics	Blonanserin					
Antiulcer agents				Lansoprazole Omeprazole		
Beta-blockers			Metoprolol Pindolol Timolol	Propranolol	Betaxolol[4]	Labetalol
Beta$_2$-agonist (long acting)	Salmeterol					
Calcium channel blockers	Beprildil	Amlodipine Diltiazem Felodipine Nifedipine				

		Nimodipine Verapamil				
Cancer chemotherapy	Apalutamide Neratinib	Abemaciclib Encorafenib Tamoxifen Dasatinib Ivosidenib Nilotinib	Etoposide Fostamatinib's metabolite R406 Paclitaxel Vinblastine Vincristine	Cyclophosphamide[3] Ifosfamide[3]	Apalutamide[4] Daunorubicin[4] Doxorubicin[4]	
Ergot alkaloides and derivatives	Dihydroergotamine Ergonovine[4] Erogotamine Methylergonovine[4]	Bromocriptine			Methysergide[4]	
Gonadotropin releasing hormone (GnRH) receptor antagonist					Elagolix[4]	
Herbal products	St. John's Wort					
HCV Antivirals		Glecaprevir/pibrentasvir				
Corticosteroids/ steroid hormones		Dexamethasone Finasteride Flutamide Prednisone Fluticasone*	Anabolic steroids Levonorgestrel Medroxyprogest-erone Norethinderone Prednisone Testosterone			Ethynyloestradiol
HIV-antivirals		Atazanavir Darunavir (Fos)amprenavir Indinavir* Saquinavir* Tipranavir	Maraviroc		Nevirapine[4]	Didanosine Zidovudine
Hypoglycaemics				Glimepiride Glipizide Glibenclamide Glyburide Tolbutamide		
Hypolipidaemics	Lomitapide Lovastatin Simvastatin	Fluvastatin Atorvastatin	Pravastatin Rosuvastatin		Gemfibrozil	
Immunosupress-ants		Cyclosporin Everolimus[4] Tacrolimus Sirolimus (rapamycin)				
Neuroleptics	Pimozide		Chlorpromazine Haloperidol Perphenazine Risperidone Thioridazine			Clozapine
PDE5 inhibitors	Sildenafil indicated for PAH	Avanafil Sildenafil indicated for ED Tadalafil Vardenafil				
Sedative/hypnotic	Midazolam Triazolam	Clonazepam Buspirone	Clorazepate Diazepam Estazolam Flurazepam Zolpidem			Lorazepam Oxazepam Propofol Temazepam
Steroids		Dexamethasone Fluticasone*	Prednisone			Ethinylestradiol*
Stimulants/ Decongestants/ Antitussives			Dextromethor-phan Dexfenfluramine Methampheta-mine		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 drugs.
4 A possible increase in concentration is more likely when combined with ritonavir
* Clinical drug interaction study has been performed

PREGNANCY AND LACTATION

Pregnancy, Fertility and Reproduction

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 dosages were not feasible due to hepatic toxicity.

No treatment-related malformations were observed with ritonavir in either rats or rabbits. Developmental toxicity observed in rats (early resorptions, decreased fetal 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 fetal weights) occurred at a maternally toxic dosage of 110 mg/kg/day.
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 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.
Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefits clearly outweigh the potential risks.

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

Pediatric Patients
The safety and pharmacokinetic profile of ritonavir in pediatric patients below the age of two years have not been established. In HIV-infected patients age 2 to 16 years, the adverse event profile seen during a clinical trial and post marketing experience was similar to that for adult patients. The evaluation of the antiviral activity of ritonavir in pediatric patients in clinical trials is ongoing.

ADVERSE REACTIONS

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

The most frequently reported clinical drug reactions, among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances (including paresthesias and oral paresthesia); 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 to IV Studies (N = 1,755)

Adverse Reactions*	**n**	**%**
Immune system disorders		
Hypersensitivity including urticaria and face edema*	114	8.2
Metabolism and nutrition disorders		
Edema and Peripheral Edema*	110	6.3
Gout*	24	1.4
Hypercholesterolemia*	52	3.0
Hypertriglyceridemia*	158	9.0
Psychiatric disorders		
Confusion*	52	3.0
Disturbance in attention	44	2.5
Nervous system disorders		
Dizziness*	274	15.6
Dysgeusia*	285	16.2
Paresthesia (including oral paresthesia)*	889	50.7
Peripheral neuropathy	178	10.1
Syncope	58	3.3
Eye disorders		
Blurred vision	113	6.4
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal Pain*	279	15.9

Coughing*	380	21.7
Gastrointestinal disorders		
Abdominal pain (upper and lower)*	464	26.4
Diarrhea Including Severe with Electrolyte Imbalance*	1,192	67.9
Dyspepsia	201	11.5
Flatulence	142	8.1
Gastrointestinal hemorrhage*	41	2.3
Gastroesophageal Reflux Disease (GERD)	19	1.1
Nausea	1,007	57.4
Vomiting*	559	31.9
Hepatobiliar disorders		
Blood bilirubin increased (including jaundice)*	25	1.4
Hepatitis (including increased AST, ALT, GGT)*	153	8.7
Skin and subcutaneous tissue disorders		
Acne*	67	3.8
Pruritus*	214	12.2
Rash (includes erythematous and maculopapular)*	475	27.1
Musculoskeletal and connective tissue disorders		
Arthralgia and back pain*	326	18.6
Myopathy/creatine phosphokinase increased*	66	3.8
Myalgia	156	8.9
Renal and urinary disorders		
Increased urination*	74	4.2
General disorders and administration site conditions		
Fatigue including asthenia*	811	46.2
Vascular procedures		
Flushing, feeling hot*	232	13.2
Hypertension*	58	3.3
Hypotension Including Orthostatic Hypotension*	30	1.7
Peripheral coldness*	21	1.2

* Represents a medical concept including several similar MedDRA PTs

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Adverse events occurring in less than 2% of adult patients receiving NORVIR® in all Phase 2/Phase 3 studies and considered at least possibly related or of unknown relationship to treatment and of at least moderate intensity are listed below by body system.

Body as a Whole:	Abdomen enlarged, accidental injury, cachexia, chest pain, chills, facial pain, flu syndrome, hormone level altered, hypothermia, kidney pain, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, and substernal chest pain.
Cardiovascular System:	Cardiovascular disorder, cerebral ischemia, cerebral venous thrombosis, hemorrhage, migraine, myocardial infarct, palpitation, peripheral vascular disorder, phlebitis, postural hypotension, tachycardia, and vasospasm.
Digestive System:	Abnormal stools, bloody diarrhea, cheilitis, cholangitis, cholestatic jaundice, colitis, dry mouth, dysphagia, eructation, esophageal ulcer, esophagitis, gastritis, gastroenteritis, gastrointestinal disorder, gingivitis, hepatic coma, hepatomegaly, hepatosplenomegaly, ileitis, ileus, liver damage, melena, mouth ulcer, oral moniliasis, pancreatitis, periodontal abscess, pseudomembranous colitis, rectal disorder, rectal hemorrhage, sialadenitis, stomatitis, tenesmus, thirst, tongue edema, and ulcerative colitis.
Endocrine System:	Adrenal cortex insufficiency and diabetes mellitus.
Hemic and Lymphatic System:	Acute myeloblastic leukemia, anemia, ecchymosis, leukopenia, lymphadenopathy, lymphocytosis, myeloproliferative disorder, and thrombocytopenia.
Metabolism and Nutritional Disorders:	Albuminuria, alcohol intolerance, avitaminosis, BUN increased, dehydration, enzymatic abnormality, glycosuria, and xanthomatosis.
Musculoskeletal System:	Arthritis, arthrosis, bone disorder, bone pain, extraocular palsy, joint disorder, leg cramps, muscle cramps, muscle weakness, myositis, and twitching.

Nervous System:	Abnormal dreams, abnormal gait, agitation, amnesia, aphasia, ataxia, coma, convulsion, dementia, depersonalization, diplopia, emotional lability, euphoria, grand mal convulsion, hallucinations, hyperesthesia, hyperkinesia, hypesthesia, incoordination, libido decreased, manic reaction, nervousness, neuralgia, neuropathy, paralysis, peripheral neuropathic pain, peripheral sensory neuropathy, personality disorder, sleep disorder, speech disorder, stupor, subdural hematoma, tremor, urinary retention, vertigo, and vestibular disorder.
Respiratory System:	Asthma, bronchitis, dyspnea, epistaxis, hiccup, hypoventilation, interstitial pneumonia, larynx edema, lung disorder, rhinitis, and sinusitis.
Skin and Appendages:	Contact dermatitis, dry skin, eczema, erythema multiforme, exfoliative dermatitis, folliculitis, fungal dermatitis, furunculosis, molluscum contagiosum, onychomycosis, psoriasis, pustular rash, seborrhea, skin discoloration, skin disorder, skin hypertrophy, skin melanoma, and vesiculobullous rash.
Special Senses:	Abnormal electro-oculogram, abnormal electroretinogram, abnormal vision, amblyopia/blurred vision, blepharitis, conjunctivitis, ear pain, eye disorder, eye pain, hearing impairment, increased cerumen, iritis, parosmia, photophobia, taste loss, tinnitus, uveitis, visual field defect, and vitreous disorder.
Urogenital System:	Acute kidney failure, breast pain, cystitis, dysuria, hematuria, impotence, kidney calculus, kidney failure, kidney function abnormal, kidney pain, menorrhagia, penis disorder, polyuria, pyelonephritis, urethritis, urinary frequency, urinary tract infection, and vaginitis.

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

Patient Exceeding Extreme Limit Criteria for Clinical Chemistry and Hematology Variables in Phase II/III Combined Studies

Variable		**n**	**%**
CHEMISTRY			
Glucose	(high) > 250 mg/dL	6	1
Glucose	(low) < 40 mg/dL	1	<1
BUN	(high) > 120 mg/dL	0	0
Creatinine	(high) > 3.6 mg/dL	1	<1
Uric Acid	(high) > 12 mg/dL	20	2
Sodium	(high) > 157 mEq/L	2	<1
Sodium	(low) < 123 mEq/L	2	<1
Potassium	(high) > 6 mEq/L	5	<1
Potassium	(low) < 3 mEq/L	15	2
Chloride	(high) > 122 mEq/L	4	<1
Chloride	(low) < 84 mEq/L	1	<1
Calcium, total	(high) > 12.6 mEq/L	1	<1
Calcium, total	(low) < 6.9 mEq/L	8	1
Inorg. Phosphorus	(high) > 7.0 mg/dL	1	<1
Inorg. Phosphorus	(low) < 1.4 mg/dL	0	0
Magnesium	(high) > 2.9 mEq/L	10	1
Magnesium	(low) < 1.0 mEq/L	5	<1
Albumin	(high) > 6.7 g/dL	0	0
Albumin	(low) < 2 g/dL	2	<1
Total Bilirubin	(high) > 3.6 mg/dL	11	1
Alkaline Phosphatase	(high) > 550 IU/L	10	1
SGOT (AST)	(high) > 180 IU/L	37	4
SGPT (ALT)	(high) > 215 IU/L	53	6
LDH	(high) > 1170 IU/L	5	<1

GGT	(high) > 300 IU/L	102	12
Cholesterol	(high) > 5 x ULN[1]	0	0
Triglycerides	(high) > 1500 mg/dL	69	7
Amylase	(high) > 2 x ULN[1]	20	2
CPK	(high) > 1000 IU/L	71	8
HEMATOLOGY			
Hemoglobin	(high) > 21 g/dL	0	0
Hemoglobin	(low) < 8 g/dL	23	3
Hematocrit	(low) < 30%	77	8
RBC	(low) < 3.0 x 10^{12}/L	89	9.5
WBC	(high) > 25 x 10^9/L	8	1
WBC	(low) < 2.5 x 10^9/L	146	16
Platelet count	(low) < 20 x 10^9/L	4	<1
Neutrophils	(high) > 20 x 10^9/L	9	1
Neutrophils	(low) < 0.5 x 10^9/L	25	3
Eosinophils	(high) > 1.0 x 10^9/L	15	2
Prothrombin Time	(high) > 1.5 x ULN[1]	6	1
Activated Partial Thromboplastin time	(high) > 2.3 x ULN[1]	3	<1

1 ULN = upper limit of the normal range

Metabolic Parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see **WARNINGS AND PRECAUTIONS**).

OVERDOSAGE
Human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg/day for two days and reported paresthesias which resolved after the dose was decreased. A post-marketing case of renal failure with eosinophilia has been reported with ritonavir overdose.
Ritonavir has a low order of acute toxicity when administered orally. The ALD (approximate lethal dose) or LD50 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 the **PRE-CLINICAL SAFETY DATA** section of this document.

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

DOSAGE AND ADMINISTRATION

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

Adults
Tablets
The recommended dose of ritonavir tablets is 600 mg (six tablets) twice daily by mouth and should be given with food. Ritonavir tablets should be swallowed whole and not chewed, broken or crushed.
Patients who take the 600 mg twice daily soft gel capsule dose may experience more gastrointestinal side effects such as nausea, vomiting, abdominal pain or diarrhea when switching from the soft gel capsule to the tablet formulation because of greater maximum plasma concentration (C_{max}) achieved with the tablet formulation relative to the soft gel capsule (see **CLINICAL PHARMACOLOGY**).

Use of a dose titration schedule may help to reduce treatment emergent adverse events while maintaining appropriate ritonavir plasma levels. Ritonavir should be started at no less than 300 mg twice daily for a period of three days and increased by 100 mg twice daily increments up to 600 mg twice daily over a period of no longer than 14 days. Patients should be aware that frequently observed adverse events, such as mild to moderate gastrointestinal disturbances and paresthesias, may diminish as therapy is continued. Patients should not remain on 300 mg twice daily for more than three days.

Pediatric Patients
Ritonavir should be used in combination with other antiretroviral agents. The recommended dosage of ritonavir is 400 mg/ m^2 of body surface area twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m^2 and increased at two to three day intervals by 50 mg/ m^2 twice daily until the recommended twice daily dose is achieved. If patients do not tolerate the maximum daily dose due to adverse events, the highest tolerated dose should be used for maintenance therapy in combination with other antiretroviral agents.

Pediatric Dosage Guidelines				
Body Surface Area (m^2)	**Twice Daily Dose 250 mg/m^2**	**Twice Daily Dose 300 mg/m^2**	**Twice Daily Dose 350 mg/m^2**	**Twice Daily Dose 400 mg/m^2**
0.25	62.5 mg	75 mg	87.5 mg	100 mg
0.50	125 mg	150 mg	175 mg	200 mg
1.00	250 mg	300 mg	350 mg	400 mg
1.25	312.5 mg	375 mg	437.5 mg	500 mg
1.50	375 mg	450 mg	525 mg	600 mg

*Body surface area can be calculated with the following equation: BSA (m^2) = SQR RT ([Height (cm) x Weight (kg)] / 3600) or ([Height (cm) x Weight (kg)] / 3600)$^{1/2}$

The tablet formulation may not be suitable for paediatric use in some cases.

STORAGE
Ritonavir tablets should be stored at or below 30ºC.
Store in the original bottle in order to protect from moisture.

HOW SUPPLIED
Tablets
Ritonavir tablets are white film-coated oval tablets debossed with “NK” on one side providing 100 mg ritonavir.
Ritonavir tablets are available in bottles containing 30 or 60 tablets.

Not all pack sizes may be available locally.

MANUFACTURER
Tablets
AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

CCDS02340822
Date of Issue: DD MMM YYYY