RITONAVIR

PRODUCT NAME

Ritonavir tablets

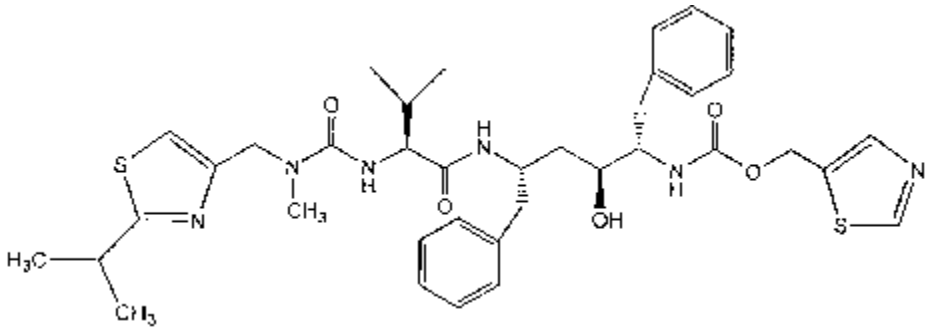
Trade Name
Norvir®

DESCRIPTION

Ritonavir is an inhibitor of HIV protease with activity against the Human Immunodeficiency Virus (HIV).

Ritonavir is a white to light (off white) 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)-2,4,7,12-tetraazatridecan-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/sorbitan laurate, colloidal sillicon 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, hydroxypropyl cellulose talc, polyethylene glycol 3350/macrogol type 3350, colloidal silicon dioxide/colloidal silica anhydrous, and polysorbate 80.

INDICATIONS AND USAGE

Norvir Tablet
Ritonavir is indicated as a pharmacokinetic enhancer of co-administered protease inhibitors as part of antiretroviral combination therapy for the treatment of patients with HIV-1 infection.

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.

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

When ritonavir tablets are used as a pharmacokinetic enhancer for another antiretroviral protease inhibitor up to a maximum daily dose of 200 mg, the Prescribing Information of the particular protease inhibitor should be consulted.

Adults

Tablets

When ritonavir is used as a pharmacokinetic enhancer for another antiretroviral protease inhibitor, the Prescribing Information of the particular protease inhibitor should be consulted.

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

Dual PI Containing Combination Regimens

Ritonavir extensively inhibits the metabolism of most available protease inhibitors. Hence, any consideration of dual therapy with ritonavir should take into account the pharmacokinetic interaction and safety data of involved agents. There is extensive cross-resistance in this class of agents. The combination of two PIs with the least overlapping patterns of resistance should be considered. The use of ritonavir in such regimens should be guided by these factors.

Pediatric

Ritonavir should be used in combination with other antiretroviral agents. When ritonavir is used as a pharmacokinetic enhancer for another antiretroviral protease inhibitor, the Prescribing Information of the particular protease inhibitor should be consulted. The highest tolerated dose should be used for maintenance therapy in combination with other antiretroviral agents. When possible, dose should be administered using a calibrated dosing syringe.

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**
Alpha1-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 blonaserin. 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 coadministration 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:	lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.

Microsomal triglyceride transfer protein (MTTP) Inhibitor	lomitapide	Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated (see prescribing information for lomitapide).
Long acting beta-adrenoceptor agonist	salmeterol	May result in potential increased risk of cardiovascular adverse events associated with salmeterol.
PDE5 inhibitor	sildenafil* (Revatio®) only when used for the treatment of pulmonary arterial hypertension (PAH)	Increased potential for sildenafil associated adverse events (which include hypotension and syncope).
Sedative/hypnotics	midazolam, triazolam	Ritonavir is likely to produce large increases in these highly metabolized sedatives and hypnotics resulting in the potential for prolonged or increased sedation or respiratory depression.
*see Warnings and Precautions and Drug Interactions for coadministration 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 hepatic impairment (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 toxicities (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, or injectable triamcinolone (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. Coadministration 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 coadministration 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 dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see **Table 1**).

Alpha$_1$-Adrenoreceptor Antagonist

Based on results of a drug interaction study with ketoconazole, another potent inhibitor of CYP3A4, and alfuzosin, a significant increase in alfuzosin exposure is expected in the presence of ritonavir (600 mg twice daily). 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 200 mg ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity.

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.

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including Norvir. During the initial phase of combination antiretroviral treatment when the immune system responds, patients may develop an inflammatory response to asymptomatic or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci pneumonia*, or tuberculosis), which may necessitate further evaluation and treatment.

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

DRUG INTERACTIONS

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

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

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% decrease in the AUC of ritonavir.

Effects On Coadministered Drugs

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms with the following ranked order: CYP3A4 > CYP2D6 > CYP2C9 > CYP2C19 >> CYP2A6, CYP1A2, CYP2E1. There is evidence that ritonavir may induce glucuronosyl transferase, CYP1A2, CYP2C9, and CYP2C19 enzymes; thus, decreased plasma concentrations of the other drug and loss of therapeutic effects during ritonavir co-administration may signify the need for dosage alteration of these agents. In addition to the drugs listed in 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 coadministered with disopyramide, mexiletine, nefazodone, or fluoxetine. The possibility of drug interaction cannot be excluded.

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%). Similarly, a statistically significant effect was observed on the sedation effect curve but not on the extent of sedation. Mild psychomotor impairment was confounded by a learning effect. These pharmacokinetic and pharmacodynamic results are inconsistent when considering the pharmacologic effect of alprazolam. These results were not considered clinically significant.

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 section 4 above).

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 concentrations (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 metabolized 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.

Clarithromycin: A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg q.8h. and clarithromycin 500 mg q.12h. resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31%, C_{min} increased by 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-[R]-hydroxy-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be

necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 gm/day should not be coadministered 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 100mg 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 400 mg three times daily with ritonavir 600 mg 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 about 75%. Based on comparison to historical data, the pharmacokinetics of delavirdine did not appear to be affected by ritonavir. When used in combination with delavirdine, a dose reduction of ritonavir should be considered.

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 q.12h. and didanosine (ddI) 200 mg q.12h. 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 ritonavir therapy should not be necessary; however, dosing of the two drugs should be separated by 2.5 hours to avoid formulation incompatibility.

Digoxin: A literature report has shown that coadministration of ritonavir (300 mg 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.

Efavirenz: In healthy volunteers receiving 500 mg ritonavir twice daily with efavirenz 600 mg once daily, the steady state AUC of efavirenz was increased by 21%. An associated increase in the AUC of ritonavir of 17% was observed.

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 metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Consider alternatives to fluticasone propionate budesonide, and injectable triamcinolone, particularly for longterm use (see **WARNINGS AND PRECAUTIONS**).

Fusidic Acid: Coadministration 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 (H*ypericum 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. Coadministration of ritonavir with indinavir will result in increased indinavir serum concentrations. There are limited safety or efficacy data available on the use of this combination in patients. The risk of nephrolithiasis may be increased when doses of indinavir equal to or greater than 800 mg twice daily are given with ritonavir. Adequate hydration and monitoring of the patients is warranted.

Ketoconazole: Concomitant administration of ritonavir (500 mg q.12h.) and ketoconazole (200 mg q.d.) 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 of ketoconazole 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: Coadministration 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 400 mg twice daily significantly increases the concentrations of M8 (the major active metabolite of nelfinavir), and results in a smaller increase in nelfinavir concentrations. In a study in ten patients nelfinavir 750 mg and ritonavir 400 mg twice daily yielded slightly higher nelfinavir AUC (160%), C_{max} (121%) and C_{trough} (123%) than historical data for nelfinavir 750 mg three times daily monotherapy. The AUC of M8 was increased by 347%.

Oral Contraceptives or Patch Contraceptives: A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg q.12h. and a fixed-combination oral contraceptive resulted in reductions of the ethinyl estradiol mean C_{max} and mean AUC by 32% and 40%, respectively. Increased doses of oral contraceptives or patch contraceptives containing ethinyl estradiol, or alternate methods of contraception, should be considered.

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 500 mg q.12h. and rifabutin resulted in an approximate 4 fold and 35 fold increase in the AUC of rifabutin and its active metabolite 25-O-deacetyl rifabutin, respectively. The significance of this interaction has been confirmed in clinical trials.

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

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

Saquinavir: A pharmacokinetic study demonstrated that ritonavir extensively inhibits the metabolism of saquinavir resulting in greatly increased saquinavir plasma concentrations.

Following approximately four weeks of a combination regimen of saquinavir hard gel capsules (400 or 600 mg b.i.d.) and ritonavir (400 or 600 mg b.i.d.) in HIV-infected patients, saquinavir AUC values were at least 17-fold greater than historical AUC values from patients who received saquinavir 600 mg t.i.d. without ritonavir. When used in combination therapy for up to 24 weeks, doses greater than 400 mg b.i.d. of either ritonavir or saquinavir were associated with an increase in adverse events. Plasma exposures achieved with Invirase® (saquinavir mesylate hard gel capsules) (400 mg b.i.d.) and ritonavir (400 mg b.i.d.) are similar to those achieved with Fortovase™ (saquinavir soft gel capsules) (400 mg b.i.d.) and ritonavir (400 mg b.i.d.).

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. Coadministration of ritonavir with sildenafil is expected to substantially increase sildenafil concentrations (11-fold increase in AUC) and may result in an increase in sildenafil-associated adverse events, including hypotension, syncope, visual changes, and prolonged erection.

Concomitant use of sildenafil with ritonavir is contraindicated in pulmonary arterial hypertension (PAH) patients (see **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS**).

Tadalafil: Use tadalafil for the treatment of erectile dysfunction with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events (see **WARNINGS AND PRECAUTIONS: Drug Interactions**). When tadalafil is used concomitantly with ritonavir in patients with pulmonary arterial hypertension, refer to the tadalafil label for prescribing information.

Vardenafil: Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events. (see **WARNINGS AND PRECAUTIONS: Drug Interactions**).

Sulfamethoxazole/Trimethoprim: A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg q.12h. and sulfamethoxazole/trimethoprim resulted in a 20% reduction of the sulfamethoxazole AUC and a 20% increase of the

trimethoprim AUC. Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.

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

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 400 mg 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 coadministration. The net effect of ritonavir coadministration 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 coadministration is indicated.

Zidovudine: A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 300 mg q.6h. and zidovudine (AZT) 200 mg q.8h. resulted in a reduction of the zidovudine C_{max} and AUC of 27% and 25%, respectively. In contrast, little if any effect was noted on ritonavir pharmacokinetics. Dose alteration of AZT during concomitant ritonavir therapy should not be necessary.

Table 2

Effect on AUC and C_{max} of Coadministration 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	200mg 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, 200 mg 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	300 mg 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 Coadministered With Ritonavir
(Contraindicated Medications are Listed in Column 1)

Drug Category		**Representative Drugs by Theoretical Prediction of Interaction Category**				
	Contraindicated Medication	Large [1] ↑AUC[2]	Moderate[1] ↑ AUC[2]	Moderate[1] ↑ or ↓AUC[2]	Unknown	Possible ↓ AUC[2]
Analgesic , narcotic		Alfentanil Fentanyl	Hydrocodone Oxycodone Propoxyphene Tramadol		Levamethadyl (LAAM)	Codeine Hydromorphone Meperidine* Methadone* Morphine
Analgesic, nonsteroidal				Diclofenac Flurbiprofen Ibuprofen Indomethacin	Nabumetone Sulindac	Ketoprofen Ketorolac Naproxen
Antiarrhythmics	Amiodarone Dronedarone Encainide Flecainide Propafenone Quinidine	Lidocaine	Disopyramide Mexiletine		Tocainide[4]	
Antiasthmatic						Theophylline*
Antibiotic, macrolide		Erythromycin	Clarithromycin*			
Antibiotic, steroidal	Fucidic Acid					
Anticonvulsants		Carbamazepine	Clonazepam Ethosuximide		Phenobarbital	Divalproex Lamotrigine Phenytoin
Antidepressants, tricyclic			Amitriptyline Clomipramine Desipramine* Imipramine Maprotiline Nortriptyline Trimipramine		Doxepin[4]	
Antidepressants, SSRIs and non-tricyclic		Nefazodone Sertraline	Fluoxetine Paroxetine Trazodone Venlafaxine		Fluvoxamine	Bupropion
Antidiarrheal						Diphenoxylate Loperamide
Antiemetics, Prokinetics	Cisapride		Dronabinol Ondansetron		Prochlorperazine[4] Promethazine[4]	Metoclopramide
Antifungal agents	Voriconazole	Itraconazole Ketoconazole* Miconazole				
Antigout	Colchicine					
Antihistamine	Astemizole Terfenadine	Loratidine				
Antihypertensives	Alfuzosin	Bosentan		Losartan	Doxazosin[4] Prazosin[4] Terazosin[4]	
Antimycobacterial		Rifabutin*			Ethionamide	
Antiparasitics		Quinine		Proguanil	Albendazole Chloroquine Primaquine Pyrimethamine Trimetrexate	Atovaquone
Antipsychotics	Blonanserin					
Antiulcer Agents				Lansoprazole Omeprazole		
β -blockers			Metoprolol Penbutolol Pindolol Timolol	Propranolol	Betaxolol[4]	
β –agonist (long acting)	Salmeterol					
Calcium channel blockers	Bepridil	Amlodipine Diltiazem Felodipine Isradipine Nicardipine Nifedipine Nimodipine				

		Nisoldipine Nitrendipine Verapamil				
Cancer chemotherapeutic agents	Apalutamide Neratinib	Abemaciclib Encorafenib Tamoxifen Dasatinib Ivosidenib Nilotinib	Etoposide Fostamatinib's metabolite R406 Paclitaxel Vinblastine Vincristine	Cyclophosphamide[3] Ifosfamide[3]	Apalutamide[4] Daunorubisin[4] Doxorubicin[4]	
Ergot alkaloids and derivatives	Dihydroergotamine Ergonovine[4] Ergotamine Methylergonovine[4]	Bromocriptine			Methysergide[4]	
Gonadotropin releasing hormone (GnRH) receptor antagonist					Elagolix[4]	
Hemorheologic agent					Pentoxifylline	
Herbal Products	St. John's Worts					
HCV Antivirals		Glecaprevir/pibrentasvir				
HIV Antivirals		Atazanavir Darunavir (fos) amprenavir Indinavir* Saquinavir* Tipranavir	Maraviroc		Nevirapine[4]	
Hypoglycemics				Gimipiride Glipizide Glyburide Tolbutamide		
Hypolipidemics	Lomitapide Lovastatin Simvastatin	Atorvastatin	Rosuvastatin		Gemfibrozil	Clofibrate
Immunosuppressants		Cyclosporine Everolimus[4] Tacrolimus Sirolimus (rapamycin)				
Neuroleptics	Pimozide		Chlorpromazine Haloperidol Perphenazine Risperidone Thioridazine			Clozapine
PDE5 inhibitor	Sildenafil indicated for PAH	Avanafil Sildenafil indicated for ED Tadalafil Vardenafil				
Sedative/hypnotics	Midazolam Triazolam	Buspirone	Cloazepate Diazepam Estazolam Flurazepam Zolpidem			Lorazepam Oxazepam Propofol Temazepam
Steroids		Dexamethasone Fluticasone*	Prednisone			Ethinyl Estradiol*
Stimulants			Dexfenfluramine Methamphetamine		Methylphenidate	

[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 the 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

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.

Pregnancy

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.

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.

Lactation

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

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

ADVERSE REACTIONS

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

Adults

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

Adverse Reactions	n	%
Eye disorders		

Blurred vision	113	6.4
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
General disorders and administration site conditions		
Fatigue including asthenia*	811	46.2
Hepatobiliary disorders		
Blood bilirubin increased (including jaundice)*	25	1.4
Hepatitis (including increased AST, ALT, GGT)*	153	8.7
Immune system disorders		
Hypersensivity including urticatria 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
Musculoskeletal and connective tissue disorders		
Arthralgia and back pain*	326	18.6
Myopathy/creatine phosphokinase increased*	66	3.8
Myalgia	156	8.9
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
Psychiatric disorders		
Confusion*	52	3.0
Disturbance in attention	44	2.5
Renal and urinary disorders		
Increased urination*	74	4.2
Respiratory, thoracic and mediastinal disorders		
Coughing*	380	21.7

Oropharyngeal Pain*	279	15.9
Skin and subcutaneous tissue disorders		
Acne*	67	3.8
Pruritus*	214	12.2
Rash (includes erythematous and maculopapular)*	475	27.1
Vascular disorders		
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		

ADR- Pediatric

Treatment-Emergent Adverse Events

Ritonavir has been studied in 265 pediatric patients >1 month to 21 years of age. The adverse event profile observed during pediatric clinical trials was similar to that for adult patients.

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

Laboratory Abnormalities

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

ADR-Post-Marketing Experience

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

Metabolism and nutrition disorders: Dehydration, usually associated with gastrointestinal symptoms, and sometimes resulting in hypotension, syncope, or renal insufficiency has been reported. Syncope, orthostatic hypotension and renal insufficiency have also been reported without known dehydration.

Cardiac disorders: Myocardial infarction has been reported.

Reproductive system and breast disorders: Menorrhagia has been reported.

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

***Renal and urinary disorders**:* Nephrolithiasis

LABORATORY DETERMINATIONS

Table 5
Adult Patients Exceeding Extreme Limit Criteria for Clinical Chemistry and 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

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 LD_{50} was found to be greater than 2500 mg/kg in both mice and rats. The no-effect-level was 200 mg/kg in mice and 250 mg/kg in rats. Clinical signs observed during toxicity studies in laboratory animals are noted in the **PRE-CLINICAL SAFETY DATA** section.

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.

PHARMACOLOGIC PROPERTIES

Mechanism of Action

Pharmacokinetic enhancement by ritonavir is based on ritonavir's activity as a potent inhibitor of CYP3A-mediated metabolism. The degree of enhancement is related to the metabolic pathway of the co-administered protease inhibitor and the impact of the co-administered protease inhibitor on the metabolism of ritonavir. Maximal inhibition of metabolism of the co-administered protease inhibitor is achieved most commonly with ritonavir doses of 100 mg to 200 mg daily, and is dependent on the co-administered protease inhibitor.

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

Cross-Resistance To Other Antiretrovirals

The potential for HIV cross-resistance between protease inhibitors has not been fully explored.Therefore, it is unknown what effect ritonavir therapy will have on the activity of concordantly or subsequently administered protease inhibitors. Serial HIV isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility *in vitro* but did not demonstrate a concordant decrease in susceptibility to saquinavir *in vitro* when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decreased susceptibility to indinavir *in vitro* (8-fold). Isolates from five patients were also tested for cross-resistance to amprenavir and nelfinavir; isolates from two patients had a decrease in susceptibility to nelfinavir (12 - 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 Properties

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 .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.

After a single 600 mg dose under non-fasting conditions the 100 mg (n=57) soft gelatin capsule and the oral solution (n=18) formulations yielded mean ± SD AUCs of 121.7 ± 53.8 mcg•h/mL and 129.0 ± 39.3 mcg•h/mL, respectively. Plasma concentrations of ritonavir after administration of a single 100 mg dose tablet are similar to the 100 mg soft gelatin capsule under fed conditions.

Relative to fasting conditions, the extent of absorption of ritonavir from the soft gelatin capsule formulation was 12% higher when administered with a meal. When the liquid formulation was given under fasting conditions, peak ritonavir concentrations increased 28%, relative to nonfasting conditions. Food decreases the bioavailability of the ritonavir tablet. Administration of a single 100 mg dose of ritonavir tablet with a moderate fat meal (857 kcal, 31% calories from fat) or a high fat meal (907 kcal, 52% calories from fat) was associated with a mean decrease of 20-23% in ritonavir AUC and C_{max}.

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.

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

Pediatric

Steady-state pharmacokinetics were evaluated in 37 HIV-infected patients ages 2 to 14 years receiving doses ranging from 250 mg/m^2 twice daily to 400 mg/m2 twice daily in Pediatric AIDS Clinical Trial Group (PACTG) Study 310, and in 41 HIV-infected patients ages 1 month to 2 years at doses of 350 and 450 mg/m^2 twice-daily in PACTG Study 345. Across dose groups, ritonavir steady-state oral clearance was approximately 1.5 to1.7 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg/m^2 twice daily in pediatric patients > 2 years were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m^2) twice daily. The following observations were seen regarding ritonavir concentrations after administration with 350 or 450 mg/m2 twice-daily in children less than 2 years of age. Higher ritonavir exposures were not evident with 450 mg/m^2 twice-daily compared to the 350 mg/m^2 twice-daily. Ritonavir trough concentrations were somewhat lower than those obtained in adults receiving 600 mg twice daily. The area under the ritonavir plasma concentration-time curve and trough concentrations obtained after administration with 350 or 450 mg/m^2 twice-daily in children less than 2 years were approximately 16% and 60% lower, respectively, than that obtained in adults receiving 600 mg twice-daily.

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 (LD_{50}) was found to be greater than 2500 mg/kg in both mice and rats. The signs of toxicity at higher doses in both species included decreased activity, ataxia, 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.

STORAGE

Tablets
Preserve in tight, light-resistant containers. Stored below 30°C.

HOW SUPPLIED

Tablets
Ritonavir tablets are white to off white film-coated oval tablets debossed with the Abbvie Code “NK” providing 100 mg ritonavir. Available in bottles containing 30’s or 60’s tablets.

NAME AND ADDRESS OF MANUFACTURER

Tablets
AbbVie Deutschland GmbH & Co. KG
Knollstrasse 50, 67061 Ludwigshafen, Germany.

PRODUCT REGISTRATION HOLDER

Abbvie Sdn Bhd.
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