

Ritonavir Tablets

RITOMUNE

WARNING

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

COMPOSITION

Each tablet contains
Ritonavir100 mg

DESCRIPTION

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

PHARMACOLOGY

Pharmacodynamics

Ritonavir is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polyprotein precursor, which leads to production of non-infectious immature HIV particles.

Pharmacokinetics

The pharmacokinetics of ritonavir has been studied in healthy volunteers and HIV-infected patients (CD4 \geq 50 cells/ m L). See Table 1 for ritonavir pharmacokinetic characteristics.

Absorption

The absolute bioavailability of ritonavir has not been determined. After a 600 mg dose of oral solution, peak concentrations of ritonavir were achieved approximately 2 hours and 4 hours after dosing under fasting and non-fasting conditions (514 Kcal; 9% fat, 12% protein, and 79% carbohydrate), respectively.

Effect of Food on oral Absorption:

When the oral solution was given under non-fasting conditions, peak ritonavir concentrations decreased 23% and the extent of absorption decreased 7% relative to fasting conditions. Dilution of the oral solution, within one hour of administration, with

240 mL of chocolate milk did not significantly affect the extent and rate of ritonavir absorption. After a single 600 mg dose under non-fasting conditions, in two separate studies, the soft gelatin capsule (n = 57) and oral solution (n = 18) formulations yielded mean \pm SD areas under the plasma concentration-time curve (AUCs) of 121.7 ± 53.8 and $129.0 \pm 39.3 \mu\text{g}\cdot\text{h}/\text{mL}$, respectively. Relative to fasting conditions, the extent of absorption of ritonavir from the soft gelatin capsule formulation was 13% higher when administered with a meal (615 KCal; 14.5% fat, 9% protein, and 76% carbohydrate).

Metabolism

Nearly all of the plasma radioactivity after a single oral 600 mg dose of ^{14}C -ritonavir oral solution (n = 5) was attributed to unchanged ritonavir. Five ritonavir metabolites have been identified in human urine and feces. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent drug; however, the concentrations of this metabolite in plasma are low. *In vitro* studies utilizing human liver microsomes have demonstrated that cytochrome P450 3A (CYP3A) is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of M-2.

Elimination

In a study of five subjects receiving a 600 mg dose of ^{14}C -ritonavir oral solution, $11.3 \pm 2.8\%$ of the dose was excreted into the urine, with $3.5 \pm 1.8\%$ of the dose excreted as unchanged parent drug. In that study, $86.4 \pm 2.9\%$ of the dose was excreted in the feces with $33.8 \pm 10.8\%$ of the dose excreted as unchanged parent drug. Upon multiple dosing, ritonavir accumulation is less than predicted from a single dose possibly due to a time and dose-related increase in clearance.

Table 1. Ritonavir Pharmacokinetic Characteristics

Parameter	n	Values (Mean \pm SD)
$C_{\text{max}}\text{SS}^{\dagger}$	10	$11.2 \pm 3.6 \mu\text{g}/\text{mL}$
$C_{\text{trough}}\text{SS}^{\dagger}$	10	$3.7 \pm 2.6 \mu\text{g}/\text{mL}$
V_{β}/F^{\ddagger}	91	$0.41 \pm 0.25 \text{ L}/\text{kg}$
$t_{1/2}$		3 - 5 h
$\text{CL}/F \text{ SS}^{\dagger}$	10	$8.8 \pm 3.2 \text{ L}/\text{h}$
CL/F^{\ddagger}	91	$4.6 \pm 1.6 \text{ L}/\text{h}$
CL_{R}	62	$< 0.1 \text{ L}/\text{h}$
RBC/Plasma Ratio		0.14
Percent Bound*		98 to 99%

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

‡ Single ritonavir 600 mg dose.

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

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) time-matched difference in QTcF from placebo after baseline correction was 5.5 (7.6) milliseconds (msec) for 400 mg twice-daily ritonavir. Ritonavir 400 mg twice daily resulted in Day 3 ritonavir exposure that was approximately 1.5 fold higher than observed with ritonavir 600 mg twice daily dose at steady state.

PR interval prolongation was also noted in subjects receiving ritonavir in the same study on Day 3. The maximum mean (95% confidence interval) difference from placebo in the PR interval after baseline correction was 22 (25) msec for 400 mg twice-daily ritonavir. See **WARNINGS AND PRECAUTIONS –PR Interval Prolongation.**

Special Populations

Gender, Race and Age

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

A study of ritonavir pharmacokinetics in healthy males and females showed no statistically significant differences in the pharmacokinetics of ritonavir. Pharmacokinetic differences due to race have not been identified.

Pediatric Patients

Steady-state pharmacokinetics were evaluated in 37 HIV-infected patients ages 2 to 14 years receiving doses ranging from 250 mg/m² twice-daily to 400 mg/m² twice-daily in PACTG Study 310, and in 41 HIV-infected patients ages 1 month to 2 years at doses of 350 and 450 mg/m² twice-daily in PACTG Study 345. Across dose groups, ritonavir steady-state oral clearance (CL/F/m²) was approximately 1.5 to 1.7 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg/m² twice-daily in pediatric patients > 2 years were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice-daily. The following observations were seen regarding ritonavir concentrations after administration with 350 or 450 mg/m² twice-daily in children < 2 years of age. Higher ritonavir exposures were not evident with 450 mg/m² twice-daily compared to the 350 mg/m² 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/m² twice-daily in children < 2 years were approximately 16% and 60% lower, respectively, than that obtained in adults receiving 600 mg twice-daily.

Renal Insufficiency

Ritonavir pharmacokinetics have not been studied in patients with renal insufficiency, however, since renal clearance is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Insufficiency

Dose-normalized steady-state ritonavir concentrations in subjects with mild hepatic insufficiency (400 mg twice-daily, n = 6) were similar to those in control subjects dosed with 500 mg twice-daily. Dose-normalized steady-state ritonavir exposures in subjects with moderate hepatic impairment (400 mg twice-daily, n= 6) were about 40% lower than those in subjects with normal hepatic function (500 mg twice-daily, n = 6). Protein binding of ritonavir was not statistically significantly affected by mild or moderately impaired hepatic function. No dose adjustment is recommended in patients with mild or moderate hepatic impairment. However, health care providers should be aware of the potential for lower ritonavir concentrations in patients with moderate hepatic impairment and should monitor patient response carefully. Ritonavir has not been studied in patients with severe hepatic impairment.

INDICATIONS

RITOMUNE is indicated in combination with other antiretroviral agents for the treatment of HIV-infection.

DOSAGE AND ADMINISTRATION

RITOMUNE is administered orally. **RITOMUNE** tablets should be swallowed whole, and not chewed, broken or crushed. The effects of antacids on the absorption of ritonavir have not been studied.

Adults

Recommended Dosage for Treatment of HIV-1

The recommended dosage of ritonavir is 600 mg twice daily by mouth. 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 and increased at 2 to 3 day intervals by 100 mg twice daily.

Dose reduction of **RITOMUNE** is necessary when used with other protease inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir, saquinavir, and tipranavir. Prescribers should consult the full prescribing information and clinical study information of these protease inhibitors if they are coadministered with a reduced dose of ritonavir

(See also, **WARNINGS AND PRECAUTIONS-Drug Interactions** and Table 4, Established and Other Potentially Significant Drug Interactions.)

General Dosing Guidelines

Patients should be aware that frequently observed adverse events, such as mild to moderate gastrointestinal disturbances and paresthesias, may diminish as therapy is continued. In addition, patients initiating combination regimens with ritonavir and reverse transcriptase inhibitors may improve gastrointestinal tolerance by initiating ritonavir alone and subsequently adding reverse transcriptase inhibitors before completing two weeks of ritonavir monotherapy.

CONTRAINDICATIONS

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

RITOMUNE is contraindicated in patients with known hypersensitivity to ritonavir or any of its ingredients.

Co-administration of **RITOMUNE** is contraindicated with the drugs listed in Table 2 because ritonavir mediated CYP3A inhibition can result in serious and/or life-threatening reactions. Voriconazole and St. John's Wort are exceptions in that co-administration of ritonavir and voriconazole results in a significant decrease in plasma concentrations of voriconazole, and co-administration of ritonavir with St. John's Wort may result in decreased ritonavir plasma concentrations.

Table 2: Drugs that are contraindicated with Ritonavir Use

Drug Class	Drugs Within Class That Are Contraindicated With ritonavir **
Alpha- 1adrenoreceptor antagonist	Alfuzosin HCL
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antifungal	Voriconazole
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Herbal Products	St. John's Wort (hypericum perforatum)
HMG-CoA Reductase Inhibitors:	Lovastatin, simvastatin
Neuroleptic	Pimozide

PDE5 enzyme inhibitor	Sildenafil* only when used for the treatment of pulmonary arterial hypertension (PAH)
Sedative/hypnotics	Oral midazolam, triazolam

* see Drug Interactions, Table 4 for coadministration of sildenafil in patients with erectile dysfunction.

** For additional information for these contraindicated drugs, see also Drug Interactions, Table 3.

WARNINGS AND PRECAUTIONS

When co-administering ritonavir with other protease inhibitors, see the full prescribing information for that protease inhibitor including important **WARNINGS AND PRECAUTIONS**.

General

Ritonavir is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with impaired hepatic function (see **WARNINGS AND PRECAUTIONS** and **PHARMACOLOGY** -Hepatic Insufficiency).

Allergic Reactions

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

Hepatic Reactions

Hepatic transaminase elevations exceeding 5 times the upper limit of normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretroviral drugs. 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. Increased AST/ALT monitoring should be considered in these patients, especially during the first three months of ritonavir treatment.

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.

Pancreatitis

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and ritonavir therapy should be discontinued if a diagnosis of pancreatitis is made.

Diabetes Mellitus/Hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and 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 those 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.

Resistance/Cross-Resistance

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of ritonavir therapy following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors.

Haemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and haemarthrosis, 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 not been established.

PR Interval Prolongation

Ritonavir prolongs the PR interval in some patients. Postmarketing cases of second or third degree atrioventricular block have been reported in patients. **RITOMUNE** should be used with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease, cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities. The impact on the PR interval of co-administration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated. As a result, co-administration of ritonavir with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. Clinical monitoring is recommended. (See **PHARMACOLOGY** - Effects on Electrocardiogram).

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving protease inhibitors. The

mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Disorders

Treatment with ritonavir therapy alone or in combination with saquinavir has resulted in substantial increases in the concentration of total cholesterol and triglycerides [see **UNDESIRABLE EFFECTS**]. 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, taking into account any potential drug-drug interactions with ritonavir and HMG CoA reductase inhibitors [see **CONTRAINDICATIONS** and **Table 4** for additional information on potential drug interactions with ritonavir and HMG CoA reductase inhibitors].

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, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Information for Patients

ALERT: Find out about medicines that should NOT be taken with **RITOMUNE**.

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

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

Patients should be advised to take **RITOMUNE** with food, if possible.

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

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

RITOMUNE may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients receiving PDE5 inhibitors for erectile dysfunction (eg, sildenafil, tadalafil, or vardenafil) should be advised that they may be at an increased risk of associated adverse events including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor. Concomitant use of sildenafil with **RITOMUNE** is contraindicated in patients with pulmonary arterial hypertension (PAH).

Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with **RITOMUNE**.

Patients should be informed that **RITOMUNE** may produce changes in the electrocardiogram (eg, PR prolongation). Patients should consult their physician if they experience symptoms such as dizziness, lightheadedness, abnormal heart rhythm, or loss of consciousness.

Laboratory Tests

Ritonavir has been shown to increase triglycerides, cholesterol, SGOT (AST), SGPT (ALT), 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. For comprehensive information concerning laboratory test alterations associated with reverse transcriptase inhibitors, physicians should refer to the complete product information for each of these drugs.

Drug interactions

Ritonavir has been found to be an inhibitor of cytochrome P450 3A (CYP3A) both *in vitro* and *in vivo*. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (> 3-fold) when co-administered with ritonavir. Ritonavir also inhibits CYP2D6 to a lesser extent. Co-administration of substrates of CYP2D6 with ritonavir could result in increases (up to 2-fold) in the AUC of the other agent, possibly requiring a proportional dosage reduction. Ritonavir also appears to induce CYP3A as well as other enzymes, including glucuronosyl transferase, CYP1A2, and possibly CYP2C9.

Drugs that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed both in CONTRAINDICATIONS - Table 2 and under Drugs That Should Not Be Co-administered with ritonavir in Table 3.

Those drug interactions that have been established based on drug interaction studies. The clinical recommendations based on the results of these studies are listed in Table 4. Established and Other Potentially Significant Drug Interactions. A systematic review of over 200 medications prescribed to HIV-infected patients was performed to identify potential drug interactions with ritonavir. There are a number of agents in which CYP3A

or CYP2D6 partially contribute to the metabolism of the agent. In these cases, the magnitude of the interaction and therapeutic consequences cannot be predicted with any certainty.

When co-administering ritonavir with calcium channel blockers, immunosuppressants, some HMG-CoA reductase inhibitors, some steroids, or other substrates of CYP3A; or most antidepressants, certain antiarrhythmics, and some narcotic analgesics which are partially mediated by CYP2D6 metabolism, it is possible that substantial increases in concentrations of these other agents may occur, possibly requiring a dosage reduction (> 50%); examples are listed in Table 4 Established and Other Potentially Significant Drug Interactions.

When co-administering ritonavir with any agent having a narrow therapeutic margin, such as anticoagulants, anticonvulsants, and antiarrhythmics, special attention is warranted. With some agents, the metabolism may be induced, resulting in decreased concentrations (see Table 4. Established and Other Potentially Significant Drug Interactions).

Table 3. Drugs that Should Not be Co-administered with ritonavir

Drug Class : Drug name	Clinical Comment
Alpha Adrenergic Antagonist: alfuzosin	CONTRAINDICATED due to potential for serious reactions such as hypotension.
Antiarrhythmics: amiodarone, bepridil, flecainide, propafenone, quinidine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Antifungal: voriconazole	CONTRAINDICATED due to significant decreases in voriconazole plasma concentrations and may lead to loss of antifungal response.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

Herbal Products: St. John's wort (hypericum perforatum)	CONTRAINDICATED as the combination may lead to loss of virologic response and possible resistance to RITONAVIR or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	CONTRAINDICATED due to potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
PDE5 enzyme inhibitor: Sildenafil*	CONTRAINDICATED in the treatment of pulmonary arterial hypertension (PAH). A safe and effective dose has not been established when used with ritonavir. There is an increased potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope.
Sedative/hypnotics: oral midazolam, triazolam.	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
*see WARNINGS AND PRECAUTIONS - Drug Interactions Table 4. Established and Other Potentially Significant Drug Interactions for coadministration of sildenafil in patients with erectile dysfunction.	

Table 4: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Ritonavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		

HIV Protease Inhibitor: atazanavir	When co-administered with reduced doses of atazanavir and ritonavir ↑ atazanavir (↑ AUC, ↑ C _{max} , ↑ C _{min})	Atazanavir plasma concentrations achieved with atazanavir 300 mg q.d. and ritonavir 100 mg q.d. are higher than those achieved with atazanavir 400 mg q.d. See the complete prescribing information for atazanavir for details on co-administration of atazanavir 300 mg q.d. with ritonavir 100 mg q.d.
HIV Protease Inhibitor: darunavir	When co-administered with reduced doses of ritonavir ↑ darunavir (↑ AUC, ↑ C _{max} , ↑ C _{min})	See the complete prescribing information for darunavir for details on co-administration of darunavir 600 mg b.i.d. with ritonavir 100 mg b.i.d. or darunavir 800 mg q.d. with ritonavir 100 mg q.d.
HIV Protease Inhibitor: fosamprenavir	When co-administered with reduced doses of ritonavir ↑ amprenavir (↑ AUC, ↑ C _{max} , ↑ C _{min})	See the complete prescribing information for fosamprenavir for details on co-administration of fosamprenavir 700 mg b.i.d. with ritonavir 100 mg b.i.d., fosamprenavir 1400 mg q.d. with ritonavir 200 mg q.d. or fosamprenavir 1400 mg q.d. with ritonavir 100 mg q.d.
HIV Protease Inhibitor: indinavir	When co-administered with reduced doses of indinavir and ritonavir ↑ indinavir (↔ AUC, ↓ C _{max} , ↑ C _{min})	Alterations in concentrations are noted when reduced doses of indinavir are co-administered with ritonavir. Appropriate doses for this combination, with respect to efficacy and safety, have not been established.
HIV Protease Inhibitor: saquinavir	When co-administered with reduced doses of ritonavir ↑ saquinavir (↑ AUC, ↑ C _{max} , ↑ C _{min})	See the complete prescribing information for saquinavir for details on co-administration of saquinavir 1000 mg b.i.d. with ritonavir 100 mg b.i.d. 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.
HIV Protease Inhibitor: tipranavir	When co-administered with reduced doses of ritonavir ↑ tipranavir (↑ AUC, ↑ C _{max} , ↑ C _{min})	See the complete prescribing information for tipranavir for details on co-administration of tipranavir 500 mg b.i.d. with ritonavir 200 mg b.i.d. There have been reports of clinical hepatitis and hepatic decompensation including some fatalities. All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as

		these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating therapy with tipranavir/ritonavir, and frequently throughout the duration of treatment.
--	--	---

Non-Nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ ritonavir (↑AUC, ↑C _{max} , ↑ C _{min})	Appropriate doses of this combination with respect to safety and efficacy have not been established.
HIV CCR5 – antagonist: maraviroc	↑ maraviroc	Concurrent administration of maraviroc with ritonavir will increase plasma levels of maraviroc. For specific dosage adjustment recommendations, please refer to the complete prescribing information for maraviroc.

Other Agents		
Analgesics, Narcotic: tramadol, propoxyphene		A dose decrease may be needed for these drugs when co-administered with ritonavir.
Anesthetic: meperidine	↓ meperidine/ ↑ normeperidine (metabolite)	Dosage increase and long-term use of meperidine with ritonavir are not recommended due to the increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g., seizures).
Antialcoholics: disulfiram/ metronidazole		Ritonavir formulations contain alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
Antiarrhythmics: disopyramide, lidocaine, mexiletine	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with ritonavir, if available.

Anticancer Agents: vincristine, vinblastine	↑ anticancer agents	Concentrations of vincristine or vinblastine may be increased when co-administered with ritonavir resulting in the potential for increased adverse events usually associated with these anticancer agents. Consideration should be given to temporarily withholding the ritonavir containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when ritonavir is administered concurrently with vincristine or vinblastine. Clinicians should be aware that if the ritonavir containing regimen is withheld for a prolonged period, consideration should be given to altering the regimen to not include a CYP3A or P-gp inhibitor in order to control HIV-1 viral load.
Anticoagulant: warfarin	↓ R-warfarin ↓↑ S-warfarin	Initial frequent monitoring of the INR during ritonavir and warfarin co-administration is indicated.

Anticonvulsants: carbamazepine, clonazepam, ethosuximide	↑ anticonvulsants	Use with caution. A dose decrease may be needed for these drugs when co-administered with ritonavir and therapeutic concentration monitoring is recommended for these anticonvulsants, if available.
Anticonvulsants: divalproex, lamotrigine, phenytoin	↓ anticonvulsants	Use with caution. A dose increase may be needed for these drugs when co-administered with ritonavir and therapeutic concentration monitoring is recommended for these anticonvulsants, if available.
Antidepressants: nefazodone, selective serotonin reuptake inhibitors (SSRIs), tricyclics	↑ antidepressants	A dose decrease may be needed for these drugs when co-administered with ritonavir.
Antidepressant: bupropion	↓ bupropion ↓ active metabolite, hydroxybupropion	Concurrent administration of bupropion with ritonavir may decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion). Patients receiving ritonavir and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: desipramine	↑ desipramine	Dosage reduction and concentration monitoring of desipramine is recommended.

Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and ritonavir increases plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. 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.
Antiemetic: dronabinol	↑ dronabinol	A dose decrease of dronabinol may be needed when coadministered with ritonavir.
Antifungal: ketoconazole itraconazole voriconazole	↑ ketoconazole ↑ itraconazole ↓ voriconazole	High doses of ketoconazole or itraconazole (> 200 mg/day) are not recommended. Co-administration of voriconazole and ritonavir doses of 400 mg every 12 hours or greater is contraindicated. Co-administration of voriconazole and ritonavir 100 mg should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
Anti-gout: colchicine	↑ colchicine	<p>Patients with renal or hepatic impairment should not be given colchicine with ritonavir.</p> <p>Treatment of gout flares-co-administration of colchicine in patients on ritonavir:</p> <p>0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days.</p> <p>Prophylaxis of gout flares-co-administration of colchicine in patients on ritonavir: If the original colchicine regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day.</p> <p>If the original colchicine regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.</p> <p>Treatment of familial Mediterranean fever (FMF)-co-administration of colchicine in patients on ritonavir:</p> <p>Maximum daily dose of 0.6 mg (may be</p>

		given as 0.3 mg twice a day).
Anti-infective: clarithromycin	↑ clarithromycin	For patients with renal impairment the following dosage adjustments should be considered: <ul style="list-style-type: none"> • For patients with CLCR30 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%. No dose adjustment for patients with normal renal function is necessary.

Antimycobacterial: rifabutin	↑ rifabutin and rifabutin metabolite	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.
Antimycobacterial: rifampin	↓ ritonavir	May lead to loss of virologic response. Alternate antimycobacterial agents such as rifabutin should be considered (see Antimycobacterial: rifabutin, for dose reduction recommendations).
Antiparasitic: atovaquone	↓ atovaquone	Clinical significance is unknown; however, increase in atovaquone dose may be needed.
Antiparasitic: quinine	↑ quinine	A dose decrease of quinine may be needed when coadministered with ritonavir.
β-Blockers: metoprolol, timolol	↑ Beta-Blockers	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with ritonavir.
Bronchodilator: theophylline	↓ theophylline	Increased dosage of theophylline may be required; therapeutic monitoring should be considered.

Calcium channel blockers: diltiazem, nifedipine, verapamil	↑ calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with ritonavir.
Digoxin	↑ digoxin	Concomitant administration of ritonavir with digoxin may increase digoxin levels. Caution should be exercised when co-administering ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.
Endothelin receptor antagonists: bosentan	↑ bosentan	Co-administration of bosentan in patients on ritonavir: In patients who have been receiving ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Co-administration of ritonavir in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
HMG-CoA Reductase Inhibitor: atorvastatin rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with ritonavir.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus (rapamycin)	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with ritonavir.
Inhaled Steroid: Fluticasone	↑ fluticasone	Concomitant use of fluticasone propionate and ritonavir increases plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Co-administration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Long-acting beta-adrenoceptor agonist: salmeterol	↑ salmeterol	Concurrent administration of salmeterol and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Narcotic Analgesic: methadone	↓ methadone	Dosage increase of methadone may be considered.
Neuroleptics: perphenazine, risperidone, thioridazine	↑ neuroleptics	A dose decrease may be needed for these drugs when co-administered with ritonavir.
Oral Contraceptives or Patch Contraceptives: ethinyl estradiol	↓ ethinyl estradiol	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. Alternate methods of contraception should be considered.
PDE5 Inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	<p>Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil in patients receiving ritonavir. Co-administration of ritonavir with these drugs is expected to substantially increase their concentrations and may result in an increase in PDE5 inhibitor associated adverse events, including hypotension, syncope, visual changes, and prolonged erection.</p> <p><u>Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):</u> Sildenafil is contraindicated only when used for the treatment of pulmonary arterial hypertension (PAH) because a safe and effective dose has not been established when used with ritonavir (see CONTRAINDICATIONS and PRECAUTIONS - Drug Interactions). The following dose adjustments are recommended for use of tadalafil with ritonavir:</p> <p><u>Co-administration of tadalafil in patients on ritonavir:</u></p>

		<p>In patients receiving ritonavir for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><u>Co-administration of ritonavir in patients on tadalafil:</u></p> <p>Avoid use of tadalafil during the initiation of ritonavir. Stop tadalafil at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p>Use of PDE5 inhibitors for the treatment of erectile dysfunction: It is recommended not to exceed the following doses:</p> <ul style="list-style-type: none"> • Sildenafil: 25 mg every 48 hours • Tadalafil: 10 mg every 72 hours • Vardenafil: 2.5 mg every 72 hours <p>Use with increased monitoring for adverse events.</p>
--	--	--

Sedative/hypnotics : buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ sedative/ hypnotics	A dose decrease may be needed for these drugs when co-administered with ritonavir.
Sedative/hypnotics : Parenteral midazolam	↑midazolam	Co-administration of oral midazolam with ritonavir is CONTRAINDICATED . Concomitant use of parenteral midazolam with ritonavir may increase plasma concentrations of midazolam. Co-administration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.

Steroids: dexamethasone, fluticasone, prednisone		A dose decrease may be needed for these drugs when co-administered with ritonavir.
Stimulant: methamphetamine	↑ methamphetamine	Use with caution. A dose decrease of methamphetamine may be needed when co-administered with ritonavir.

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Ritonavir produced no effects on fertility in rats at drug exposures approximately 40% (male) and 60% (female) of that achieved with the proposed therapeutic dose. Higher dosages were not feasible due to hepatic toxicity.

No treatment related malformations were observed when ritonavir was administered to pregnant 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 at an exposure equivalent to approximately 30% of that achieved with the proposed therapeutic dose. A slight increase in the incidence of cryptorchidism was also noted in rats at an exposure approximately 22% of that achieved with the proposed therapeutic dose.

Developmental toxicity observed in rabbits (resorptions, decreased litter size and decreased fetal weights) also occurred at a maternally toxic dosage equivalent to 1.8 times the proposed therapeutic dose based on a body surface area conversion factor.

Lactation

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether ritonavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving ritonavir.

Pediatric Use

In HIV-infected patients age greater than 1 month to 21 years, the antiviral activity and adverse event profile seen during clinical trials and through postmarketing experience were similar to that for adult patients.

Geriatric Use

Clinical studies of ritonavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low

end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

No dose adjustment of ritonavir is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of ritonavir in subjects with severe hepatic impairment, therefore, ritonavir is not recommended for use in patients with severe hepatic impairment [see **PHARMACOLOGY**, *hepatic insufficiency*].

UNDESIRABLE EFFECTS

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

Adults — Clinical Trials Experience

The safety of ritonavir alone and in combination with nucleoside reverse transcriptase inhibitors was studied in 1270 adult patients. Table 5 lists treatment-emergent adverse events (at least possibly related and of at least moderate intensity) that occurred in 2% or greater of adult patients receiving ritonavir alone or in combination with nucleoside reverse transcriptase inhibitors in Study 245 or Study 247 and in combination with saquinavir in study 462. In that study, 141 protease inhibitor-naive, HIV-infected patients with mean baseline CD4 of 300 cells/ μ L were randomized to one of four regimens of ritonavir + saquinavir, including ritonavir 400 mg twice-daily + saquinavir 400 mg twice-daily. Overall the most frequently reported clinical adverse events, other than asthenia, among adult patients receiving ritonavir were gastrointestinal and neurological disturbances including nausea, diarrhea, vomiting, anorexia, abdominal pain, taste perversion, and circumoral and peripheral paresthesias. Similar adverse event profiles were reported in adult patients receiving ritonavir in other trials.

Table 5: Percentage of Patients with Treatment-emergent Adverse Events¹ of Moderate or Severe Intensity Occurring in \geq 2% of Adult Patients Receiving ritonavir

Adverse Events	Study 245 Naive Patients ²			Study 247 Advanced Patients ³		Study 462 PI-Naive Patients ⁴
	Ritonavir + ZDV n = 116	Ritonavir n = 117	ZDV n = 119	Ritonavir n = 541	Placebo n = 545	Ritonavir + Saquinavir n=141

Body as a Whole						
Abdominal Pain	5.2	6.0	5.9	8.3	5.1	2.1
Asthenia	28.4	10.3	11.8	15.3	6.4	16.3
Fever	1.7	0.9	1.7	5.0	2.4	0.7
Headache	7.8	6.0	6.7	6.5	5.7	4.3
Malaise	5.2	1.7	3.4	0.7	0.2	2.8
Pain (unspecified)	0.9	1.7	0.8	2.2	1.8	4.3
Cardiovascular						
Syncope	0.9	1.7	0.8	0.6	0.0	2.1
Vasodilation	3.4	1.7	0.8	1.7	0.0	3.5
Digestive						
Abnormalities	5.2	2.6	0.0	3.0	0.4	2.1
Abnormal	8.6	1.7	0.2	7.8	4.2	4.3
Constipation	3.4	0.0	0.8	0.2	0.4	1.4
Diarrhea	25.0	15.4	2.5	23.3	7.9	22.7
Dyspepsia	2.6	0.0	0.7	0.9	0.4	0.7
Fecal Incontinence	0.0	0.0	0.0	0.0	0.0	2.8
Pharyngitis	0.9	2.6	0.0	0.4	0.4	1.4
Flatulence	2.6	0.9	1.7	1.7	0.7	3.5
Skin and Appendages						
Rash	0.9	0.0	0.8	3.5	1.5	0.7
Swelling	46.4	25.6	126.1	129.8	8.4	188.4
Special Senses	23.3	13.7	12.6	17.4	4.4	7.1
Metabolic and Nutritional	7.2	11.1	8.4	7.0	2.2	5.0
Urogenital	0.0	0.0	0.0	2.4	1.7	0.0
Musculoskeletal	0.0	0.0	0.0	0.2	0.0	2.8
Arthralgia	0.0	0.0	0.0	1.7	0.7	2.1
Myalgia	1.7	1.7	0.8	2.4	1.1	2.1
Nervous						
Anxiety	0.9	0.0	0.8	1.7	0.9	2.1
Circumoral Paresthesia	5.2	3.4	0.0	6.7	0.4	6.4
Confusion	0.0	0.9	0.0	0.6	0.6	2.1
Depression	1.7	1.7	2.5	1.7	0.7	7.1
Dizziness	5.2	2.6	3.4	3.9	1.1	8.5
Insomnia	3.4	2.6	0.8	2.0	1.8	2.8

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

² The median duration of treatment for patients randomized to regimens containing ritonavir in Study 245 was 9.1 months.

³ The median duration of treatment for patients randomized to regimens containing ritonavir in Study 247 was 9.4 months.

⁴ The median duration of treatment for patients in Study 462 was 48 weeks.

Adverse events occurring in less than 2% of adult patients receiving ritonavir in all phase II/phase III 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, allergic reaction, back pain, cachexia, chest pain, chills, facial edema, 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, hypertension, hypotension, migraine, myocardial infarct, palpitation, peripheral vascular disorder, phlebitis, postural hypotension, tachycardia and vasospasm.

Digestive System

Abnormal stools, bloody diarrhea, cheilitis, cholestatic jaundice, colitis, dry mouth, dysphagia, eructation, esophageal ulcer, esophagitis, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gingivitis, hepatic coma, hepatitis, hepatomegaly, hepatosplenomegaly, ileus, liver damage, melena, mouth ulcer, pancreatitis, 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.

Metabolic and Nutritional Disorders

Albuminuria, alcohol intolerance, avitaminosis, BUN increased, dehydration, edema, enzymatic abnormality, glycosuria, gout, hypercholesteremia, peripheral edema, 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 neuropathy, 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, increased cough, interstitial pneumonia, larynx edema, lung disorder, rhinitis, and sinusitis.

Skin and Appendages

Acne, contact dermatitis, dry skin, eczema, erythema multiforme, exfoliative dermatitis, folliculitis, fungal dermatitis, furunculosis, maculopapular rash, molluscum contagiosum, onychomycosis, pruritus, psoriasis, pustular rash, seborrhea, skin discoloration, skin disorder, skin hypertrophy, skin melanoma, urticaria, 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, urethritis, urinary frequency, urinary tract infection, and vaginitis.

Post-Marketing Experience

The following adverse events have been reported during post-marketing use of ritonavir. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to ritonavir exposure.

Body as a Whole

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.

Co-administration of ritonavir with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.

Redistribution/accumulation of body fat has been reported (see **WARNINGS AND PRECAUTIONS - Fat Redistribution**).

Cardiovascular System

First –degree AV block, second-degree AV block, third-degree AV block, right bundle branch block have been reported (See **WARNINGS AND PRECAUTIONS – PR Interval Prolongation**).

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

Endocrine System

Cushing's syndrome and adrenal suppression have been reported when ritonavir has been coadministered with fluticasone propionate.

Hemic and Lymphatic System

There have been reports of increased bleeding in patients with hemophilia A or B (see **WARNINGS AND PRECAUTIONS - Hemophilia**).

Nervous System

There have been postmarketing reports of seizure. Also, see Cardiovascular System.

Laboratory Abnormalities

Table 6 shows the percentage of adult patients who developed marked laboratory abnormalities.

Table 6: Percentage of Adult Patients, by Study and Treatment Group, with Chemistry and Hematology Abnormalities Occurring in > 3% of Patients Receiving ritonavir

		Study 245 Naive Patients			Study 247 Advanced Patients		Study 462 PI-Naive Patients
Variable	Limit	Ritonavir + ZDV	Ritonavir	ZDV	Ritonavir	Placebo	Ritonavir + Saquinavir
Chemistry	High						

Cholesterol	> 240 mg/dL	30.7	44.8	9.3	36.5	8.0	65.2
CPK	> 1000 IU/L	9.6	12.1	11.0	9.1	6.3	9.9
GGT	> 300 IU/L	1.8	5.2	1.7	19.6	11.3	9.2
SGOT (AST)	> 180 IU/L	5.3	9.5	2.5	6.4	7.0	7.8
SGPT (ALT)	> 215 IU/L	5.3	7.8	3.4	8.5	4.4	9.2
Triglycerides	> 800 mg/dL	9.6	17.2	3.4	33.6	9.4	23.4
Triglycerides	> 1500 mg/dL	1.8	2.6	-	12.6	0.4	11.3
Triglycerides Fasting	> 1500 mg/dL	1.5	1.3	-	9.9	0.3	-
Uric Acid	> 12 mg/dL	-	-	-	3.8	0.2	1.4
Hematology	Low						
Hematocrit	< 30%	2.6	-	0.8	17.3	22.0	0.7
Hemoglobin	< 8.0 g/dL	0.9	-	-	3.8	3.9	-
Neutrophils	≤ 0.5 x 10 ⁹ /L	-	-	-	6.0	8.3	-
RBC	< 3.0 x 10 ¹² /L	1.8	-	5.9	18.6	24.4	-
WBC	< 2.5 x 10 ⁹ /L	-	0.9	6.8	36.9	59.4	3.5
- Indicates no events reported.							

Pediatrics

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%).

OVERDOSAGE

Acute Overdosage

Human Overdose Experience

Human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg/day for two days. The patient reported paresthesias which resolved after the dose was decreased. A post-marketing case of renal failure with eosinophilia has been reported with ritonavir overdose.

The approximate lethal dose was found to be greater than 20 times the related human dose in rats and 10 times the related human dose in mice.

Management of Overdosage

Treatment of overdose with ritonavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with ritonavir. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. 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. A Certified Poison Control Center should be consulted for up-to-date information on the management of overdose with ritonavir.

PACKAGING INFORMATION

RITOMUNE Container of 60 tablets

Last updated: October 2010