

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Ritonavir tablets safely and effectively. See full prescribing information for Ritonavir tablets.

Ritonavir Tablets USP, for oral use 25 mg, 50 mg

WARNING: DRUG-DRUG INTERACTIONS LEADING TO POTENTIALLY SERIOUS AND/OR LIFE THREATENING REACTIONS

See full prescribing information for complete boxed warning

Co-administration of ritonavir with several classes of drugs including sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations may result in potentially serious and/or life-threatening adverse events due to possible effects of ritonavir on the hepatic metabolism of certain drugs. Review medications taken by patients prior to prescribing ritonavir or when prescribing other medications to patients already taking ritonavir [see Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Clinical Pharmacology (12.3)].

INDICATIONS AND USAGE

Ritonavir is a CYP3A inhibitor indicated to increase systemic exposure of darunavir and atazanavir, in combination with other HIV-1 antiretroviral agents for the treatment of HIV-1 infection (1). These tablet strengths are intended for pediatric patients.

DOSAGE AND ADMINISTRATION

Ritonavir must be coadministered with darunavir or atazanavir at the same time, with food. (2)

Pediatric patients: Dosage of ritonavir in combination with darunavir or atazanavir is based on body weight (2).

DOSAGE FORMS AND STRENGTHS

- Tablet: 25 mg and 50 mg ritonavir (3)

CONTRAINDICATIONS

- Ritonavir is contraindicated in patients with known hypersensitivity to ritonavir (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome) or any of its ingredients. (4)
- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events. (4)
- Co-administration with drugs that significantly reduce ritonavir. (4)

WARNINGS AND PRECAUTIONS

The following have been observed in patients receiving ritonavir:

- Drug Interactions: Consider drug-drug interaction potential to reduce risk of serious or life-threatening adverse reactions. (5.1)

- Hepatic Reactions: Fatalities have occurred. Monitor liver function before and during therapy, especially in patients with underlying hepatic disease, including hepatitis B and hepatitis C, or marked transaminase elevations. (5.3, 8.6)
- Pancreatitis: Fatalities have occurred; suspend therapy as clinically appropriate. (5.4)
- Allergic Reactions/Hypersensitivity: Allergic reactions have been reported and include anaphylaxis, toxic epidermal necrolysis, Stevens-Johnson syndrome, bronchospasm and angioedema. Discontinue treatment if severe reactions develop. (5.5, 6.3)
- PR interval prolongation may occur in some patients. Cases of second and third degree heart block have been reported. Use with caution with patients with preexisting conduction system disease, ischemic heart disease, cardiomyopathy, underlying structural heart disease or when administering with other drugs that may prolong the PR interval. (5.6, 12.3)
- Total cholesterol and triglycerides elevations: Monitor prior to therapy and periodically thereafter. (5.7)
- Patients may develop new onset or exacerbations of diabetes mellitus, hyperglycemia. (5.8)
- Patients may develop immune reconstitution syndrome. (5.9)
- Patients may develop redistribution/accumulation of body fat. (5.10)
- Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required. (5.11)

ADVERSE REACTIONS

The most frequently reported adverse drug reactions among pediatric patients receiving ritonavir in combination darunavir or atazanavir, in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain), jaundice/scleral icterus, rash, pruritis, headache, anorexia, fever, fatigue and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd. at 1-866-604-3268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Coadministration of ritonavir can alter the concentrations of other drugs. The potential for drug-drug interactions must be considered prior to and during therapy. (4, 5.1, 7, 12.3)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving ritonavir. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: DRUG-DRUG INTERACTIONS LEADING TO POTENTIALLY SERIOUS AND/OR LIFE THREATENING REACTIONS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Drug Interactions

5.3 Hepatic Reactions

5.4 Pancreatitis

5.5 Allergic Reactions/Hypersensitivity

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.6 Hepatic Impairment

10 OVERDOSAGE

10.1 Acute Overdosage - Human Overdose Experience

10.2 Management of Overdosage

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

12.4 Microbiology

- 5.6 PR Interval Prolongation
- 5.7 Lipid Disorders
- 5.8 Diabetes Mellitus/Hyperglycemia
- 5.9 Immune Reconstitution Syndrome
- 5.10 Fat Redistribution
- 5.11 Patients with Hemophilia
- 5.12 Resistance/Cross-resistance
- 5.13 Laboratory Tests

6 ADVERSE REACTIONS

- 6.1 Pediatric Clinical Trial Experience
- 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Potential for Ritonavir to Affect Other Drugs
- 7.2 Established and Other Potentially Significant Drug Interactions

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 Ritonavir Tablets, 25 mg and 50 mg

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: DRUG-DRUG INTERACTIONS LEADING TO POTENTIALLY SERIOUS AND/OR LIFE THREATENING REACTIONS

Co-administration of ritonavir with several classes of drugs including sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations may result in potentially serious and/or life-threatening adverse events due to possible effects of ritonavir on the hepatic metabolism of certain drugs. Review medications taken by patients prior to prescribing ritonavir or when prescribing other medications to patients already taking ritonavir [see *Contraindications (4)*, *Warnings and Precautions (5.1)*, *Drug Interactions (7)*, and *Clinical Pharmacology (12.3)*].

1 INDICATIONS AND USAGE

Ritonavir tablets USP is a CYP3A inhibitor indicated to increase systemic exposure of darunavir and atazanavir in the treatment of HIV-1 infection in combination with other HIV-1 antiretroviral agents. These tablet strengths are intended for pediatric patients.

2 DOSAGE AND ADMINISTRATION

Ritonavir must be co-administered with darunavir or atazanavir at the same time and with food. Ritonavir tablets should be swallowed whole, and not chewed, broken or crushed.

Before prescribing ritonavir tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a tablet, the use of alternative ritonavir formulation should be considered.

Pediatric Patients

The recommended doses of ritonavir given with darunavir or atazanavir is based on body weight (see Tables 1, 2, and 3). See also *Drug Interactions (7)* and consult the full prescribing information for darunavir and atazanavir.

Ritonavir coadministered with Darunavir (pediatric patients aged 3 years to less than 18 years)

Table 1: Recommended dose for pediatric patients 3 years of age or older and weighing at least 12 kg who are treatment-naïve or treatment-experienced with no darunavir resistance associated substitutions*

Body Weight (kg)	Darunavir Dose	Ritonavir dose with tablets
	Dose: Once daily with food	
12 kg to less than 13 kg	420 mg	75 (one 50 mg + one 25 mg)
13 kg to less than 14 kg	455 mg	75 (one 50 mg + one 25 mg)
14 kg to less than 15 kg	490 mg	100 (two 50 mg tablets)
15 kg to less than 30 kg	600 mg	100 (two 50 mg tablets)
30 kg to less than 40 kg	675 mg	100 (two 50 mg tablets)
Greater than or equal to 40 kg	800 mg	100 (two 50 mg tablets)
* darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V		

Table 2: Recommended dose for pediatric patients 3 years of age or older and weighing at least 12 kg who are treatment-experienced with at least one darunavir resistance associated substitution*

Body Weight (kg)	Darunavir Dose	Ritonavir dose with tablets
	Dose: Twice daily with food	
12 kg to less than 13 kg	240 mg	50 (one 50 mg tablet)
13 kg to less than 14 kg	260 mg	50 (one 50 mg tablet)
14 kg to less than 15 kg	280 mg	50 (one 50 mg tablet)
15 kg to less than 30 kg	375 mg	50 (one 50 mg tablet)
30 kg to less than 40 kg	450 mg	75 (one 50 mg + one 25 mg)
Greater than or equal to 40 kg	600 mg	100 (two 50 mg tablets)
* darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V		

Ritonavir coadministered with Atazanavir [pediatric patients (6 years to less than 18 years of age)]

Table 3: Recommended dose for atazanavir with ritonavir in pediatric patients 6 years of age or older

Body Weight	Atazanavir dose	Ritonavir dose
	Dose: Once daily with food	
15 kg to less than 20 kg	150 mg	100 mg (two 50 mg tablets)
20 kg to less than 40 kg	200 mg	100 mg (two 50 mg tablets)
at least 40 kg	300 mg	100 mg (two 50 mg tablets)

3 DOSAGE FORMS AND STRENGTHS

- Ritonavir Tablets, 25 mg and 50 mg

Ritonavir tablet contains 25 mg of Ritonavir. “White coloured, oval shaped, shallow, film coated tablets debossed with “25” on one side & plain on other side”.

Ritonavir tablet contains 50 mg of Ritonavir. “White coloured, oval shaped, shallow, film coated tablets debossed with “50” on one side & plain on other side”.

4 CONTRAINDICATIONS

- When co-administering ritonavir with other protease inhibitors, see the full prescribing information for that protease inhibitor including contraindication information.
- Ritonavir is contraindicated in patients with known hypersensitivity (e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to ritonavir or any of its ingredients.
- Co-administration of ritonavir with several classes of drugs (including sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations) is contraindicated and may result in potentially serious and/or life-threatening adverse events due to possible effects of ritonavir on the hepatic metabolism of these drugs (see Table 4). 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 4. Drugs that are Contraindicated with Ritonavir

Drug Class	Drugs Within Class That Are Contraindicated With Ritonavir **	Clinical Comments
Alpha ₁ -adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension.
Antiarrhythmics	Amiodarone, flecainide, propafenone, quinidine	Potential for cardiac arrhythmias.
Antifungal	Voriconazole	Coadministration of voriconazole with ritonavir 400 mg every 12 hours significantly decreases voriconazole plasma concentrations and may lead to loss of antifungal response. Voriconazole is contraindicated with ritonavir doses of 400 mg every 12 hours or greater [<i>see Drug Interactions (7.2)</i>].
Ergot Derivatives	Dihydroergotamine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias.
Herbal Products	St. John's Wort (hypericum perforatum)	Co-administration of ritonavir with St. John's Wort may result in decreased ritonavir plasma concentrations and 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	Potential for myopathy including rhabdomyolysis.
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
PDE5 enzyme inhibitor	Sildenafil* (Revatio [®]) only when used for 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 [<i>see Drug Interactions (7.2)</i>].
Sedative/hypnotics	Oral midazolam, triazolam	Prolonged or increased sedation or respiratory depression [<i>see Drug Interactions (7.2)</i>].
* <i>see Drug Interactions (7)</i> for co-administration of sildenafil in patients with erectile dysfunction.		
** For additional information for these contraindicated drugs, <i>see also Drug Interactions (7)</i> .		

5 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.

5.1 Drug Interactions

Ritonavir is a CYP3A inhibitor. Initiating treatment with ritonavir in patients receiving medications metabolized by CYP3A or initiating medications metabolized by CYP3A in patients already maintained on ritonavir may result in increased plasma concentrations of concomitant medications. Higher plasma concentrations of concomitant medications can result in increased or prolonged therapeutic or adverse effects, potentially leading to severe, life-threatening or fatal events. The potential for drug-drug interactions must be considered prior to and during therapy with ritonavir. Review of other medications taken by patients and monitoring of patients for adverse effects is recommended during therapy with ritonavir.

See Table 4 for a listing of drugs that are contraindicated with ritonavir due to potentially life-threatening adverse events, significant drug interactions, or loss of virologic activity. Also, see Table 5 for a listing of drugs with established and other significant drug interactions [*see Contraindications (4), Drug Interactions (7), and Clinical Pharmacology (12.3)*].

5.3 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 or ritonavir treatment [*see Use in Specific Populations (8.6)*].

There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients taking multiple concomitant medications and/or with advanced AIDS.

5.4 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 [*see Warnings and Precautions (5.7)*]. 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.

5.5 Allergic Reactions/Hypersensitivity

Allergic reactions including urticaria, mild skin eruptions, bronchospasm, and angioedema have been reported. Cases of anaphylaxis, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome have also been reported. Discontinue treatment if severe reactions develop.

5.6 PR Interval Prolongation

Ritonavir prolongs the PR interval in some patients. Post marketing cases of second or third degree atrioventricular block have been reported in patients.

Ritonavir 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 Drug Interactions (7), and Clinical Pharmacology (12.3)*].

5.7 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 Adverse Reactions (6.1)*]. 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 (4) and Drug Interactions (7)*].

5.8 Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing 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.

5.9 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 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.

5.10 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.11 Patients with 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 between protease inhibitor therapy and these events has not been established.

5.12 Resistance/Cross-resistance

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of ritonavir 600 mg twice daily following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors [*see Microbiology (12.4)*].

5.13 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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Drug Interactions [*see Warnings and Precautions (5.1)*]
- Hepatotoxicity [*see Warnings and Precautions (5.3)*]
- Pancreatitis [*see Warnings and Precautions (5.4)*]
- Allergic Reactions/Hypersensitivity [*see Warnings and Precautions (5.5)*]

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

6.1 Pediatric Clinical Trial Experience

Ritonavir co-administered with darunavir

Darunavir co-administered with ritonavir has been studied in combination with other antiretroviral agents in pediatric subjects ages 3 years to less than 18 years of age. Across the trials, the frequency, type and severity of ADRs in pediatric subjects were comparable to those observed in adults (*see full prescribing information for darunavir*). Clinical ADRs reported with darunavir/ritonavir include vomiting, diarrhea, abdominal pain, headache, anorexia, rash,

pruritis, nausea and fatigue. Grade 3 or 4 laboratory abnormalities included ALT and/or AST increase, pancreatic amylase and/or lipase increase.

Refer to the full prescribing information for darunavir for additional information.

Ritonavir co-administered with atazanavir

The safety and tolerability of atazanavir co-administered with ritonavir in combination with other antiretroviral agents has been evaluated in pediatric patients 6 years of age and older.

Adverse events reported in the pediatric trial were generally similar to those observed in clinical studies in adults (*see full prescribing information for atazanavir*). The most common adverse events reported in pediatric patients included cough, fever, jaundice/scleral icterus, rash, vomiting, diarrhea and headache. The most common Grade 3-4 laboratory abnormalities were elevation of total bilirubin, neutropenia, and hypoglycemia.

Refer to the full prescribing information for atazanavir additional details.

6.3 Postmarketing Experience

The following adverse events (not previously mentioned in the labeling) 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.

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 (5.6)*].

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 co-administered with fluticasone propionate or budesonide.

Nervous System

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

Skin and subcutaneous tissue disorders

Toxic epidermal necrolysis (TEN) has been reported.

7 DRUG INTERACTIONS

See also *Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*

When co-administering ritonavir with other protease inhibitors (atazanavir and darunavir), see the full prescribing information for that protease inhibitor including important information for drug interactions.

7.1 Potential for Ritonavir to Affect Other Drugs

Ritonavir has been found to be an inhibitor of cytochrome P450 3A (CYP3A) and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (greater than 3-fold) when co-administered with ritonavir. Thus, co-administration of ritonavir with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 5.

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, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

7.2 Established and Other Potentially Significant Drug Interactions

Table 5 provides a list of established or potentially clinically significant drug interactions. Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction [see *Clinical Pharmacology (12.3) for magnitude of interaction*].

Table 5. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Ritonavir or Concomitant Drug	Clinical Comment
<i>HIV-Antiviral Agents</i>		
HIV-1 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 once daily and ritonavir 100 mg once daily are higher than those achieved with atazanavir 400 mg once daily. See the complete prescribing information for Reyataz [®] (atazanavir) for details on co-administration of atazanavir 300

		mg once daily with ritonavir 100 mg once daily.
HIV-1 Protease Inhibitor: darunavir	When co-administered with reduced doses of ritonavir ↑ darunavir (↑ AUC, ↑ C _{max} , ↑ C _{min})	See the complete prescribing information for Prezista [®] (darunavir) for details on co-administration of darunavir 600 mg twice daily with ritonavir 100 mg twice daily or darunavir 800 mg once daily with ritonavir 100 mg once daily.
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-1 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 Selzentry [®] (maraviroc).
Integrase Inhibitor: Raltegravir	↓ raltegravir	The effects of ritonavir on raltegravir with ritonavir dosage regimens greater than 100 mg twice daily have not been evaluated, however raltegravir concentrations may be decreased with ritonavir coadministration.
<i>Other Agents</i>		
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,	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is

mexiletine		recommended for antiarrhythmics when co-administered with ritonavir, if available.
Anticancer Agents: dasatinib, nilotinib, vincristine, vinblastine	↑ anticancer agents	<p>Concentrations of these drugs may be increased when co-administered with ritonavir resulting in the potential for increased adverse events usually associated with these anticancer agents.</p> <p>For vincristine and vinblastine, 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. A decrease in the dosage or an adjustment of the dosing interval of nilotinib and dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as ritonavir. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions.</p>
Anticoagulant: warfarin	↓ R-warfarin ↓↑ S-warfarin	Initial frequent monitoring of the INR during ritonavir and warfarin co-administration is indicated.
Anticoagulant: rivaroxaban	↑ rivaroxaban	Avoid concomitant use of rivaroxaban and ritonavir. Co-administration of ritonavir and rivaroxaban is expected to result in increased exposure of rivaroxaban which may lead to risk of increased bleeding.
Anticonvulsants:	↑ anticonvulsants	Use with caution. A dose decrease

carbamazepine, clonazepam, ethosuximide		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): e.g. fluoxetine, paroxetine, tricyclics: e.g. amitriptyline, nortriptyline	↑ 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 co-administered with ritonavir.

<p>Antifungal: ketoconazole itraconazole voriconazole</p>	<p>↑ ketoconazole ↑ itraconazole ↓ voriconazole</p>	<p>High doses of ketoconazole or itraconazole (greater than 200 mg/day) are not recommended.</p> <p>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.</p>
<p>Anti-gout: colchicine</p>	<p>↑ colchicine</p>	<p>Patients with renal or hepatic impairment should not be given colchicine with ritonavir.</p> <p><u>Treatment of gout flares-co-administration of colchicine in patients on ritonavir:</u> 0.6 mg (one tablet) for one dose, followed by 0.3 mg (half tablet) one hour later. Dose to be repeated no earlier than three days.</p> <p><u>Prophylaxis of gout flares-co-administration of colchicine in patients on ritonavir:</u> 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><u>Treatment of familial Mediterranean fever (FMF)-co-administration of colchicine in patients on ritonavir:</u> Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).</p>
<p>Anti-infective: clarithromycin</p>	<p>↑ clarithromycin</p>	<p>For patients with renal impairment the following dosage adjustments</p>

		<p>should be considered:</p> <ul style="list-style-type: none"> For patients with CL_{CR} 30 to 60 mL per min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} less than 30 mL per min the dose of clarithromycin should be decreased by 75%. <p>No dose adjustment for patients with normal renal function is necessary.</p>
Antimycobacterial: rifabutin	↑ rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least three-quarters of the usual dose of 300 mg per 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 co-administered 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 coadministering

		ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.
Endothelin receptor antagonists: bosentan	↑ bosentan	<p><u>Co-administration of bosentan in patients on ritonavir:</u> 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.</p> <p><u>Co-administration of ritonavir in patients on bosentan:</u> Discontinue use of bosentan at least 36 hours prior to initiation of ritonavir.</p> <p>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.</p>
HCV-Protease Inhibitor: simeprevir	↑ simeprevir	It is not recommended to co-administer ritonavir with simeprevir
HMG-CoA Reductase Inhibitor: atorvastatin rosuvastatin	↑ atorvastatin ↑ rosuvastatin	<p>Titrate atorvastatin and rosuvastatin dose carefully and use the lowest necessary dose.</p> <p>If ritonavir is used with another protease inhibitor, see the complete prescribing information for the concomitant protease inhibitor for details on co-administration with atorvastatin and rosuvastatin.</p>
Immunosuppressants: cyclosporine, tacrolimus, sirolimus (rapamycin)	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with ritonavir.
Inhaled or Intranasal Steroid e.g.: Fluticasone Budesonide	↑ glucocorticoids	Concomitant use of ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Concomitant use may result in increased steroid concentrations and reduced serum

		<p>cortisol concentrations.</p> <p>Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients when ritonavir has been coadministered with fluticasone propionate or budesonide.</p>
<p>Long-acting beta-adrenoceptor agonist: salmeterol</p>	<p>↑ salmeterol</p>	<p>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.</p>
<p>Narcotic Analgesic: methadone fentanyl</p>	<p>↓ methadone ↑ fentanyl</p>	<p>Dosage increase of methadone may be considered.</p> <p>Concentrations of fentanyl are expected to increase. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir.</p>
<p>Neuroleptics: perphenazine, risperidone, thioridazine</p>	<p>↑ neuroleptics</p>	<p>A dose decrease may be needed for these drugs when co-administered with ritonavir.</p>
<p>Oral Contraceptives or Patch Contraceptives: ethinyl estradiol</p>	<p>↓ ethinyl estradiol</p>	<p>Alternate methods of contraception should be considered.</p>
<p>PDE5 Inhibitors: avanafil, sildenafil, tadalafil, vardenafil</p>	<p>↑ avanafil ↑ sildenafil ↑ tadalafil ↑ vardenafil</p>	<p>Do not use ritonavir with avanafil because a safe and effective avanafil dosage regimen has not been established.</p> <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</p>

		<p>changes, and prolonged erection.</p> <p>Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):</p> <p>Sildenafil (Revatio[®]) is contraindicated 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 <i>Contraindications (4)</i>].</p> <p>The following dose adjustments are recommended for use of tadalafil (Adcirca[™]) with ritonavir:</p> <p><u>Co-administration of ADCIRCA in patients on ritonavir:</u></p> <p>In patients receiving ritonavir for at least one week, start ADCIRCA 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 ADCIRCA:</u></p> <p>Avoid use of ADCIRCA during the initiation of ritonavir. Stop ADCIRCA at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume ADCIRCA 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:</p> <p>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
--	--	---

		Use with increased monitoring for adverse events.
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 (systemic) e.g.: budesonide, dexamethasone, prednisone	↑ glucocorticoids	Concomitant use of glucocorticoids that are metabolized by CYP3A is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Concomitant use may result in increased steroid concentrations and reduced serum cortisol concentrations. This may increase the risk for development of systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.
Stimulant: methamphetamine	↑ methamphetamine	Use with caution. A dose decrease of methamphetamine may be needed when co-administered with ritonavir.

8 USE IN SPECIFIC POPULATIONS

When co-administering ritonavir with other protease inhibitors, see the full prescribing information for the co-administered protease inhibitor including important information for use in special populations.

8.1 Pregnancy

Because ritonavir is co-administered with darunavir or atazanavir, also refer to the darunavir and atazanavir prescribing information for its pregnancy category.

Pregnancy Category B

Human Data:

There are no adequate and well-controlled studies in pregnant women. Ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry:

As of January 2012, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 3860 exposures to ritonavir containing regimens (1567 exposed in the first trimester and 2293 exposed in the second and third trimester). Birth defects occurred in 35 of the 1567 (2.2%) live births (first trimester exposure) and 59 of the 2293 (2.6%) live births (second/third trimester exposure).

Among pregnant women in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between ritonavir and overall birth defects observed in the APR.

Animal Data

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 approximately 3.6-fold of that achieved with the proposed therapeutic dose (100 mg twice-daily). A slight increase in the incidence of cryptorchidism was also noted in rats at an exposure approximately 2.7-fold 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 11 times the proposed therapeutic dose based on a body surface area conversion factor.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed 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 breastfeed if they are receiving ritonavir.

8.4 Pediatric Use

In HIV-infected patients, the adverse event profile seen during clinical trials and through postmarketing experience were similar to that for adult patients.

See full prescribing information for darunavir and atazanavir for additional information.

8.6 Hepatic Impairment

No dose adjustment of ritonavir is necessary for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C), therefore, ritonavir is not recommended for use in patients with severe hepatic impairment [see *Warnings and Precautions (5.3), Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

10.1 Acute Overdosage - Human Overdose Experience

Human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg per 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.

10.2 Management of Overdosage

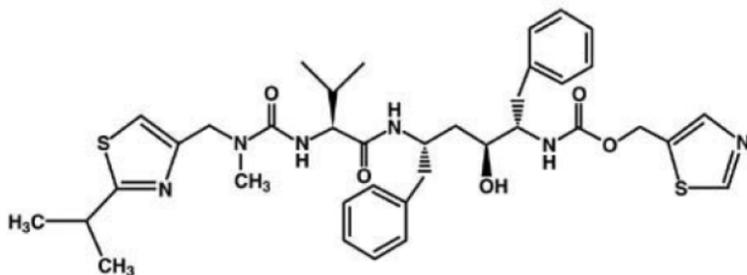
Treatment of overdose with ritonavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with ritonavir. If indicated, elimination of unabsorbed drug should be achieved by gastric 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.

11 DESCRIPTION

Ritonavir is an inhibitor of cytochrome P-450 (CYP) enzyme of the CYP3A family.

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

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Ritonavir is a white-to-light-tan powder. Ritonavir has a bitter metallic taste. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

Ritonavir tablets USP are available for oral administration in strengths of 25 mg and 50 mg ritonavir with the following inactive ingredients: Colloidal silicon dioxide, Copovidone (Kollidon VA64), Dibasic calcium phosphate (Anhydrous) (A Tab), Hypromellose (HPMC-6-cps), Isopropyl Alcohol, Opadry White YS-1-7003, Sodium Lauryl Sulfate, Sorbitan monolaurate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ritonavir is a mechanism-based inhibitor of cytochrome P450 3A (CYP3A). Inhibition of CYP3A-mediated metabolism by ritonavir increases the systemic exposure of CYP3A substrates.

12.3 Pharmacokinetics

The pharmacokinetics of ritonavir have been studied in healthy volunteers and HIV-infected patients (CD₄ greater than or equal to 50 cells/ μ L). See Table 6 for ritonavir pharmacokinetic characteristics.

Absorption

The absolute bioavailability of ritonavir has not been determined.

Ritonavir tablets are not bioequivalent to ritonavir capsules. Under moderate fat conditions (857 kcal; 31% fat, 13% protein, 56% carbohydrates), when a single 100 mg ritonavir dose was administered as a tablet compared with a capsule, AUC_(0- ∞) met equivalence criteria but mean C_{max} was increased by 26% (92.8% confidence intervals: \uparrow 15 - \uparrow 39%).

No information is available comparing ritonavir tablets to ritonavir capsules under fasting conditions.

Effect of Food on Oral Absorption

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

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

Metabolism

Nearly all of the plasma radioactivity after a single oral 600 mg dose of ¹⁴C-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 ¹⁴C-ritonavir oral solution, 11.3 ± 2.8% of the dose was excreted into the urine, with 3.5 ± 1.8% of the dose excreted as unchanged parent drug. In that study, 86.4 ± 2.9% of the dose was excreted in the feces with 33.8 ± 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 6. Ritonavir Pharmacokinetic Characteristics

Parameter	N	Values (Mean ± SD)
V _β /F [†]	91	0.41 ± 0.25 L/kg
t _{1/2}		3 - 5 h
CL/F SS [†]	10	8.8 ± 3.2 L/h
CL/F [‡]	91	4.6 ± 1.6 L/h
CL _R	62	< 0.1 L/h
RBC/Plasma Ratio		0.14
Percent Bound*		98 to 99%

† SS = steady state; patients taking ritonavir 600 mg q12h.
 ‡ Single ritonavir 600 mg dose.
 * Primarily bound to human serum albumin and alpha-1 acid glycoprotein over the ritonavir concentration range of 0.01 to 30 µg/mL.

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* (5.6)].

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 greater than 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 less than 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 less than 2 years were approximately 16% and 60% lower, respectively, than that obtained in adults receiving 600 mg twice daily.

Renal Impairment

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

Hepatic Impairment

Dose-normalized steady-state ritonavir concentrations in subjects with mild hepatic impairment (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.

Drug Interactions

[see also Contraindications (4) and Warnings and Precautions (5.1), and Drug Interactions (7)]

Table 7 and Table 8 summarize the effects on AUC and C_{max}, with 95% confidence intervals (95% CI), of co-administration of ritonavir with a variety of drugs. For information about clinical recommendations see Table 5 in *Drug Interactions (7)*.

Table 7. Drug Interactions - Pharmacokinetic Parameters for Ritonavir in the Presence of the Co-administered Drug

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Ritonavir (mg)	N	AUC % (95% CI)	C _{max} (95% CI)	C _{min} (95% CI)
Clarithromycin	500 q12h, 4 d	200 q8h, 4 d	22	↑ 12% (2, 23%)	↑ 15% (2, 28%)	↑ 14% (-3, 36%)
Didanosine	200 q12h, 4 d	600 q12h, 4 d	12	↔	↔	↔
Fluconazole	400 single dose, day 1; 200 daily, 4 d	200 q6h, 4 d	8	↑ 12% (5, 20%)	↑ 15% (7, 22%)	↑ 14% (0, 26%)
Fluoxetine	30 q12h, 8 d	600 single dose, 1 d	16	↑ 19% (7, 34%)	↔	ND
Ketoconazole	200 daily, 7 d	500 q12h, 10 d	12	↑ 18% (-3, 52%)	↑ 10% (-11, 36%)	ND
Rifampin	600 or 300 daily, 10 d	500 q12h, 20 d	7, 9*	↓ 35% (7, 55%)	↓ 25% (-5, 46%)	↓ 49% (-14, 91%)
Voriconazole	400 q12h, 1 d; then 200 q12h, 8 d	400 q12h, 9 d		↔	↔	ND
Zidovudine	200 q8h, 4 d	300 q6h, 4 d	10	↔	↔	↔

Table 8. Drug Interactions - Pharmacokinetic Parameters for Co-administered Drug in the Presence of the Ritonavir

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Ritonavir (mg)	N	AUC % (95% CI)	C _{max} (95% CI)	C _{min} (95% CI)
Alprazolam	1, single dose	500 q12h, 10 d	12	↓ 12% (-5, 30%)	↓ 16% (5, 27%)	ND
Avanafil	50, single dose	600 q12h	14 ⁶	↑ 13-fold	↑ 2.4-fold	ND
Clarithromycin	500 q12h, 4 d	200 q8h, 4 d	22	↑ 77% (56, 103%)	↑ 31% (15, 51%)	↑ 2.8-fold (2.4, 3.3X)
14-OH clarithromycin metabolite				↓ 100%	↓ 99%	↓ 100%
Desipramine	100, single dose	500 q12h, 12 d	14	↑ 145% (103, 211%)	↑ 22% (12, 35%)	ND
2-OH desipramine metabolite				↓ 15% (3, 26%)	↓ 67% (62, 72%)	ND

Didanosine	200 q12h, 4 d	600 q12h, 4 d	12	↓ 13% (0, 23%)	↓ 16% (5, 26%)	↔
Ethinyl estradiol	50 µg single dose	500 q12h, 16 d	23	↓ 40% (31, 49%)	↓ 32% (24, 39%)	ND
Fluticasone propionate aqueous nasal spray	200 mcg qd, 7 d	100 mg q12h, 7 d	18	↑ approximately 350-fold ⁵	↑ approximately 25-fold ⁵	
Indinavir ¹	400 q12h, 15 d	400 q12h, 15 d	10			
Day 14				↑ 6% (-14, 29%)	↓ 51% (40, 61%)	↑ 4-fold (2.8, 6.8X)
Day 15				↓ 7% (-22, 28%)	↓ 62% (52, 70%)	↑ 4-fold (2.5, 6.5X)
Ketoconazole	200 daily, 7 d	500 q12h, 10 d	12	↑ 3.4-fold (2.8, 4.3X)	↑ 55% (40, 72%)	ND
Meperidine	50 oral single dose	500 q12h, 10 d	8	↓ 62% (59, 65%)	↓ 59% (42, 72%)	ND
Normeperidine metabolite			6	↑ 47% (-24, 345%)	↑ 87% (42, 147%)	ND
Methadone ²	5, single dose	500 q12h, 15 d	11	↓ 36% (16, 52%)	↓ 38% (28, 46%)	ND
Raltegravir	400, single dose	100 q12h, 16 d	10	↓ 16% (-30, 1%)	↓ 24% (-45, 4%)	↓ 1% (-30, 40%)
Rivaroxaban	10, single dose (days 0 and 7)	600 q12h (days 2 to 7)	12	↑ 150% (130-170%) ⁷	↑ 60% (40-70%) ⁷	ND
Rifabutin	150 daily, 16 d	500 q12h, 10 d	5,	↑ 4-fold (2.8, 6.1X)	↑ 2.5-fold (1.9, 3.4X)	↑ 6-fold (3.5, 18.3X)
25-O-desacetyl rifabutin metabolite			11 *	↑ 38-fold (28, 56X)	↑ 16-fold (13, 20X)	↑ 181-fold (ND)
Sildenafil	100, single dose	500 twice daily, 8 d	28	↑ 11-fold	↑ 4-fold	ND
Simeprevir	200 mg qd, 7 d	100 mg bid, 15 d	12	↑ 618% (463%-815%) ⁸	↑ 370% (284%-476%) ⁸	↑ 1335% (929%-1901%) ⁸
Sulfamethoxazole ³	800, single dose	500 q12h, 12 d	15	↓ 20% (16, 23%)	↔	ND
Tadalafil	20 mg, single dose	200 mg q12h		↑ 124%	↔	ND

Theophylline	3 mg/kg q8h, 15 d	500 q12h, 10 d	13, 11*	↓ 43% (42, 45%)	↓ 32% (29, 34%)	↓ 57% (55, 59%)
Trazodone	50 mg, single dose	200 mg q12h, 4 doses	10	↑ 2.4-fold	↑ 34%	
Trimethoprim ³	160, single dose	500 q12h, 12 d	15	↑ 20% (3, 43%)	↔	ND
Vardenafil	5 mg	600 q12h		↑ 49-fold	↑ 13-fold	ND
Voriconazole	400 q12h, 1 d; then 200 q12h, 8 d	400 q12h, 9 d		↓ 82%	↓ 66%	
	400 q12h, 1 d; then 200 q12h, 8 d	100 q12h, 9 d		↓ 39%	↓ 24%	
Warfarin S-Warfarin R-Warfarin	5, single dose	400 q12h, 12d	12	↑ 9% (-17, 44%) ⁴ ↓ 33% (-38, -27%) ⁴	↓ 9% (-16, -2%) ⁴ ↔	ND ND
Zidovudine	200 q8h, 4 d	300 q6h, 4 d	9	↓ 25% (15, 34%)	↓ 27% (4, 45%)	ND

1 Ritonavir and indinavir were co-administered for 15 days; Day 14 doses were administered after a 15%-fat breakfast (757 Kcal) and 9%-fat evening snack (236 Kcal), and Day 15 doses were administered after a 15%-fat breakfast (757 Kcal) and 32%-fat dinner (815 Kcal). Indinavir C_{min} was also increased 4-fold. Effects were assessed relative to an indinavir 800 mg q8h regimen under fasting conditions.

2 Effects were assessed on a dose-normalized comparison to a methadone 20 mg single dose.

3 Sulfamethoxazole and trimethoprim taken as single combination tablet.

4 90% CI presented for R- and S-warfarin AUC and C_{max} ratios.

5 This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol AUC.

6 For the reference arm: N=14 for C_{max} and AUC_(0-inf), and for the test arm: N=13 for C_{max} and N=4 for AUC_(0-inf).

7 90% CI presented for rivaroxaban

8 90% CI presented for simeprevir (change in exposure presented as percentage increase)

↑ Indicates increase.

↓ Indicates decrease.

↔ Indicates no change.

* Parallel group design; entries are subjects receiving combination and control regimens, respectively.

12.4 Microbiology

Mechanism of Action

Ritonavir is a peptidomimetic inhibitor of the HIV-1 protease. 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.

Ritonavir, at the recommended dose, is not intended for use as an inhibitor of the HIV-1 protease (See *Indications and Usage (1), Dosage and Administration (2) and Mechanism of Action 12.1*).

See full prescribing information for Norvir for additional information on its antiviral activity.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 3.6-fold for males that of the exposure in humans with the recommended therapeutic dose (100 mg twice-daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 7.2-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the recommended therapeutic dose. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known.

Mutagenesis

However, ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Impairment of Fertility

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.

14 CLINICAL STUDIES

Pediatric Patients

Darunavir co-administered with ritonavir

The pharmacokinetic profile, safety and antiviral activity of darunavir co-administered with ritonavir were evaluated in 3 randomized, open-label, multicenter studies. In treatment experienced pediatric subjects 3 to less than 6 years of age, the proportion of subjects with HIV-1 RNA less than 50 copies/mL at Week 48 was 71%; in subjects 6 to less than 18 years of age, the proportion with HIV-1 RNA less than 50 copies/mL at Week 24 was 50%. In treatment naïve adolescents (12- <18 years old), the proportion of subjects with HIV-1 RNA less than 50 copies/mL at Week 48 was 83%.

See full prescribing information for darunavir for additional details.

Atazanavir co-administered with ritonavir

Assessment of the pharmacokinetics, safety, tolerability, and efficacy of atazanavir is based on data from one open-label, multicenter clinical trial conducted in patients 6 to less than 18 years of age. One-hundred five patients (treated with the atazanavir capsule, with or without ritonavir) were evaluated. The proportion of antiretroviral- naïve and -experienced subjects with HIV-1 RNA less than 50 copies/mL at Week 96 were 47% and 24%, respectively.

See full prescribing information for atazanavir for additional details.

15 REFERENCES

1. Sewester CS. Calculations. In: Drug Facts and Comparisons. St. Louis, MO: J.B. Lippincott Co; January, 1997:xix.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ritonavir tablets are available in the following strengths and package sizes:

Ritonavir Tablets USP 25 mg is available as follows:

Bottle of 60 tablets- (NDC 69097-267-03)

Ritonavir Tablets USP 50 mg is available as follows:

Bottle of 60 tablets- (NDC 69097-268-03)

16.1 Ritonavir Tablets USP, 25 mg and 50 mg

Ritonavir tablets 25 mg is “white colored, oval shaped, shallow, film coated tablets debossed with “25” on one side & plain on other side.

Ritonavir tablets 50 mg is “white colored, oval shaped, shallow, film coated tablets debossed with “50” on one side & plain on other side.

Ritonavir tablets 25 and 50 mg are available as follows:

Bottle of 60 tablets

Storage

Store at room temperature below 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient information)Patients or parents of patients should be informed that:

General Information

- They should pay special attention to accurate administration of their dose to minimize the risk of accidental overdose or underdose of ritonavir.
- They should inform their healthcare provider if their children’s weight changes in order to make sure that the child’s ritonavir dose is the correct one.

- Take ritonavir with meals.
- Patients should remain under the care of a physician while using ritonavir. Patients should be advised to take ritonavir and other concomitant antiretroviral therapy every day as prescribed. Ritonavir should be used as a protease inhibitor booster of darunavir and atazanavir. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of ritonavir is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.
- Ritonavir is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using ritonavir.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if ritonavir can be passed to the baby through breast milk and whether it could harm the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.
- Sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death.

Drug Interactions

- Ritonavir 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.
- If they are receiving estrogen-based hormonal contraceptives, additional or alternate contraceptive measures should be used during therapy with ritonavir.

Potential Adverse Effects

- Pre-existing liver disease including Hepatitis B or C can worsen with use of ritonavir. This can be seen as worsening of transaminase elevations or hepatic decompensation. Patients should be advised that their liver function tests will need to be monitored closely especially during the first several months of ritonavir treatment and that they should notify their healthcare provider if they develop the signs and symptoms of worsening liver disease including loss of appetite, abdominal pain, jaundice, and itchy skin.
- Pancreatitis, including some fatalities, has been observed in patients receiving ritonavir therapy. Your patients should let you know of signs and symptoms (nausea, vomiting, and abdominal pain) that might be suggestive of pancreatitis.
- Skin rashes ranging in severity from mild to Stevens-Johnson syndrome have been reported in patients receiving ritonavir. Patients should be advised to contact their healthcare provider if they develop a rash while taking ritonavir. The healthcare provider will determine if treatment should be continued or an alternative antiretroviral regimen used.

- Ritonavir may produce changes in the electrocardiogram (e.g., PR prolongation). Patients should consult their physician if they experience symptoms such as dizziness, lightheadedness, abnormal heart rhythm or loss of consciousness.
- Treatment with ritonavir therapy can result in substantial increases in the concentration of total cholesterol and triglycerides.
- New onset of diabetes or exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported. Patients should be advised to notify their healthcare provider if they develop the signs and symptoms of diabetes mellitus including frequent urination, excessive thirst, extreme hunger or unusual weight loss and/or an increased blood sugar while on ritonavir as they may require a change in their diabetes treatment or new treatment.
- Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including ritonavir.
- 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.
- Patients with hemophilia may experience increased bleeding when treated with protease inhibitors such as ritonavir.
- If they are receiving avanafil, sildenafil, tadalafil, or vardenafil for the treatment of erectile dysfunction, they may be at an increased risk of associated adverse reactions including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor. They should seek medical assistance immediately if they develop a sustained penile erection lasting more than 4 hours while taking ritonavir and a PDE 5 Inhibitor such as Stendra[®], Viagra[®], Cialis[®] or Levitra[®]. If they are currently using or planning to use avanafil or tadalafil (for the treatment of pulmonary arterial hypertension) they should ask their doctor about potential adverse reactions these medications may cause when taken with ritonavir. The doctor may choose not to keep them on avanafil, or may adjust the dose of tadalafil while initiating treatment with ritonavir. Concomitant use of Revatio[®] (sildenafil) with ritonavir is contraindicated in patients with pulmonary arterial hypertension (PAH).

Ritonavir Tablets are manufactured by:

CIPLA LTD. INDIA.

Patient Information

Ritonavir tablets USP, for oral use 25 mg and 50 mg

Read this Patient Information before your child starts taking ritonavir and each time you get a refill. There may be new information. This information does not take the place of talking to the doctor about your child's medical condition or treatment.

What is the most important information I should know about Ritonavir?

- Ritonavir can interact with other medicines and cause serious side effects. It is important to know the medicines that should not be taken with ritonavir. See the section "Who should not take Ritonavir?"

What is Ritonavir?

Ritonavir is a prescription medicine used with the antiretroviral HIV-1 medicine darunavir or atazanavir to increase the amount of that medicine in your blood.

You must also take the antiretroviral HIV-1 medicines prescribed by your healthcare provider even if you take ritonavir with darunavir or atazanavir.

Ritonavir does not cure HIV infection or AIDS and you or your child may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Your child should remain under the care of a doctor when using ritonavir.

Avoid doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, of blood.

Who should not take Ritonavir?

Do not give ritonavir if you or your child is allergic to ritonavir or any of the ingredients in ritonavir tablets. See the end of this leaflet for a complete list of ingredients in ritonavir tablets.

Do not give Ritonavir to your child with any of the following medicines:

- alfuzosin (Uroxatral)
- amiodarone (Cordarone, Nexterone, Pacerone), flecainide (Tambocor), propafenone (Rhythmol) or quinidine (Nuedext, Quinaglute, Cardioquin, Quinidex, and others)
- voriconazole (VFend) if ritonavir dose is 400 mg every 12 hours or greater
- dihydroergotamine (D.H.E. 45, Embolex, Migranal), ergotamine (Cafergot, Ergomar) methylergonovine (Methergine)
- cisapride (Propulsid)
- St. John's Wort (*Hypericum perforatum*)

- the cholesterol lowering medicines lovastatin (Mevacor, Altoprev, Advicor) or simvastatin (Zocor, Simcor, Vytorin)
- pimozide (Orap)
- sildenafil (Revatio) only when used for the treatment of pulmonary arterial hypertension
- oral midazolam or triazolam (Halcion)

Serious problems can happen if your child takes any of these medicines with ritonavir.

What should I tell my child's doctor before my child takes Ritonavir?

Before giving Ritonavir, tell the doctor if your child:

- has liver problems, including Hepatitis B or Hepatitis C.
- has heart problems.
- has high blood sugar (diabetes).
- has bleeding problems or hemophilia.

Tell the doctor about all the medicines your child takes including prescription and nonprescription medicines, vitamins, and herbal supplements. Taking ritonavir and certain other medicines may affect each other causing serious side effects. Ritonavir may affect the way other medicines work and other medicines may affect how ritonavir works.

Especially tell the doctor if your child takes:

- medicine to treat HIV
- medicine for pain such as tramadol (Ryzolt, Ultracet, Conzip, Ultram), propoxyphene, or meperidine (Demerol)
- medicine to treat alcohol abuse such as disulfiram (Antabuse)
- medicine for your heart such as disopyramide (Norpace), lidocaine (Xylocaine Viscous), mexiletine, digoxin (Lanoxin), nifedipine (Procardia, Adalat, Afeditab CR), diltiazem (Cardiem, Dilacor, Cartia, Diltzac, Dilt, Taztia, Tiazac) or verapamil (Calan, Covera, Isoptin, Tarka, Verelan)
- medicines for panic disorder or anxiety such as buspirone, clorazepate, diazepam, estazolam, flurazepam, and zolpidem
- medicine for cancer such as dasatinib (Sprycel), nilotinib (Tasigna) vincristine, or vinblastine
- warfarin (Coumadin, Jantoven), rivaroxaban (Xarelto)
- medicine for seizures such as carbamazepine (Carbatrol, Equetro, Tegretol, Epitol), clonazepam (Klonopin), ethosuximide (Zarontin, Ethosuximide), divalproex (Depakote, Divalproex Sodium), lamotrigine (Lamictal) or phenytoin (Dilantin, Phenytek)
- medicine for depression such as nefazodone, bupropion (Wellbutrin, Aplenzin, Zyban), desipramine (Norpramin) or trazadone, fluoxetine (Prozac), paroxetine (Paxil), amitriptyline, or nortriptyline
- medicine for nausea and vomiting such as dronabinol (Marinol) or perphenazine
- medicine for fungal infections such as ketoconazole (Nizoral), itraconazole (Sporanox, Onmel) or voriconazole (VFend)
- colchicine (Colcrys, Col-Probenecid, Probenecid and Colchine)

- medicine for infections such as clarithromycin (Prevpac, Biaxin), rifabutin (Mycobutin), rifampin (Rimactane, Rifadin, Rifater, Rifamate), atovaquone (Mepron, Malarone), quinine (Qualaquin) or metronidazole (Flagyl, Helidac, Metrocream)
- medicine used to treat blood pressure, a heart attack, heart failure, or to lower pressure in the eye such as metoprolol (Lopressor, Toprol-XL), timolol (Cosopt, Betimol, Timoptic, Isatolol, Combigan)
- medicine for lung disease such as theophylline and salmeterol (Serevent)
- bosentan (Tracleer)
- medicine to prevent organ transplant failure such as cyclosporine (Gengraf, Sandimmune, Neoral), tacrolimus (Prograf,) sirolimus (Rapamune)
- steroids such as dexamethasone, fluticasone (Advair Diskus, Veramyst, Flovent, Flonase), budesonide (Entocort EC, Pulmicort, Rhinocort), or prednisone
- a narcotic medicine such as methadone (Methadose, Dolophine Hydrochloride) or fentanyl (Abstral, Actiq, Fentora, Lazanda, Onsolis, Duragesic)
- medicine to treat schizophrenia such as risperidone (Risperdal) or thioridazine
- medicine to treat pulmonary hypertension such as avanafil (Stendra), sildenafil (Viagra, Revatio), vardenafil (Levitra, Staxyn), tadalafil (Cialis, Adcirca).
- midazolam by injection
- methamphetamine (Desoxyn)
- cholesterol lowering medicine such as atorvastatin (Lipitor) or rosuvastatin (Crestor)

This is not a complete list of medicines that you should tell your child's doctor that your child is taking. Ask your child's doctor, provider or pharmacist if you are not sure if your child's medicine is one that is listed above.

Know the medicines your child takes. Keep a list of them to show the doctor or pharmacist when your child gets a new medicine. Do not start any new medicines while your child is taking ritonavir without first talking with the doctor.

How should my child take Ritonavir?

- Give ritonavir to your child exactly as prescribed by your child's doctor.
- Your child should stay under a doctor's care when taking ritonavir. Do not change the dose of ritonavir or stop the treatment without talking with your child's doctor first.
- If your child is taking ritonavir, your child's doctor will decide the right dose based on your child's weight. Tell your doctor if your child's weight changes. Your child should take ritonavir with food. If your child does not tolerate ritonavir tablets, ask your child's doctor for advice.
- Swallow ritonavir tablets whole. Do not chew, break, or crush tablets before swallowing. If your child cannot swallow ritonavir tablets whole, tell the doctor. Your child may need a different medicine.
- Give ritonavir to your child with meals.
- Do not run out of ritonavir. Get the ritonavir prescription refilled from your child's doctor or pharmacy before you run out.

- If your child misses a dose of ritonavir, give it as soon as possible and then give the next scheduled dose at its regular time. If it is almost time for the next dose, wait and give the next dose at the regular time. Do not double the next dose.
- If your child takes too much ritonavir, call the local poison control center or go to the nearest hospital emergency room right away.

What are the possible side effects of Ritonavir?

Ritonavir can cause serious side effects including:

- See “What is the most important information I should know about Ritonavir?”
- **Liver disease.** Some people taking ritonavir in combination with other anti-HIV medicines have developed liver problems which may be life-threatening. Your child’s doctor should do regular blood tests during your child’s combination treatment with ritonavir. If your child has chronic hepatitis B or C infection, the doctor should check your child’s blood tests more often because your child has an increased chance of developing liver problems. Tell the doctor if your child has any of the below signs and symptoms of liver problems:
 - loss of appetite
 - pain or tenderness on the right side below the ribs
 - yellowing of your skin or whites of the eyes
 - itchy skin
- **Swelling of the pancreas (Pancreatitis).** Ritonavir can cause serious pancreas problems, which may lead to death. Tell the doctor right away if your child has signs or symptoms of pancreatitis such as:
 - nausea
 - vomiting
 - stomach (abdominal) pain
- **Allergic Reactions.** Sometimes these allergic reactions can become severe and require treatment in a hospital. You should call your child’s doctor right away if your child develops a rash. Stop giving ritonavir and get medical help right away if your child has any of the following symptoms of a severe allergic reaction:
 - trouble breathing
 - wheezing
 - dizziness or fainting
 - throat tightness or hoarseness
 - fast heartbeat or pounding in your child’s chest (tachycardia)
 - sweating
 - swelling of your child’s face, lips or tongue
 - muscle or joint pain
 - blisters or skin lesions
 - mouth sores or ulcers
- **Changes in the electrical activity of your child’s heart called PR prolongation. PR prolongation can cause irregular heartbeats.** Tell the doctor right away if your child has symptoms such as:
 - dizziness
 - lightheadedness
 - feel faint or pass out

- abnormal heart beat
- **Increase in cholesterol and triglyceride levels.** Treatment with ritonavir may increase your child's blood levels of cholesterol and triglycerides. The doctor should do blood tests before your child starts the treatment with ritonavir and regularly to check for an increase in the cholesterol and triglycerides levels.
- **Diabetes and high blood sugar (hyperglycemia).** Some people who take protease inhibitors including ritonavir can get high blood sugar, develop diabetes, or the diabetes can get worse. Tell the doctor if you often notice an increase in thirst or urination in your child while taking ritonavir.
- **Changes in the immune system (Immune reconstitution syndrome)** can happen when your child starts taking HIV medicines. Immune system may get stronger and begin to fight infections that have been hidden in your child's body for a long time. Call the doctor right away if your child starts having new symptoms after starting the HIV medicine.
- **Change in body fat.** These changes can happen in people who take antiretroviral therapy. The changes may include an increase amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back and stomach area. Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **Increased bleeding for hemophiliacs.** Some people with hemophilia have increased bleeding with protease inhibitors including ritonavir.

The most common side effects of Ritonavir include:

- diarrhea
- nausea
- vomiting
- upper and lower stomach (abdomen) pain
- tingling feeling or numbness in hands or feet or around the lips
- rash
- feeling weak or tired

Tell the doctor if your child has any side effect that bothers or that does not go away.

These are not all of the possible side effects of ritonavir. For more information, ask your child's doctor or pharmacist.

Call your child's doctor for medical advice about side effects. You may report side effects to **Cipla Ltd. at 1-866-604-3268 or FDA at 1-800-FDA-1088.**

How do I Store Ritonavir?

- Store at room temperature below 30°C (86°F).
- Store ritonavir tablets in the original container given to you by the pharmacist.
- Exposure of ritonavir tablets to high humidity outside the original container for longer than 2 weeks is not recommended.
- Use ritonavir tablets by the expiration date on the bottle.

Keep Ritonavir and all medicines out of the reach of children.

General information about Ritonavir

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use this medicine for a condition for which it was not prescribed. Do not share this medicine with other people.

This leaflet summarizes the most important information about ritonavir. If you would like more information, talk to your doctor. You can ask your child's doctor or pharmacist for information about ritonavir that is written for healthcare professionals.

For more information, call **Cipla Ltd. at 1-866-604-3268.**

What are the ingredients in Ritonavir?

Active ingredient: Ritonavir

Inactive ingredients:

Colloidal silicon dioxide, Copovidone (Kollidon VA64), Dibasic calcium phosphate (Anhydrous) (A Tab), Hypromellose (HPMC-6-cps), Isopropyl Alcohol, Opadry White YS-1-7003, Sodium Lauryl Sulfate, Sorbitan monolaurate.

This Patient Information has been approved by the U.S. Food and Drug Administration.

* The brands listed are trademarks of their respective owners and are not trademarks of Cipla Ltd.

CIPLA LTD. INDIA

Rev. 03/2015



Unvarnished Area for M.L., LOT, MFG & EXP.

Ritonavir Tablets USP
25 mg

JS79 A

NDC 69097-267-03
Rx only **60 Tablets**

Ritonavir Tablets USP
25 mg

NDC 69097-267-03
Rx only **60 Tablets**

Ritonavir Tablets USP
25 mg

Ritonavir Tablets USP
25 mg

Each film coated tablet contains:
Ritonavir USP 25 mg

Usual dosage:
See package insert for dosage and administration.

Do not use if safety seal under cap is broken or missing

Store below 30°C (86°F)

KEEP OUT OF REACH OF CHILDREN

Ritonavir Tablets USP
25 mg



Mfd. by **CIPLA LTD.**
MIDC, Patalganga,
M.S. 410 220 INDIA

Cipla

Cipla



Carton Size: 53 x 55 x 82 mm
Pharmacode : 736_STD
■ PANTONE 348 C
■ Black
Date: 02-03-2015



Unvarnished Area for
M.L., LOT, MFG & EXP.

50 mg
Ritonavir Tablets USP

JS82 A

NDC 69097-268-03
Rx only **60 Tablets**

Ritonavir Tablets USP
50 mg

NDC 69097-268-03
Rx only **60 Tablets**

Ritonavir Tablets USP
50 mg

Ritonavir Tablets USP
50 mg

Each film coated tablet contains:
Ritonavir USP 50 mg

Usual dosage:
See package insert for dosage and administration.

Do not use if safety seal under cap is broken
or missing

Store below 30°C (86°F)

KEEP OUT OF REACH OF CHILDREN

Ritonavir Tablets USP
50 mg



Mfd. by **CIPLA LTD.**
MIDC, Patalganga,
M.S. 410 220 INDIA

Cipla

Cipla



Carton Size: 53 x 55 x 82 mm
Pharmacode : 1248 STD
■ PANTONE 7649 C
■ Black
Date: 02-03-2015

Unwinding Direction ←

Each film coated tablet contains:
Ritonavir USP 25 mg

Usual dosage:
See package insert for dosage and administration.

Do not use if safety seal under cap is broken or missing

Store below 30°C (86°F)

KEEP OUT OF REACH OF CHILDREN

NDC 69097-267-03
Rx only 60 Tablets

Ritonavir Tablets USP
25 mg

Cipla



Mfd. by **CIPLA LTD.**
MIDC, Patalganga,
M.S. 410 220 INDIA



J578 A

← **Area for Overprinting details**
M.L., LOT, MFD, & EXP.

Label Size: 100 x 30 mm

Pharmacode : 736_MINI

PANTONE 348 C

Black

Date: 02-03-2015

Unwinding Direction ←

Each film coated tablet contains:
Ritonavir USP 50 mg

Usual dosage:
See package insert for dosage and administration.

Do not use if safety seal under cap is broken or missing

Store below 30°C (86°F)

KEEP OUT OF REACH OF CHILDREN

NDC 69097-268-03
Rx only 60 Tablets

Ritonavir Tablets USP

50 mg

Cipla



Mfd. by **CIPLA LTD.**
MIDC, Patalganga,
M.S. 410 220 INDIA

JS81 A

Area for Overprinting details
M.L., LOT, MFD. & EXP.

Label Size: 100 x 30 mm

Pharmacode : 1248_MINI

PANTONE 7649 C

Black

Date: 02-03-2015