

Each film-coated tablet contains 100 mg ritonavir USP.
Do not accept if seal over bottle opening is broken or missing.
Take Ritonavir Tablets with meals. Tablets should be swallowed whole and not chewed, broken, or crushed.
Usual Dosage: See package insert for full prescribing information.
Store at or below 30°C (86°F). Exposure to temperatures up to 50°C (122°F) for seven days permitted.
For patient use: exposure of this product to high humidity outside the original or USP equivalent tight container (60 mL or less) for longer than 2 weeks is not recommended.
Dispense in original container or USP equivalent tight container (60 mL or less).

Manufactured by:
Cipla Limited,
Patalganga,
Maharashtra, India

Manufactured for:
Roxane Laboratories, Inc.
Columbus, Ohio 43216

NDC 0054-0407-13 30 Tablets

Ritonavir Tablets USP

100 mg

Attention Pharmacist and Patients:
Tablet formulation: Store at room temperature (see side panel). Take Ritonavir Tablets with meals.

Alert: Find out about medicines that should NOT be taken with Ritonavir Tablets.

Note to Pharmacist: Do not cover ALERT box with pharmacy label. Package insert is provided with tear-off patient information.

R_x only



Bechinger Ingelheim
Roxane Laboratories

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Manufactured by:
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Columbus, Ohio 43216

NDC 0054-0407-23

120 Tablets

Ritonavir Tablets USP

100 mg

**Attention Pharmacist and Patients:
Tablet formulation: Store at room
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**Alert: Find out about medicines that
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**Note to Pharmacist: Do not cover
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Package insert is provided with tear-off
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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RITONAVIR TABLETS USP safely and effectively. See full prescribing information for RITONAVIR TABLETS USP.

RITONAVIR TABLETS USP for Oral Use
Initial U.S. Approval: 1996

WARNING: DRUG-DRUG INTERACTIONS LEADING TO POTENTIALLY SERIOUS AND/OR LIFE-THREATENING REACTIONS
Co-administration of Ritonavir Tablets with several classes of drugs including sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations may result in potentially serious and/or life-threatening adverse effects of Ritonavir Tablets on the hepatic metabolism of certain drugs. Review the following full prescribing information for Ritonavir Tablets 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 Tablets USP are an HIV protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection (1).

ADVERSE REACTIONS
The most frequently reported adverse drug reactions among patients receiving Ritonavir Tablets alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances (including paresthesia and oral paresthesia), rash, and fatigue/asthenia (6, 16).

DOSE AND ADMINISTRATION
Dose modification for Ritonavir Tablets is necessary when used with other protease inhibitors (2).
Adult patients: 600 mg twice-daily with meals (2.1).
Pediatric patients: The recommended twice daily doses for children greater than one month of age are based on body surface area and should not exceed 600 mg twice daily with meals (2.2).

DOSE FORMS AND STRENGTHS
Tablets: 100 mg ritonavir, (3).

CONTRAINDICATIONS
Ritonavir Tablets are 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 effects (4).

WARNINGS AND PRECAUTIONS
The following have been observed in patients receiving ritonavir:
Drug Interactions: Consider drug-drug interaction potential to reduce full prescribing information, **CONTENTS** (7).

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1.2 Nursing Mothers
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1.4 Geriatric Use
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10.1 Acute Overdosage - Human Overdose Experience
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Table 2: Drugs That Are Contraindicated with Ritonavir Tablets

Drug Class	Drugs Within Class That Are Contraindicated with Ritonavir	Clinical Comments
Alpha-1 Adrenergic Antagonist	Alfuzosin HCl	Potential for hypotension.
Antiarrhythmic	Amiodarone, flecainide, propafenone, quinidine	Potential for cardiac arrhythmias.
Antifungal	Voriconazole	Co-administration of voriconazole with ritonavir 400 mg every 12 hours significantly decreased voriconazole plasma concentrations. Voriconazole is contraindicated with ritonavir doses of 400 mg every 12 hours or greater (see Drug Interactions (7.2)).
Ergot Derivative	Dihydroergotamine, ergonovine, ergolamine, methylergovanine	Potential for acute ergot toxicity characterized by vasoconstriction 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 Tablets 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 Inhibitor	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Neuroleptic	Fluphenazine	Hypertensive crisis.
PDDES 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 (see Drug Interactions (7.2)).
Sedative/Hypnotic	Oral midazolam, triazolam	Prolonged or increased duration of respiratory depression (see Drug Interactions (7.2)).

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The safety of ritonavir alone and in combination with other antiretroviral agents was studied in 1,755 adult patients. Table 3 lists treatment-emergent Adverse Reactions (with possible or probable relationship to study drug) occurring in greater than or equal to 1% of adult patients receiving ritonavir in combined Phase HIV studies.

The most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances (including paresthesia and oral paresthesia), rash, and fatigue/asthenia.

Table 3: Treatment-Emergent Adverse Reactions (With Possible or Probable Relationship to Study Drug) Occurring in Greater than or Equal to 1% of Adult Patients Receiving Ritonavir in Combined Phase HIV Studies (N = 1,755)

Adverse Reactions	n	%
Eye Disorders		
Bleurred Vision	113	6.4
General Disorders		
Abdominal Pain (Upper and Lower)*	464	26.4
Diarrhea (Including Severe With Electrolyte Imbalance)*	1192	67.9
Dysgeusia	201	11.5
Fatigue	142	8.1
Gastrointestinal Hemorrhage*	14	0.8
Gastrointestinal Perforation Disease (GERD)	19	1.1
Nausea	1007	57.4
Vomiting*	559	31.9
General Disorders and Administration Site Conditions		
Fatigue Including Asthenia*	811	46.2
Hepatitis Disorders		
Blood Bilirubin Increased (Including Jaundice)*	25	1.4
Hepatitis (Including Increased AST, ALT, GGT)*	153	8.7
Immune System Disorders		
Hypersensitivity Including Urticaria and Face Edemas*	114	6.2
Metabolism and Nutrition Disorders		
Edema and Peripheral Edema*	110	6.3
Diabetes Mellitus*	19	1.1
Hypercholesterolemia*	12	0.7
Hypertriglyceridemia*	158	9.0
Lipodystrophy*	51	2.9
Musculoskeletal and Connective Tissue Disorders		
Arthralgia and Back Pain*	329	18.8
Myalgia	156	8.9
Nervous System Disorders		
Dryness*	274	15.6
Dysgeusia*	285	16.2
Headache (Including Oral Paresthesia)*	689	39.3
Peripheral Neuropathy*	178	10.1
Syncope*	58	3.3
Psychiatric Disorders		
Depression*	52	3.0
Disturbance in Attention	44	2.5
Respiratory Disorders		
Respiratory Infection*	74	4.2
Respiratory, Thoracic and Mediastinal Disorders		
Cough*	380	21.7
Chrysalis Pain*	279	15.9
Skin and Subcutaneous Tissue Disorders		
Rash*	67	3.8
Pruritus*	214	12.2
Rash (Includes Erythematous and Maculopapular)*	475	27.1
Flushing, Feeling Hot*	232	13.2
Hypertension*	58	3.3
Headache (Including Orthostatic Hypotension)*	30	1.7
Peripheral Coldness*	21	1.2

* Represents a medical concept including several similar MedDRA PTs
Laboratory Abnormalities: Table 4 shows the percentage of adult patients who developed marked laboratory abnormalities.

Table 4: Percentage of Adult Patients, by Study and Treatment Group, with Chemistry and Hematology Abnormalities Occurring in Greater Than 2% of Patients Receiving Ritonavir

Variable	Limit	Study 245 New Patients		Study 247 Advanced Patients		Study 462 PI-Naive Patients	
		Ritonavir + ZDV	Ritonavir	Ritonavir	Placebo	Ritonavir	Saquinavir
Chemistry							
Cholesterol	>240 mg/dL	30.7	44.8	9.3	36.5	8	65.2
Hematology							
Hemoglobin	<100 g/L	9.6	12.1	1.7	9.6	9	9.9
GGT	>300 U/L	1.8	1.2	1.7	19.6	11.3	4.2
SGOT (AST)	>180 U/L	5.3	9.5	2.5	6.4	7	7.8
SGPT (ALT)	>120 U/L	5.3	7.8	3.4	4.4	4.4	4.2
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	11.1
Triglycerides	>1500 mg/dL	1.5	1.3	-	9.9	0.3	9.3
Fasting							
Uric Acid	>12 mg/dL	-	-	-	3.8	0.2	1.4
Hematology							
Hemoglobin	<10 g/dL	2.6	-	0.8	17.3	22	0.7
Hemoglobin	<8.0 g/dL	0.9	-	-	3.8	3.9	-
Neutrophils	>8.5 x 10 ⁹ /L	-	-	-	8.3	1.7	-
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.

6.2. Pediatrics Clinical Trial Experience
Ritonavir has been studied in 265 pediatric patients greater than 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/erythema were the only drug-related clinical adverse events of moderate to severe intensity observed in greater than or equal to 2% of pediatric patients enrolled in ritonavir clinical trials.

Body as a Whole: Defaturation, usually associated with gastrointestinal symptoms, and sometimes resulting in hypotension, syncope, or oral insufficiency have also been reported with ritonavir and these events have not been established.

Autonomic Disorders (such as Graves' disease, polymyositis, and Guillain-Barre 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 (11.6)**).

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:
7. Drug Interactions (see **Warnings and Precautions (5.1)**)
8. Immunogenicity (see **Warnings and Precautions (5.3)**)
9. Pediatrics (see **Warnings and Precautions (5.4)**)
10. 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 contraindications (4), Warnings and Precautions (5), Drug Interactions (7), and Clinical Pharmacology (12.3).

- If your child is taking ritonavir, your child's doctor will decide the right dose based on your child's height and weight. Tell your doctor if your child's weight changes. Your child should take ritonavir with food. If your child does not tolerate Ritonavir Oral Solution, ask your child's doctor for advice.
- Swallow ritonavir tablets whole. Do not chew, break, or crush tablets before swallowing. If you cannot swallow ritonavir tablets whole, tell your doctor. You may need a different medicine.
- Take ritonavir with meals.
- Do not run out of ritonavir. Get your ritonavir prescription refilled from your doctor or pharmacy before you run out.

- If you miss a dose of ritonavir, take it as soon as possible and then take your next scheduled dose at its regular time. If it is almost time for your next dose, wait and take the next dose at the regular time. Do not double the next dose.
- If you take too much ritonavir, call your 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 doctor should do regular blood tests during your combination treatment with ritonavir. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Tell your doctor if you have any of the below signs and symptoms of liver problems:
 - loss of appetite
 - pain or tenderness on your right side below your ribs
 - yellowing of your skin or whites of your eyes
 - itchy skin

- **Swelling of your pancreas (Pancreatitis).** Ritonavir can cause serious pancreas problems, which may lead to death. Tell your doctor right away if you have signs or symptoms of pancreatitis such as:
 - nausea
 - vomiting
 - stomach (abdomen) pain

- **Allergic Reactions.** Sometimes these allergic reactions can become severe and require treatment in a hospital. You should call your doctor right away if you develop a rash. Stop taking ritonavir and get medical help right away if you have 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 chest (tachycardia)
 - sweating
 - swelling of your face, lips or tongue
 - muscle or joint pain
 - blisters or skin lesions
 - mouth sores or ulcers

- **Changes in the electrical activity of your heart called PR prolongation. PR prolongation can cause irregular heartbeats.** Tell your doctor right away if you have 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 blood levels of cholesterol and triglycerides. Your doctor should do blood tests before you start your treatment with ritonavir and regularly to check for an increase in your cholesterol and triglyceride levels.
- **Diabetes and high blood sugar (hyperglycemia).** Some people who take protease inhibitors including ritonavir can get high blood sugar, develop diabetes, or your diabetes can get worse. Tell your doctor if you notice an increase in thirst or urinate often while taking ritonavir.

- **Changes in your immune system (immune reconstitution syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Call your doctor right away if you start having new symptoms after starting your 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.

ple with hemophilia have increased bleeding with protease inhibitors including ritonavir.

- The most common side effects of ritonavir include:**
- diarrhea
 - nausea
 - vomiting
 - upset and lower stomach (abdomen) pain
 - tingling feeling or numbness in hands or feet or around the lips
 - rash
 - feeling weak or tired

Ritonavir liquid contains a large amount of alcohol. If a toddler or young child accidentally drinks more than the recommended dose of ritonavir, it could make him/her sick from too much alcohol. Contact your local poison control center or emergency room immediately if this happens.

Tell your doctor if you have any side effect that bothers you or that does not go away.

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ritonavir?

- Store Ritonavir Tablets below 30°C (86°F). Exposure to temperatures up to 50°C (122°F) for seven days does not affect the safety or efficacy of ritonavir tablets.
- 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 Tablets. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about Ritonavir Tablets that is written for healthcare professionals. For more information, call 1-800-962-8364.

What are the ingredients in Ritonavir Tablets?

Active ingredient: ritonavir
Inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, hypromellose, isopropyl alcohol, poly sorbate 80, polyethylene glycol, purified water, sodium stearoyl fumarate, sorbitan monolaurate and titanium dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.
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1000000/01

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Sedative/hypnotic, parenteral midazolam	1 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 cases 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), budesonide, dexamethasone, prednisone	1 glucocorticoids	Concomitant use of glucocorticoids that are metabolized by CYP3A4 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	1 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
Teratogenic Effects: Pregnancy Category B. Antiretroviral Pregnancy Registry. To monitor maternal-fetal outcomes of pregnant women exposed to ritonavir, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

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 3865 exposures to ritonavir containing regimens (1567 exposure in the first trimester and 2293 exposure in the second and third trimester). Birth defects occurred in 51 of the 1567 (3.2%) live births (first trimester exposure) and 91 of the 2293 (3.9%) 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 equivalent to approximately 30% of that achieved with the proposed therapeutic dose. A slight increase in the incidence of cytotrichodermis 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 1.4 times the proposed therapeutic dose based on body weight.

8.3 Nursing Mothers
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid transmitting 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 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.

8.5 Geriatric Use

Clinical studies with 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.

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 patients 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

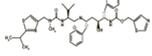
10.1 Acute Overdose
Human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg/day for two days. The patient reported symptoms including weakness after the dose was decreased. A post-marketing case of renal failure with eczematous rash was reported 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 Overdose

Ritonavir oral solution contains 43% alcohol by volume. Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol. Treatment of overdose with ritonavir consists of general supportive measures including monitoring vital signs of the clinical status of the patient. There is no specific antidote for overdose with ritonavir. If indicated, activated charcoal should be administered by emesis or gastric lavage, using 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. However, dialysis can remove both alcohol and propylene glycol, the cause of overdose with ritonavir oral solution. A Certified Poison Control Center should be consulted for up-to-date information on the management of overdose with ritonavir.

11 DESCRIPTION

Ritonavir Tablets USP are an inhibitor of HIV protease with activity against the Human Immunodeficiency Virus (HIV). Ritonavir is chemically designated as 10-Hydroxy-2-methyl-6-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bispheno(methyl)-2,4,7,12-tetraazadiazene-13-one acid, 5-thiazolylmethyl ester, [S-(R)-RIF, 10R, 11R]. Its molecular formula is C₂₇H₃₄N₆O₇S₂, and its molecular weight is 720.66. 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 containing 100 mg ritonavir in the following inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, hypromellose, isopropyl alcohol, poly sorbate 80, polyethylene glycol, purified water, sodium stearoyl fumarate, sorbitan monolaurate and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ritonavir is an antiviral drug [see Microbiology (12.4)].

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/mL). See Table 6 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 (514 Kcal; 9% fat, 12% protein, and 79% carbohydrates) conditions, respectively.

Ritonavir tablets are not bioequivalent to ritonavir capsules. Under moderate fat conditions (857 kcal; 21% fat, 12% protein, 56% carbohydrates), when a single 100 mg ritonavir dose was administered as a tablet compared with a capsule, AUC(0-∞) (net exposure criteria but mean C_{max} was increased by 26% (92.8% confidence interval: 115 - 139%).

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

Effect of Food on Oral Absorption: When the oral solution was given under non-fasting conditions, peak ritonavir concentrations decreased 20% 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, Advantix or Ensure® did not significantly affect the extent and rate of ritonavir absorption. Administration of a single 600 mg dose oral solution under non-fasting conditions yielded mean ± SD areas under the plasma concentration-time curve (AUC(0-∞) of 129 ± 59.3 ng/mL.

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 (1907 kcal; 52% fat, 15% protein, 33% carbohydrates), a 20% decrease in mean AUC_{0-∞} (90% confidence interval: 130% - 110%), and a 23% decrease in mean C_{max} (90% confidence interval: 134% - 111%) was observed relative to fasting conditions. Under moderate fat conditions, a 21% decrease in mean AUC(0-∞) (90% confidence interval: 128% - 119%), and a 22% decrease in mean C_{max} (90% confidence interval: 133% - 19%) 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 isopropylthiazolidine 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 vivo studies utilizing human liver microsome have demonstrated that cytochrome P450 3A (CYP3A) is the major isozyme 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 ± 2.0% of the dose was excreted in the feces with 38.8 ± 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)
t _{1/2} (hr)	91	0.41 ± 0.25 (log)

t _{1/2}	3 to 5 h
CL/F SSB	10 8.8 ± 3.2 L/h
CL/F	91 4.6 ± 1.8 L/h
CL _R	62 <0.1 L/h
RBC/Plasma Ratio	0.14
Plasma Protein Binding	98.2%

SSB = steady state; patients taking ritonavir 600 mg q12h; n = Single ritonavir 600 mg dose.
c = primarily bound to human serum albumin and alpha-2-glycoprotein over the ritonavir concentration range of 0.01 to 300 mg/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% confidence interval) time-matched difference in QTcF from placebo after baseline correction was 5.5 (7.4) milliseconds (ms) 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.

Diabetic Patients: Steady-state pharmacokinetics were evaluated in 37 HIV-infected patients ages 2 to 14 years receiving doses ranging from 250 mg per m² twice-daily to 400 mg per m² twice-daily in PACTO Study 310, and in 41 HIV-infected patients age 1 month to 2 years at doses of 350 and 450 mg per m² twice-daily in PACTO Study 345. Across dose groups, ritonavir steady-state oral clearance (CL_{ss}) was approximately 1.5 to 1.7 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg per m² twice-daily in pediatric patients greater than 2 years were comparable to those obtained in adults receiving 600 mg (approximately 300 mg per m²) twice-daily. The following observations were seen regarding ritonavir concentrations after administration with 350 or 450 mg per 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 per 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 pharmacokinetics 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 moderate to severe hepatic impairment.

Drug Interactions: [see also Contraindications (5.1), 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	1.12% (2, 23%)	1.15% (2, 28%)	114% (-3, 36%)
Didanosine	200 q12h, 4 d	600 q12h, 4 d	12	—	—	—
Fluconazole	400 single dose, day 1; 200 daily, day 2	200 q8h, 4 d	8	1.12% (5, 20%)	1.15 (7, 22%)	114% (0, 26%)
Fluoxetine	30 q12h, 8 d	600 single dose, day 1	16	1.19% (7, 24%)	—	—
Ketoconazole	200 daily, 7 d	500 q12h, 10 d	12	1.18% (-3, 52%)	1.10% (-11, 36%)	—
Rilpivirin	600 q12h, 10 d	500 q12h, 20 d	7, 9*	1.55% (7, 25%)	1.49% (-5, 46%)	-14% (-14, 91%)
Voriconazole	400 q12h, 1 d, then 200 q12h, 8 d	400 q12h, 9 d	—	—	—	—
Zidovudine	200 q8h, 4 d	300 q8h, 4 d	10	—	—	—

Table 8: Drug Interactions - Pharmacokinetic Parameters for Co-Administered Drug in the Presence of 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	1.12% (-5, 30%)	1.16% (5, 27%)	ND
Anastrozole	50, single dose	600 q12h, 14 d	1	1.34-fold (103, 111%)	1.24-fold (102, 136%)	ND
Chlorzoxipron 14-OH	500 q12h, 4 d	200 q8h, 4 d	22	1.7% (56, 103%)	1.91% (15, 51%)	2.33-fold (4, 13.8%)
Chlorzoxipron Metabolite	—	—	—	1.00% (1, 99%)	1.99% (1, 100%)	—
Desipramine 2-OH	100, single dose	500 q12h, 12 d	14	1.45% (3, 28%)	1.22% (8, 21%)	—
Desipramine Metabolite	—	—	—	1.19% (3, 28%)	1.67% (8, 22%)	—
Didanosine	200 q12h, 4 d	600 q12h, 4 d	12	1.13% (0, 23%)	1.16% (5, 26%)	—
Ethinyl Estradiol	50 mg single dose	500 q12h, 16 d	23	1.40% (31, 49%)	1.32% (24, 36%)	—
Fluconazole	200 mg q12h, 7 d	100 mg q12h, 7 d	18	1 approximately 350-fold	1 approximately 25-fold	—
Propafenone Aqueous Nasal Spray	—	—	—	—	—	—
Indinavir	400 q12h, 15 d	400 q12h, 15 d	10	1.41, 20% (-14, 29%)	1.61% (40, 61%)	1.4-fold (2.8, 6.8)
Day 15	—	—	—	1.7% (-22, 28%)	1.62% (52, 70%)	1.4-fold (2.5, 6.5)
Ketoconazole	200 daily, 7 d	800 q12h, 10 d	12	1.42% (103, 113%)	1.55% (42, 72%)	—
Meprednisolone Normalized Metabolite	50 oral single dose	800 q12h, 10 d	8	1.62% (89, 65%)	1.69% (42, 72%)	ND
Methadone	5, single dose	500 q12h, 15 d	11	1.47% (-24, 345%)	1.38% (42, 147%)	ND
Raltegravir	400, single dose	100 q12h, 16 d	10	1.16% (16, 35%)	1.24% (45, 41%)	1.1% (30, 42%)
Rilpivirin	100, single dose (days 0 and 7)	600 q12h (days 2 to 7)	12	1.150% (150, 170%)	1.70% (140, 203)	—
Rilpivirin 25-O-desacetyl metabolite	150, single dose	500 q12h, 10 d	5	1.4-fold (2.8, 6.1)	1.2-fold (1.9	