

# Ritonavir

**Brand Name:** Norvir



## Drug Description

Ritonavir is a synthetic peptidomimetic HIV protease inhibitor. Its chemical structure was designed based on structure of HIV protease. The symmetric nature of ritonavir results in a highly selective, potent inhibitor of HIV protease. [1]

## HIV/AIDS-Related Uses

Ritonavir was approved by the FDA on March 1, 1996, for the treatment of HIV infection in adults and in pediatric patients. Ritonavir is used in combination with other antiretroviral agents. Because ritonavir inhibits the metabolism of other protease inhibitors, it is increasingly used for boosting and maintaining plasma concentrations of protease inhibitors.[2] [3] [4]

## Pharmacology

Ritonavir is a selective, competitive, reversible inhibitor of HIV protease. It is active against HIV-1 and, to a lesser extent, HIV-2. This enzyme plays an essential role in the HIV replication cycle. During HIV replication, HIV protease cleaves viral polypeptide products to form structural proteins of the virion core and essential viral enzymes. By interfering with the formation of essential proteins and enzymes, ritonavir blocks the maturation of the virus and causes formation of nonfunctional, immature, noninfectious virions. Ritonavir targets the HIV replication cycle after translation and before assembly. Thus, the drug is active in chronically infected cells that generally are not affected by nucleoside reverse transcriptase inhibitors.[5]

Unlike nucleoside analogue antiretroviral agents, the antiviral activity of ritonavir does not depend on intracellular conversion to an active metabolite. HIV protease inhibitors (PIs), including ritonavir, act at different stages of the HIV replication cycle than nucleoside and nonnucleoside reverse transcriptase inhibitors.[6]

Ritonavir inhibits enzymes that limit the bioavailability or speed the metabolism of other PIs. It is used increasingly to boost and maintain

plasma concentrations of other protease inhibitors. At high doses, ritonavir has direct antiretroviral activity; at low doses (100 mg twice daily) it acts as a pharmacoenhancer of indinavir, amprenavir, saquinavir, lopinavir, and nelfinavir. Using a pharmacoenhancer with a PI increases exposure to the PI, raises trough plasma levels, and, in most cases, prolongs elimination half-lives.[7]

Ritonavir is well absorbed following oral administration, with peak plasma concentrations (C<sub>max</sub>) attained within 2 to 4 hours. Essentially all of an oral dose reaches systemic circulation as unchanged ritonavir. Presence of food in the gastrointestinal (GI) tract may affect the rate and extent of absorption of oral ritonavir; this varies depending on dosage form. Administration of ritonavir oral solution with food generally decreases the rate and extent of absorption, but ritonavir capsules given with a meal may increase the extent of absorption.[8]

The volume of ritonavir distribution following a single 600 mg oral dose averages 0.41 L/kg. In a study of patients receiving ritonavir concomitantly with saquinavir, ritonavir concentrations in cerebrospinal fluid ranged from 1.9 to 23 ng/ml.[9]

Ritonavir is in FDA Pregnancy Category B. There have been no adequate and controlled studies of ritonavir in pregnant women. Animal studies with ritonavir levels equivalent to twice the usual dosage in humans revealed no evidence of embryotoxicity or teratogenicity. Ritonavir should be used during pregnancy only when clearly needed. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to antiretroviral drugs, including ritonavir. Physicians may register patients by calling 1-800-258-4263 or at the following website: <http://www.APRegistry.com>. It is not known whether ritonavir is distributed into human milk; women should not breast-feed while they are receiving ritonavir.[10]

Ritonavir is 98% to 99% bound to plasma proteins. The plasma half-life of ritonavir in adults averages 3 to 5 hours. Preliminary studies in HIV-infected children 2 to 14 years of age indicate that ritonavir

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## Pharmacology (cont.)

clearance is 1.5 times greater than in adults. The drug is metabolized in the liver; five metabolites have been identified in urine and feces. Some 86.4% of a 600 mg dose is eliminated through the feces, both as unchanged drug (33.8%) and as metabolites, and 11.3% is excreted in the urine (3.5% as unchanged drug).[11]

The frequency of ritonavir-resistant HIV isolates existing in patients who are treatment naive or patients who previously received antiretroviral therapy with nucleoside analogue agents is not known. HIV variants containing mutations known to contribute to resistance to HIV PIs have been isolated from patients who have not previously received an HIV PI. Cross-resistance between ritonavir and nucleoside or nonnucleoside reverse transcriptase inhibitors is highly unlikely because these drugs have different target enzymes.[12]

Resistance to ritonavir develops in vitro, and strains of HIV-1 resistant to ritonavir have emerged during therapy. Although the complete mechanism of resistance to ritonavir has not been fully determined, mutation of HIV protease appears to be a principal mechanism of resistance. Acquisition of multiple mutations appears to be necessary for high-level resistance to ritonavir: the greater the number of mutations, the higher the level of resistance. The antiretroviral effects of ritonavir and some nucleoside reverse transcriptase inhibitors are additive or synergistic against HIV-1. The use of multidrug regimens that suppress HIV replication to undetectable levels is associated with a lower viral mutation rate and may delay or prevent the emergence of resistance.[13]

## Adverse Events/Toxicity

One of the more serious adverse effects of ritonavir is potentially fatal pancreatitis. Patients with symptoms of pancreatitis, including nausea, vomiting, abdominal pain, and increased serum lipase or amylase concentrations, should be evaluated and ritonavir therapy discontinued if a diagnosis of pancreatitis is made.[14]

Other serious adverse effects include body fat redistribution and accumulation, increased bleeding

in patients with hemophilia type A or B, hyperglycemia, hyperlipidemia, new-onset diabetes mellitus, and exacerbation of existing diabetes mellitus.[15]

The most frequently reported adverse effects of ritonavir include asthenia, nausea, diarrhea, vomiting, anorexia, abdominal pain, taste perversion, and circumoral and peripheral paresthesias. Less common adverse effects include fever, headache, malaise, vasodilation, constipation, dyspepsia, flatulence, local throat irritation, myalgia, dizziness, insomnia, somnolence, abnormal thinking, pharyngitis, rash, sweating, increase in creatine phosphokinase, and hyperlipidemia.[16]

## Drug and Food Interactions

When ritonavir oral solution is given with food, peak plasma concentrations and absorption decrease. When the soft gelatin capsule is given with food, absorption increases. The manufacturer recommends that ritonavir be taken with food if possible.[17]

The boosting effect of ritonavir on other PIs has led to its increased use as a pharmacoenhancer to help raise and maintain the plasma concentrations of other PIs. In addition, when ritonavir is given as a pharmacoenhancer, the dosage of the other PIs may be reduced, which generally results in fewer and/or milder adverse effects.[18] [19]

Drug interactions may occur when ritonavir is coadministered with a wide variety of other drugs, mostly due to pharmacokinetic interactions. Ritonavir is metabolized by isoforms of the cytochrome P-450 enzyme system. When it is administered with other drugs that are extensively metabolized by these isoenzymes, competition for the isoenzymes may occur, resulting in decreased metabolism and elevated plasma concentration of these drugs.[20]

Concomitant use of ritonavir with lovastatin or simvastatin is not recommended. Caution should be used when any PI, including ritonavir, is used concurrently with other HMG-CoA reductase inhibitors (atorvastatin or cerivastatin). The risk of myopathy or rhabdomyolysis may be increased

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## **Drug and Food Interactions (cont.)**

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when PIs are used with these drugs. Concomitant use of ritonavir and St. John's wort (*Hypericum perforatum*) or products containing St. John's wort may substantially decrease PI concentrations and is not recommended. Coadministration of ritonavir and sildenafil is expected to substantially increase sildenafil concentration and the risk of sildenafil-associated adverse effects, including hypotension, syncope, visual changes, and prolonged erection. Ritonavir should not be coadministered with astemizole, cisapride, or terfenadine (no longer available in the United States).[21]

Ritonavir may produce an increase or decrease in plasma levels of certain drugs. When coadministered with ritonavir, the following drugs should be used with caution and may require dosing increase, decrease, or separation: atorvastatin, atovaquone, bupropion, carbamazepine, clarithromycin, clonazepam, clorazepate, cyclosporine, desipramine, dexamethasone, diazepam, didanosine, diltiazem, disulfiram, disopyramide, divalproex, dronabinol, estazolam, ethosuximide, flurazepam, fluticasone, indinavir, itraconazole, ketoconazole, lamotrigine, lidocaine, meperidine, methadone, methamphetamine, metoprolol, metronidazole, mexilitene, nefazodone, nifedipine, oral contraceptives, perphenazine, phenytoin, prednisone, propoxyphene, quinine, rifabutin, rifampin, risperidone, saquinavir, selective serotonin reuptake inhibitors, sirolimus, tacrolimus, theophylline, thioridazine, timolol, tramadol, tricyclic antidepressants, verapamil, warfarin, and zolpidem.[22]

Ritonavir is a potent CYP450 inducer and CYP3A4 inhibitor and substrate. Ritonavir given at 400 mg every 12 hours for 9 days decreased the steady state C<sub>max</sub> and area under the plasma concentration-time curve (AUC) of voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 8 days) by an average of 66% and 82%, respectively, in healthy subjects.[23] Coadministration of voriconazole with ritonavir (400 mg every 12 hours) is contraindicated because ritonavir at this dosage significantly decreases plasma voriconazole concentrations in healthy subjects.[24]

In vitro drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with CYP3A4 inhibitors. Ritonavir, a potent CYP3A4 inhibitor, increased the C<sub>max</sub>, AUC, and elimination half-life, and decreased clearance of trazodone after administration of ritonavir twice daily for 2 days.[25]

## **Contraindications**

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Ritonavir is contraindicated in patients hypersensitive to the drug or to any ingredient in the formulations. Ritonavir should be used with caution in patients with pre-existing liver disease, liver enzyme abnormalities, or hepatitis.[26]

Ritonavir should not be coadministered with amiodarone, bepridil, flecainide, propafenone, quinidine, astemizole, terfenadine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, midazolam, or triazolam. Competition for CYP3A could inhibit metabolism of these drugs, creating the potential for life-threatening reactions, including cardiac arrhythmias, prolonged or increased sedation, or respiratory depression.[27]

## **Clinical Trials**

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For information on clinical trials that involve Ritonavir, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Ritonavir AND HIV Infections.

## **Dosing Information**

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Mode of Delivery: Oral.[28]

Dosage Form: Soft gelatin capsules containing 100 mg of ritonavir and oral solution containing 80 mg/ml of ritonavir. The recommended adult dosage of ritonavir is 600 mg twice daily by mouth. Ritonavir should be started at no less than 300 mg twice daily and increased at 2 to 3 day intervals by 100 mg twice daily. The recommended pediatric dosage of ritonavir is 400 mg/m<sup>2</sup> twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m<sup>2</sup> and increased at 2 to 3 day intervals by 50 mg/m<sup>2</sup> twice daily.[29]

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## Dosing Information (cont.)

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Storage: Store capsules at 2 C to 8 C (36 F to 46 F) and protect from light. Refrigerated storage of soft gelatin capsules by patients is recommended but not required if used within 30 days and stored below 25 C (77 F). Store oral solution at 20 C to 25 C (68 F to 77 F). Do not refrigerate oral solution. Avoid exposure of capsules and oral solution to excessive heat.[30]

## Chemistry

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CAS Name: 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-(2-(1-methylethyl)-4-thiazolyl)-3,6-dioxo-8,11-bis(phenylmethyl)-,5-thiazolymethyl ester, (5S-(5R\*,8R\*,10R\*,11R\*))-[31]

CAS Number: 155213-67-5[32]

Molecular formula: C<sub>37</sub>H<sub>48</sub>N<sub>6</sub>O<sub>5</sub>S<sub>2</sub>[33]

C61.64%, H6.71%, N11.66%, O11.10%, S8.90%[34]

Molecular weight: 720.95[35]

Physical Description: White to light tan powder with bitter metallic taste.[36]

Stability: The capsules are stable for 30 days when kept at 25 C (77 F).[37]

Solubility: Freely soluble in alcohol; practically insoluble in water.[38]

## Other Names

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A-84538[39]

Abbott 84538[40]

ABT-538[41]

RTV[42]

5-Thiazolymethyl [(alphaS)-alpha-[(1S,3S-1-hydroxy-3-[(2S)-2-[3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido]-3-methylbutyramido]-4-phenylbutyl]phenethyl]

carbamate[43]

## Further Reading

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## Manufacturer Information

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Ritonavir  
Abbott Laboratories  
One Hundred Abbott Park Rd  
Abbott Park, IL 60064-3500  
(800) 633-9110

Norvir  
Abbott Laboratories  
One Hundred Abbott Park Rd  
Abbott Park, IL 60064-3500  
(800) 633-9110

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## **For More Information**

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Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: [http://aidsinfo.nih.gov/live\\_help](http://aidsinfo.nih.gov/live_help) Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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