Ritonavir

Brand Name: Norvir
Drug Class: Protease Inhibitors

Drug Description

Ritonavir is a synthetic peptidomimetic HIV protease inhibitor (PI). Its chemical structure was designed based on the 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 children.[2] Ritonavir was approved by the FDA on October 3, 2005, with other anti-HIV drugs in the treatment of HIV-1 infection in patients over 1 month in age.[3] Because ritonavir inhibits the metabolism of other PIs, it is increasingly used for boosting and maintaining plasma concentrations of PIs. Because of its use as a booster, alterations in dosing of other PIs taken concurrently with ritonavir may be required.[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. Protease 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 (NRTIs).[5]

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

Low-dose ritonavir is used in conjunction with other HIV PIs to decrease metabolism and increase plasma concentrations of the other PI. Use of low-dose ritonavir in conjunction with another PI has been referred to as ritonavir pharmacokinetic enhancement or ritonavir-boosted therapy.[7] The ability of ritonavir to increase plasma trough concentrations (Cmin) of concomitantly administered PIs is perhaps the greatest clinical benefit of dual- or ritonavir-enhanced dual PI therapy, because inadequate concentrations of antiretrovirals may lead to long-term antiretroviral resistance.[8]

Ritonavir is well absorbed following oral administration, with peak plasma concentrations (Cmax) attained within 2 to 4 hours. Essentially all of an oral dose reaches systemic circulation as unchanged ritonavir. Presence of food in the gastrointestinal 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 administering ritonavir capsules with a meal may increase the extent of absorption.[9]

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.[10]

Ritonavir is in FDA Pregnancy Category B.[11] 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 online at http://www.APRegistry.com. It is not known whether ritonavir is distributed into human milk; women should not breastfeed while they are

Ritonavir

Pharmacology (cont.)

receiving ritonavir.[12]

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 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. About 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).[13]

The frequency of ritonavir-resistant HIV isolates existing in patients who are treatment naive or who previously received antiretroviral therapy with nucleoside analogue agents is not known. HIV variants containing mutations known to contribute to resistance to PIs have been isolated from patients who have not previously received a PI. Cross resistance between ritonavir and NRTIs or NNRTIs is highly unlikely because these drugs have different target enzymes.[14]

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 NRTIs 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.[15]

Adverse Events/Toxicity

One of the more serious adverse effects of ritonavir is potentially fatal pancreatitis. Patients with signs or 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.[16]

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.[17]

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.[18]

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.[19]

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.[20]

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.[21]

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

Drug and Food Interactions (cont.)

cytochrome P450 (CYP) enzyme system. When it is administered with other drugs that are extensively metabolized by these isoenzymes, competition for the isoenzymes may result in decreased metabolism and elevated plasma concentration of these drugs.[22]

Concomitant use of delavirdine and ritonavir may increase area under the plasma concentration-time curve (AUC), Cmax, and Cmin of ritonavir. Appropriate doses of this combination with respect to safety and efficacy have not been established.[23] Concomitant use of ritonavir with didanosine, methadone, or theophylline may result in decreased concentrations of the second drug; dosage adjustment may be required. Concomitant use of ritonavir with either clarithromycin, desipramine, ketoconazole, or rifabutin may result in increased concentrations of the second drug; dosage adjustment may be required.[24]

Ritonavir prolongs the PR interval in some patients and should be used with caution in patients who have preexisting structural heart disease, conduction system abnormalities, or other cardiac diseases. Ritonavir should be used with caution and with clinical monitoring in patients who are also using other drugs that prolong the PR interval, such as atazanavir, digoxin, beta blockers, or calcium channel blockers. First-, second-, and third-degree atrioventricular block have been observed in clinical trials and in postmarketing reports.[25]

Concomitant use of ethinyl estradiol-containing oral or patch contraceptives with ritonavir may result in significant reductions of mean Cmax and AUC. Alternate methods of contraception should be considered for patients who are currently taking ritonavir. A decrease in ritonavir dose may be needed when concurrently taken with certain sedatives and hypnotics, including buspirone, clorazepate, diazepam, estazolam, flurazepam, and zolpidem. Concurrent use of these sedatives with ritonavir increases the plasma concentrations of the sedative.[26]

Particular caution should be used when prescribing sildenafil with patients receiving ritonavir. Coadministration of these two drugs is expected to substantially increase sildenafil concentrations (as much as an 11-fold increase in AUC) and may result in an increase in sildenafil-associated adverse events, including hypotension, syncope, visual changes, and prolonged erection. The starting dose should not exceed 25 mg in a 48-hour period in patients concurrently receiving ritonavir. Tadalafil and vardenafil should also be prescribed with caution to patients receiving ritonavir, with increased monitoring for adverse effects. No more than 10 mg tadalafil or 2.5 mg vardenafil every 72 hours should be prescribed.[27]

Use of ritonavir with disulfiram may result in a disulfiram reaction due to ethanol content in ritonavir soft gelatin capsule and oral solution formulations; concomitant use of ritonavir and metronidazole may result in a similar disulfiram-like reaction. Concurrent use of reduced doses of ritonavir with either indinavir or saquinavir may result in increased Cmin of the second drug. Concomitant use of ritonavir and meperidine may result in increased risk for central nervous system stimulation (e.g., seizures), due to increased concentrations of meperidine's metabolite, normeperidine. Concurrent use of rifampin and ritonavir may result in decreased ritonavir concentrations and virologic response; an alternative mycobacterial is recommended.[28]

Ritonavir is a potent CYP450 inducer and CYP3A4 inhibitor and substrate. Ritonavir 400 mg given every 12 hours for 9 days decreased the steady state Cmax and 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.[29] 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.[30] [31]

In vitro drug metabolism studies suggest a potential for drug interactions when trazodone is given with CYP3A4 inhibitors. Ritonavir, a potent CYP3A4 inhibitor, increased the Cmax, AUC, and elimination half-life and decreased the clearance of trazodone after administration of ritonavir twice daily for 2 days.[32]

Ritonavir

Contraindications

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.[33]

Patients who have heart defects or conduction defects should not take ritonavir.[34]

Ritonavir should not be coadministered with amiodarone, bepridil, cisapride, dihydroergotamine, ergonovine, ergotamine, flecainide, lovastatin, methylergonovine, midazolam, pimozide, propafenone, quinidine, simvastatin, St. John's wort, or triazolam. These medications should not be coadministered with ritonavir due to the expected magnitude of interaction and potential for serious side effects. Postmarketing reports indicate that coadministration of ritonavir with dihydroergotamine or ergotamine has been associated with acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities.[35]

Clinical Trials

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

Mode of Delivery: Oral.[36]

Dosage Form: Soft gelatin capsules containing ritonavir 100 mg.[37]

Oral solution containing ritonavir 80 mg/ml.[38]

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.[39] The recommended pediatric dosage of ritonavir is 350 to 400 mg/m2 twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m2 and increased at 2 to 3 day intervals by 50 mg/m2 twice daily.[40]

Storage: Store capsules at 2 C to 8 C (36 F to 46 F) and protect from light. Refrigeration of soft gelatin capsules is recommended but not required if the capsules are used within 30 days and stored below 25 C (77 F).[41]

Store oral solution at 20 C to 25 C (68 F to 77 F). Do not refrigerate oral solution.[42]

The solution should be stored in the manufacturer-provided amber bottle and protected from light. Avoid exposure of capsules and oral solution to excessive heat.[43]

Chemistry

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-thiazolylmethyl ester, (5S-(5R*,8R*,10R*,11R*))-[44]

CAS Number: 155213-67-5[45]

Molecular formula: C37-H48-N6-O5-S2[46]

C61.64%, H6.71%, N11.66%, O11.10%, S8.90%[47]

Molecular weight: 720.95[48]

Physical Description: White to light tan powder with bitter metallic taste.[49]

Stability: The capsules are stable for 30 days when kept at 25 C (77 F).[50]

Solubility: Freely soluble in alcohol; practically insoluble in water.[51]

Other Names

RTV[52]

Further Reading

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Manufacturer Information

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Abbott Park, IL 60064-3500
(800) 633-9110

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For More Information

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 Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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