

Saquinavir

Brand Name: Fortovase, Invirase

Drug Description

Saquinavir is a peptidomimetic protease inhibitor.
[1]

HIV/AIDS-Related Uses

Saquinavir mesylate was approved by the U.S. Food and Drug Administration (FDA) on December 6, 1995 and saquinavir was approved by the FDA on November 7, 1997. Both are indicated for use in combination with other antiretroviral agents for the treatment of HIV infection. Saquinavir and saquinavir mesylate are not bioequivalent; saquinavir is the recommended formulation. Saquinavir soft gelatin capsules should be used to initiate saquinavir therapy. Rarely, saquinavir mesylate hard gelatin capsules may be used, but only if the antiretroviral regimen also includes ritonavir.[2] [3] [4]

Saquinavir (given as soft gelatin capsules) is used in conjunction with other antiretroviral agents for postexposure prophylaxis in healthcare workers and other individuals exposed occupationally to blood, tissues, or other body fluids associated with a risk for transmission of HIV.[5]

Pharmacology

Saquinavir is a structural analogue of the HIV Phe-Pro protease cleavage site and is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 protease. Saquinavir is active in both acutely and chronically infected cells; chronically infected cells are not affected by nucleoside reverse transcriptase inhibitors (NRTIs). While saquinavir does not affect early stages of the HIV replication cycle, it does interfere with the production of infectious virions, limiting further infectious spread of the virus.[6]

Bioavailability of saquinavir mesylate from hard gelatin capsules is low, averaging 4%. The relative bioavailability of saquinavir in liquid-filled soft gelatin capsules is estimated to average 331% that of saquinavir mesylate hard gelatin capsules. This represents a calculated average oral bioavailability from the soft gelatin capsules of 13%. Peak plasma

concentrations and area under the concentration-time curve (AUC) of the drug in soft gelatin capsules are about two times higher in HIV-infected patients than in healthy volunteers.[7]

Distribution of the drug into body tissues and fluids (such as cerebrospinal fluid) has not been fully characterized. Saquinavir is about 97% bound to plasma proteins in concentrations up to 30 mcg/ml. The drug is metabolized in the liver to several monohydroxylated and dihydroxylated inactive metabolites. Metabolism is mediated by cytochrome P450; the isoenzyme CYP3A4 is involved in more than 90% of this metabolism. Systemic clearance is rapid. Saquinavir is excreted primarily in the feces, both as unchanged drug and as metabolites.[8]

Saquinavir is in FDA Pregnancy Category B. It is not known whether saquinavir crosses the placenta in humans; placental transfer in laboratory animals is less than 5% of maternal plasma concentrations.[9] There are no adequate and well-controlled studies in pregnant women. Saquinavir 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 agents, including saquinavir. Physicians may register patients by calling 800-258-4263.[10] It is not known whether saquinavir is secreted in human milk; however, it is secreted in the milk of laboratory rats.[11]

Because saquinavir is metabolized by the liver, the manufacturer recommends that it be used with caution in patients with hepatic insufficiency. Patients with baseline liver function test results higher than five times the upper limit of normal were not included in clinical studies.[12]

HIV isolates with reduced susceptibility to the drug have been recovered from some patients on long-term saquinavir therapy. Genotypic analysis showed that mutations at amino acid positions 48 and/or 90 of the HIV protease gene were consistently associated with saquinavir resistance, and mutations at these positions have not been detected in isolates from protease inhibitor-naïve

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Pharmacology (cont.)

patients.[13]

Cross-resistance among protease inhibitors has been recognized; saquinavir-resistant isolates from patients on long-term therapy showed resistance to at least one of four other protease inhibitors: indinavir, nelfinavir, ritonavir, and amprenavir.[14] Cross-resistance between saquinavir and NRTIs or nonnucleoside reverse transcriptase inhibitors (NNRTIs) is unlikely because these drugs have different target enzymes.[15] In vitro studies indicate that the antiretroviral effects of HIV protease inhibitors and some NRTIs or NNRTIs may be additive or synergistic.[16]

Adverse Events/Toxicity

Saquinavir and saquinavir mesylate appear to be well tolerated. In clinical studies, the most frequently reported adverse effects included abdominal discomfort, diarrhea, and nausea. Other reactions include abdominal pain, anxiety, asthenia, buccal mucosa ulceration, constipation, depression, dizziness, dyspepsia, eczema, fatigue, flatulence, headache, insomnia, libido disorder, musculoskeletal pain, numbness in extremities, paresthesia, peripheral neuropathy, rash, taste alteration, verruca, and vomiting.[17] [18]

Body fat accumulation and redistribution, increased bleeding in hemophilia patients, hyperglycemia, exacerbation of existing diabetes mellitus, and new onset diabetes mellitus have been reported in patients receiving protease inhibitors, including saquinavir.[19]

In clinical studies there have been rare reports of serious adverse effects that may be related to treatment with saquinavir or saquinavir mesylate. These rare effects included confusion, ataxia, and weakness; seizures; headache; acute myeloblastic leukemia; hemolytic anemia; thrombocytopenia; thrombocytopenia and intracranial hemorrhage resulting in death; attempted suicide; Stevens-Johnson syndrome; bullous skin eruptions and polyarthritis; severe cutaneous reaction associated with increased liver function test results; isolated elevation of transaminase values; exacerbation of chronic liver disease with elevated

liver function tests, jaundice, ascites, and upper left and right quadrant abdominal pain; fatal pancreatitis; intestinal obstruction; portal hypertension; thrombophlebitis; peripheral vasoconstriction; drug fever; nephrolithiasis; and acute renal insufficiency.[20]

Drug and Food Interactions

Presence of food in the gastrointestinal tract can substantially increase the absorption of saquinavir and saquinavir mesylate. Administering saquinavir mesylate hard gelatin capsules with a meal increases absorption 5- to 10-fold compared with administration on an empty stomach.[21] For saquinavir liquid-filled soft gelatin capsules, the mean 12-hour AUC increased from 167 ng·h/ml under fasting conditions to 1120 ng·h/ml when administered with food.[22] Limited data indicate that the bioavailability of saquinavir is increased when the drug is administered with grapefruit juice.[23]

Metabolism of saquinavir is mediated by the cytochrome P450 isoenzyme CYP3A4. Drugs that induce this isoenzyme may reduce saquinavir plasma concentrations. Conversely, drugs that inhibit this isoenzyme may increase plasma concentrations of saquinavir. Saquinavir may alter the pharmacokinetics of other drugs that are metabolized by this enzyme system, which may create the possibility of serious adverse effects.[24]

Use of saquinavir or saquinavir mesylate with lovastatin or simvastatin is not recommended. Caution should be used when any HIV protease inhibitors, including saquinavir, are used concurrently with other HMG-CoA reductase inhibitors that are metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The resulting increased concentration of statins may increase the risk of myopathy or rhabdomyolysis.[25] [26]

Use of saquinavir or saquinavir mesylate with St. John's wort (*Hypericum perforatum*) or products containing St. John's wort may substantially decrease saquinavir concentrations and may lead to loss of virologic response and possible resistance to saquinavir or other protease inhibitors.[27] [28]

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Drug and Food Interactions (cont.)

Saquinavir should not be coadministered with astemizole, cisapride, or terfenadine (no longer available in the United States). Other drugs, including midazolam, triazolam, and ergot derivatives should not be coadministered with saquinavir. Competition for CYP3A4 by saquinavir may inhibit the metabolism of these drugs, which could potentially cause serious or life-threatening reactions, such as cardiac arrhythmias or prolonged sedation.[29] [30]

Concomitant use of certain other antiretroviral agents with saquinavir or saquinavir mesylate may significantly increase or decrease saquinavir plasma concentrations. These antiretrovirals include delavirdine, indinavir, nelfinavir, nevirapine, and ritonavir.[31] [32]

Coadministration of certain other drugs with saquinavir or saquinavir mesylate may cause an increase or decrease in plasma concentrations of saquinavir or of the coadministered drug. The manufacturer recommends caution when the following drugs are used concomitantly with saquinavir: calcium channel blockers, carbamazepine, clarithromycin, clindamycin, dapsone, dexamethasone, ketoconazole, phenobarbital, phenytoin, quinidine, rifabutin, rifampin, and sildenafil.[33] [34]

Contraindications

Saquinavir and saquinavir mesylate are contraindicated in patients with clinically significant hypersensitivity to the drugs or any components in the formulations. Caution should be used when administering saquinavir or saquinavir mesylate to patients with impaired hepatic function or hemophilia.[35]

Clinical Trials

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

Dosing Information

Mode of Delivery: Oral.[36]

Dosage Form: Saquinavir: Soft gelatin capsules containing 200 mg of saquinavir. Saquinavir Mesylate: Hard gelatin capsules containing 200 mg of saquinavir.

Saquinavir and saquinavir mesylate are not bioequivalent and cannot be used interchangeably. The recommended dose of saquinavir is 1,200 mg (six 200 mg capsules) three times a day or 1,000 mg coadministered with 100 mg of ritonavir two times a day. The recommended dose of saquinavir mesylate is 1,000 mg coadministered with 100 mg of ritonavir two times a day. Both saquinavir and saquinavir mesylate should be taken within 2 hours after a full meal.[37] [38]

Storage: Saquinavir: Store at 2 to 8 C (36 to 46 F) until dispensed. Patients can keep refrigerated capsules until expiration date. Once brought to room temperature (at or above 25 C [77 F]), capsules should be used within 3 months.[39]

Saquinavir Mesylate: Store at 15 to 30 C (59 to 86 F) in tightly closed bottle.[40]

Chemistry

CAS Name: Saquinavir: (S)-N-[(1S)-1-[(1R)-2-[(3S,4aS,8aS)-3-(tert-Butylcarbamoyl)octahydro-2(1H)-isoquinoyl]-1-hydroxy-ethyl]phenethyl]-2-quinaldamidossuccinamide.[41]

Saquinavir Mesylate: (S)-N-[(1S)-1-[(1R)-2-[(3S,4aS,8aS)-3-(tert-Butylcarbamoyl)octahydro-2(1H)-isoquinoyl]-1-hydroxyethyl]phenethyl)-2-quinaldamidossuccinamide monomethanesulfonate (salt).[42]

CAS Number: Saquinavir: 127779-20-8.
Saquinavir Mesylate: 149845-06-7.[43]

Molecular formula: Saquinavir: C₃₈H₅₀N₆O₅.
Saquinavir Mesylate:
C₃₈H₅₀N₆O₅.C₄H₄O₃S.[44]

Saquinavir: C68.04%, H7.51%, N12.53%, O11.92%.
Saquinavir Mesylate: C61.07%, H7.10%, N10.96%, O16.69%, S4.18%

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Chemistry (cont.)

[Calculated][45]

Molecular weight: Saquinavir: 670.86. Saquinavir Mesylate: 766.96.[46]

Physical Description: Saquinavir: White to off-white powder.[47] Saquinavir Mesylate: White to off-white, very fine powder.[48]

Solubility: Saquinavir: Insoluble in water at 25 C.[49] Saquinavir Mesylate: Aqueous solubility of 2.22 mg/ml at 25 C.[50]

Other Names

Ro 31-8959/000 (Saquinavir)[51]

Ro 31-8959/003 (Saquinavir Mesylate)[52]

Saquinavir monomethanesulfonate (Saquinavir Mesylate)[53]

Saquinavir Mesylate[54]

Further Reading

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Manufacturer Information

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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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