



Dear Health Care Provider,

IMPORTANT DRUG INTERACTION WARNING:

DRUG-INDUCED HEPATITIS WITH MARKED TRANSAMINASE ELEVATIONS HAS BEEN OBSERVED IN HEALTHY VOLUNTEERS RECEIVING RIFAMPIN* 600 MG ONCE DAILY IN COMBINATION WITH RITONAVIR 100 MG/SAQUINAVIR 1000 MG TWICE DAILY (RITONAVIR BOOSTED SAQUINAVIR).

In a Phase I, randomized, open-label, multiple-dose clinical pharmacology study in healthy volunteers, 11/28 (39.3%) subjects exposed to rifampin 600 mg once daily taken together with ritonavir 100 mg / saquinavir 1000 mg given twice daily (ritonavir boosted saquinavir) developed significant hepatocellular toxicity during the 28 day study period. Among these subjects, transaminase elevations of up to > 20X upper limit of normal values were noted and one subject was admitted to the hospital with marked transaminase elevations. For all study participants, dosing of all study medications was immediately terminated and the study was discontinued. Following drug discontinuation, liver function tests in all affected subjects are returning to normal, clinical symptoms have abated and no deaths from this clinical study have been reported.

The current package inserts for both INVIRASE® (saquinavir mesylate capsules and tablets) and FORTOVASE® (saquinavir soft gelatin capsules) contraindicate the use of rifampin together with saquinavir. This contraindication is based on a pharmacokinetic interaction between rifampin and saquinavir that results in reduced saquinavir plasma levels. The clinical pharmacology study reported above was undertaken to determine if boosting of saquinavir with ritonavir would overcome the interaction. However, as a result of the high incidence of hepatotoxicity in this study, Roche now advises prescribers that:

Rifampin SHOULD NOT be administered to patients also receiving saquinavir/ritonavir (ritonavir boosted saquinavir) as part of combination antiretroviral therapy (ART) for HIV infection.

Roche is collaborating closely with the U.S. FDA (Food and Drug Administration) on this issue, and appropriate changes to the package insert will be made as soon as possible.

Health care professionals are encouraged to report any unexpected events associated with the use of saquinavir/ritonavir directly to Roche Laboratories at 1-800-526-6367 or to the FDA MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178 or by mail (MED WATCH, 5600 Fishers Lane, Rockville, MD 20852-9787).

Please see important safety information at close of letter.

Yours sincerely

Lars E. Birgerson, MD, PhD
Vice President, Medical Affairs

*Rifampin is known as Rifampicin outside of the U.S.

Indication

INVIRASE in combination with ritonavir and other antiretroviral agents is indicated for the treatment of HIV infection. The twice-daily administration of INVIRASE in combination with ritonavir is supported by safety data from the MaxCMin 1 study and pharmacokinetic data. The efficacy of INVIRASE with ritonavir or FORTOVASE (with or without ritonavir coadministration) has not been compared against the efficacy of antiretroviral regimens currently considered standard of care.

FORTOVASE is indicated for use in combination with other antiretroviral agents for the treatment of HIV infection. This indication is based on studies that showed increased saquinavir concentrations and improved antiviral activity for FORTOVASE 1200 mg tid compared to INVIRASE 600 mg tid. In treatment-naïve and treatment-experienced patients, the efficacy of FORTOVASE (with or without ritonavir coadministration) has not been compared against the efficacy of antiretroviral regimens currently considered standard of care.

Important Safety Information

WARNING:

INVIRASE® (saquinavir mesylate) capsules and tablets and FORTOVASE® (saquinavir) soft gelatin capsules are not bioequivalent and cannot be used interchangeably. INVIRASE may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with FORTOVASE. When using saquinavir as the sole protease inhibitor in an antiviral regimen, FORTOVASE is the recommended formulation.

INVIRASE and FORTOVASE are contraindicated in patients with clinically significant hypersensitivity to saquinavir or to any of the components contained in the capsule. FORTOVASE and INVIRASE/ritonavir should not be administered concurrently with terfenadine, cisapride, astemizole, pimozone, triazolam, midazolam or ergot derivatives. Inhibition of CYP3A4 by saquinavir could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions, such as cardiac arrhythmias or prolonged sedation.

FORTOVASE and INVIRASE, when administered with ritonavir, are contraindicated in patients with severe hepatic impairment. Saquinavir drug pharmacokinetics/pharmacodynamics have not been studied in patients with hepatic impairment and caution should be exercised when prescribing saquinavir in this population. Concomitant use of INVIRASE or FORTOVASE with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including INVIRASE or FORTOVASE, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (eg, atorvastatin). Concomitant use of INVIRASE or FORTOVASE and St. John's wort (*hypericum perforatum*) or products containing St. John's wort is not recommended. Garlic capsules should not be used while taking unboosted saquinavir, due to the risk of decreased saquinavir plasma concentrations. For a complete list of drugs that should not be taken with saquinavir, please see TABLE 5 in the summary of complete product information.

New-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease-inhibitor therapy. No initial dose adjustment is necessary for patients with renal impairment. However, patients with severe renal impairment have not been studied, and caution should be exercised when prescribing saquinavir in this population.

There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors.

Elevated cholesterol and/or triglyceride levels have been observed in some patients taking twice daily saquinavir in combination with ritonavir. Redistribution/accumulation of body fat has been observed in patients receiving ART. A causal relationship between protease-inhibitor therapy and these events has not been established, and the long-term consequences are currently unknown.

Varying degrees of cross-resistance among protease inhibitors have been observed.

In clinical trials with saquinavir (1000 mg) in combination with ritonavir (100 mg) and other antiretrovirals, the grade 2, 3 and 4 adverse events occurring in $\geq 2\%$ of 148 patients (considered at least possibly related to study drug or of unknown relationship): abdominal pain (6.1%), back pain (2%), bronchitis (2.7%), constipation (2%), diarrhea (8.1%), diabetes mellitus/hyperglycemia (2.7%), dry lips/skin (2%), eczema (2%), fatigue (6.1%), fever (3.4%), influenza (2.7%), lipodystrophy (5.4%), nausea (10.8%), pneumonia (5.4%), pruritus (3.4%), rash (3.4%), sinusitis (2.7%) and vomiting (7.4%).

INVIRASE and FORTOVASE are not cures for HIV infection or AIDS. INVIRASE and FORTOVASE do not prevent the transmission of HIV.