Roche

Pharmaceuticals

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Dear Health Care Professional:

Roche Pharmaceuticals would like to inform you that the sale and distribution of Fortovase — the 200-mg soft-gel formulation of saquinavir — will be discontinued by February 15, 2006. Roche has taken this action because the clinical demand for Fortovase has declined significantly; this is not the result of any safety or efficacy issues regarding the product.

Invirase, which is the preferred formulation of saquinavir, will continue to be available in 200-mg and 500-mg formulations. Invirase offers patients key advantages over Fortovase, including:

- Lower pill burden – approved dosing for 500-mg Invirase is 1000 mg twice-daily with 100 mg of ritonavir BID (3 pills twice daily or a total count of 6 pills)
- Improved GI tolerability (less diarrhea and vomiting)[1] – *Department of Health and Human Services (DHHS) Guidelines* state: "The hard gel capsule appears to have much better gastrointestinal tolerance than the soft gel preparation."[2]
- Smaller capsules/tablets – both 200-mg and 500-mg Invirase formulation are smaller in size than Fortovase capsules.
- No need for refrigeration.

At this time, we encourage physicians to refrain from starting Fortovase treatment in their HIV-positive patients. If you are aware of a patient receiving Fortovase, please notify the prescribing health care provider (if someone other than yourself) and the patient regarding this announcement. We encourage you or the prescribing health care provider to discuss appropriate alternative treatment regimens with your patients currently receiving Fortovase.

Enclosed you will find the complete Product Information for Invirase (saquinavir mesylate). If you have any questions regarding the discontinuation of Fortovase, please call 1-800-526-6367.

Please see important safety information at close of letter.

Sincerely,

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

References:

1. Kurowski M, Sternfeld T, Sawyer A, et al. Pharmacokinetic and tolerability profile of twice-daily saquinavir hard gelatin capsules and saquinavir soft gelatin capsules boosted with ritonavir in healthy volunteers. *HIV Med.* 2003;4(2):94-100.

2. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection, United States Department of Health and Human Services; October 29, 2004.

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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-naive 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, pimozide, 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.