Roche

IMPORTANT DRUG WARNING

February 2008

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Dear Healthcare Professional:

Roche would like to advise you of a recent update to the INVIRASE® (saquinavir mesylate capsules and tablets) package insert (Drug Interaction and Warning Sections). The revision to the product label is the result of updated drug interaction information with a number of products, including a new Warning regarding coadministration of INVIRASE with digoxin. All of these changes are detailed below.

Updated drug interaction information has been added on five products in the revision:

1. Digoxin (see Warnings; see also Clinical Pharmacology Table 2, Precautions, Drug Interactions, Table 6) A new Warning has been added. Caution should be exercised when INVIRASE and digoxin are coadministered. Coadministration results in a significant increase in serum concentration of digoxin; therefore, the serum concentration of digoxin should be monitored and the dose of digoxin may need to be reduced.
2. Garlic capsules (see Warnings; see also Precautions, Drug Interactions) No data are available for the coadministration of INVIRASE/ritonavir with garlic capsules. A Warning has been added that the coadministration of garlic capsules and saquinavir is not recommended due to the potential for garlic capsules to induce the metabolism of saquinavir, which may result in subtherapeutic saquinavir concentrations.
3. Methadone (see Precautions, Drug Interactions; see also Clinical pharmacology, Table 2) Methadone levels are decreased and the dosage of methadone may need to be increased when coadministered with INVIRASE/ritonavir.
4. Tipranavir/ritonavir (see Precautions, Drug Interactions) Combining saquinavir with tipranavir/ritonavir is not recommended due to a decrease in saquinavir levels with coadministration.
5. Omeprazole (see Precautions, Drug Interactions) When INVIRASE/ritonavir is coadministered with omeprazole, saquinavir concentrations are increased significantly. If omeprazole or another proton pump inhibitor is taken concomitantly with INVIRASE/ritonavir, caution is advised and monitoring for potential saquinavir toxicities is recommended, particularly gastrointestinal symptoms, increased triglycerides, and deep vein thrombosis.

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In addition, as we have previously communicated to you, Roche has discontinued manufacturing and selling the FORTOVASE® formulation of saquinavir (saquinavir soft gel capsules). This has eliminated the potential for confusion between saquinavir (FORTOVASE) and saquinavir mesylate (INVIRASE); therefore, black Box warning in the label has been removed.

We encourage you to become familiar with these label revisions. If you have any questions or require additional information concerning INVIRASE, please contact the Roche Pharmaceuticals Service Center at 1-800-526-6367. An updated package insert is enclosed for your information. In addition, healthcare professionals can access the revised INVIRASE complete product information at http://www.rocheusa.com/products.

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 has not been compared against the efficacy of antiretroviral regimens currently considered standard of care.

Important Safety Information

- INVIRASE is contraindicated in patients with clinically significant hypersensitivity to saquinavir or to any of the components contained in the capsule or tablet.
- INVIRASE/ritonavir should not be administered concurrently with terfenadine, cisapride, astemizole, pimozide, triazolam, midazolam or ergot derivatives. Inhibition of CYP3A4 by saquinavir and ritonavir could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions, such as cardiac arrhythmias or prolonged sedation.
- INVIRASE when administered with ritonavir is contraindicated in patients with severe hepatic impairment. The use of INVIRASE (in combination with ritonavir) by patients with hepatic impairment has not been studied. In the absence of such studies, caution should be exercised, as increases in saquinavir levels and/or increases in liver enzymes may occur. In patients with underlying hepatitis B or C, cirrhosis, chronic alcoholism and/or other underlying liver abnormalities, there have been reports of worsening liver disease.
- Concomitant use of INVIRASE with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including INVIRASE, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (eg, atorvastatin).
- Concomitant use of INVIRASE 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 saquinavir as the sole protease inhibitor, due to the risk of decreased saquinavir plasma concentrations.
- Ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations; concomitant use of INVIRASE with ritonavir and fluticasone propionate is expected to produce the same effects. Coadministration of fluticasone propionate and INVIRASE/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

- 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 saquinavir in combination with ritonavir. Marked elevation in triglyceride levels is a risk factor for development of pancreatitis.
- Redistribution/accumulation of body fat has been observed in patients receiving antiretroviral therapy. A causal relationship between protease-inhibitor therapy and these events has not been established, and the long-term consequences are currently unknown.
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including INVIRASE.
- Varying degrees of cross-resistance among protease inhibitors have been observed.
- In clinical trials with saquinavir soft gel capsules* (1000 mg) in combination with ritonavir (100 mg), the grade 2, 3 and 4 adverse events occurring in $\geqslant$5% of patients included: lipodystrophy, nausea, vomiting, diarrhea, abdominal pain, fatigue and pneumonia.

INVIRASE is not a cure for HIV infection or AIDS.
INVIRASE does not prevent the transmission of HIV.
Please see accompanying complete product information.

Ritonavir is manufactured by Abbott Laboratories; please see the Norvir® (ritonavir) package insert for additional risk information specifically related to ritonavir.

*The term " saquinavir soft gel capsules" refers to a drug product, no longer available, that was marketed as "FORTOVASE" (saquinavir 200 mg soft gel capsule formulation)

Roche Laboratories will continue to monitor the safety of INVIRASE through established reporting mechanisms and notify regulatory authorities of any serious adverse events for evaluation. We will continue to provide you with the most current product information for INVIRASE moving forward. You can assist us in monitoring the safety of INVIRASE by reporting adverse reactions to us at 1-800-526-6367, by FAX at 1-800-532-3931, or to the FDA at www.fda.gov/medwatch, or by mail to MedWatch, HF-2, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20851.

Sincerely,

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Vice-President, Medical Affairs
Roche Laboratories, Inc.

Encl.

16-004-067-011-0208