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IMPORTANT DRUG WARNING

November 2010

Subject: Important Changes to the INVIRASE® (saquinavir mesylate) Prescribing Information: QT and PR Interval Prolongation and Drug Interactions

Dear Healthcare Professional:

Genentech Inc., a member of the Roche Group, would like to inform you of new and updated important safety information about observed QT and PR interval prolongation and potential drug interactions associated with the use of INVIRASE (saquinavir mesylate) Capsules and Tablets.

Roche conducted a dedicated QT/QTc study in healthy volunteers that demonstrated a dose-dependant prolongation of QT and PR intervals. Based on these findings, new important safety information pertaining to QT prolongation has been included in the INVIRASE prescribing information under the **CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, DRUG INTERACTIONS,** and **CLINICAL PHARMACOLOGY** sections.

New recommendations have been added for the dosing of rifabutin when used in combination with INVIRASE/ritonavir. Additionally, due to the CYP3A4 metabolism of INVIRASE, the **DRUG INTERACTIONS** section of the INVIRASE prescribing information has been revised to include new information on drug interactions with colchicine, bosentan, salmeterol, and PDE5 inhibitors. Furthermore, trazodone, dofetilide, and lidocaine (systemic) are now contraindicated for use with INVIRASE/ritonavir.

This important new safety information in the INVIRASE prescribing information is described below.

REVISIONS TO PRODUCT LABELING REGARDING QT PROLONGATION

CONTRAINDICATIONS

QT interval prolongation and torsades de pointes have been reported rarely with INVIRASE/ritonavir use. Do not use in patients with congenital long QT syndrome, those with refractory hypokalemia or hypomagnesemia, and in combination with drugs that both increase saquinavir plasma concentrations and prolong the QT interval *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.2)]*.

INVIRASE is contraindicated in patients with complete atrioventricular (AV) block without implanted pacemakers, or patients who are at high risk of complete AV block *[see Warnings and Precautions (5.2)]*.

Dofetilide and lidocaine (systemic) have been added to the list of antiarrhythmics that are contraindicated for use with INVIRASE/ritonavir due to the potential for serious and/or life-threatening cardiac arrhythmia.

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Coadministration of the antidepressant trazodone and INVIRASE/ritonavir is contraindicated due to the possibility of increased trazodone concentrations that can result in potentially life-threatening cardiac arrhythmia.

WARNINGS and PRECAUTIONS

PR Interval Prolongation

Saquinavir/ritonavir prolongs the PR interval in a dose-dependent fashion. Cases of second- or third-degree atrioventricular block have been reported rarely. Patients with underlying structural heart disease, pre-existing conduction system abnormalities, cardiomyopathies, and ischemic heart disease may be at increased risk for developing cardiac conduction abnormalities. ECG monitoring is recommended in these patients *[see Warnings and Precautions (5.3)]*.

The impact on the PR interval of coadministration of saquinavir/ritonavir with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin, and atazanavir) has not been evaluated. As a result, coadministration of saquinavir/ritonavir with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A, and clinical monitoring is recommended *[see Clinical Pharmacology (12.2)]*.

QT Interval Prolongation

Saquinavir/ritonavir causes dose-dependent QT prolongation. Torsades de pointes has been reported rarely during postmarketing surveillance. Avoid saquinavir/ritonavir in patients with long QT syndrome. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, hepatic impairment, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating saquinavir/ritonavir and monitor these electrolytes periodically during therapy. Do not use in combination with drugs that both increase saquinavir plasma concentrations and prolong the QT interval (see Tables 1 and 3) *[see Clinical Pharmacology (12.2)]*.

Patients initiating therapy with ritonavir-boosted INVIRASE:

An ECG should be performed prior to initiation of treatment. Patients with a QT interval >450 msec should not receive ritonavir-boosted INVIRASE. For patients with a QT interval <450 msec, an on-treatment ECG is suggested after approximately 3-4 days of therapy; patients with a QT interval >480 msec or prolongation over pretreatment by >20 msec should discontinue ritonavir-boosted INVIRASE.

Patients requiring treatment with medications with the potential to increase the QT interval and concomitant ritonavir-boosted INVIRASE:

Such combinations should only be used where no alternative therapy is available and the potential benefits outweigh the potential risks. An ECG should be performed prior to initiation of the concomitant therapy, and patients with a QT interval >450 msec should not initiate the concomitant therapy. If baseline QT interval is <450 msec, an on-treatment ECG should be performed after 3-4 days of therapy. For patients demonstrating a subsequent increase in QT interval to >480 msec or an increase by >20 msec after commencing concomitant therapy, the physician should use best clinical judgment to discontinue either ritonavir-boosted INVIRASE or the concomitant therapy or both.

A cardiology consult is recommended if drug discontinuation or interruption is being considered on the basis of ECG assessment.

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DRUG INTERACTIONS

Based on the finding of dose-dependent prolongations of QT and PR intervals in healthy volunteers receiving INVIRASE/ritonavir, additive effects on QT and/or PR interval prolongation may occur with certain members of the following drug classes: antiarrhythmics Class IA or Class III, neuroleptics, antidepressive agents, PDE5 inhibitors (when used for pulmonary arterial hypertension), antimicrobials, antihistaminics, and others. This effect might lead to an increased risk of ventricular arrhythmias, notably torsades de pointes. Therefore, concurrent administration of these agents with INVIRASE/ritonavir is contraindicated *[see Contraindications (4)].*

CLINICAL PHARMACOLOGY

Pharmacodynamics

QTcS interval was evaluated in a randomized, placebo, and active (moxifloxacin 400 mg once daily) controlled crossover study in 59 healthy adults, with ECG measurements on Day 3. The maximum mean (95% upper confidence bound) differences in QTcS interval from placebo after baseline-correction were 18.9 (22.0) and 30.2 (33.4) ms for 1000/100 mg twice daily and supratherapeutic 1500/100 mg twice daily of INVIRASE/ritonavir, respectively. There is a delayed effect between QTc interval change and drug concentrations, with the maximum placebo-adjusted baseline-corrected QTcS observed at about 12-20 hours postdose. INVIRASE/ritonavir 1500/100 mg twice daily resulted in a Day 3 mean C_{max} of INVIRASE approximately 1.4-fold higher than the mean C_{max} observed on Day 3 with the approved therapeutic dose in healthy volunteers (within the same study). QTcS in this study was $QT/RR^{0.319}$ for males and $QT/RR^{0.337}$ for females, which are similar to Fridericia's correction ($QTcF=QT/RR^{0.3333}$).

PR and QRS interval prolongations were also noted in subjects receiving INVIRASE/ritonavir in the same study on Day 3. The maximum mean (95% upper confidence bound) differences from placebo in the PR interval after baseline-correction were 28.6 (31.6) and 38.4 (41.4) ms for 1000/100 mg twice daily and supratherapeutic 1500/100 mg twice daily saquinavir/ritonavir, respectively. The maximum mean (95% upper confidence bound) differences from placebo in QRS interval after baseline correction were 2.9 (3.9) and 4.4 (5.3) ms for 1000/100 mg twice daily and supratherapeutic 1500/100 mg twice daily INVIRASE/ritonavir, respectively. In this study using healthy subjects, PR interval prolongation of >200 ms was also observed in 40% and 47% of subjects receiving INVIRASE/ritonavir 1000/100 mg bid and 1500/100 mg bid, respectively, on Day 3. Three (3%) of subjects in the active control moxifloxacin arm and 5% in the placebo arm experienced PR prolongation of >200 ms.

Pharmacokinetics

The pharmacokinetics of INVIRASE/ritonavir 1000/100 mg twice daily have been evaluated in HIV-1-infected patients and healthy subjects. Steady-state saquinavir AUC, C_{max}, and C_{min} in healthy subjects are approximately 50% higher than observed in HIV-1-infected patients.

REVISIONS TO PRODUCT LABELING REGARDING DRUG INTERACTIONS

CONTRAINDICATIONS

Use of sildenafil (Revatio®) is contraindicated when used for the treatment of pulmonary arterial hypertension due to an increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope). A safe and effective dose has not been established when used with INVIRASE/ritonavir.

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Coadministration of the alpha 1-adrenoreceptor antagonist alfuzosin and INVIRASE/ritonavir can potentially lead to increased alfuzosin concentrations, which could result in hypotension.

DRUG INTERACTIONS

The following information has been added to the **DRUG INTERACTIONS** section of the label. Table 3 (**Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or on Predicted Interaction with INVIRASE/ritonavir**) of the package insert.

- Coadministration of rifabutin and INVIRASE/ritonavir may increase rifabutin levels (see Table 3 in the enclosed INVIRASE package label for dosage and monitoring recommendations).
- Coadministration of colchicine and INVIRASE/ritonavir may increase colchicine levels (see Table 3 in the enclosed INVIRASE package label for dosage recommendations). Patients with renal or hepatic impairment should not be given colchicine with INVIRASE/ritonavir.
- Coadministration of bosentan and INVIRASE/ritonavir may increase bosentan levels (see Table 3 in the enclosed package label for dosage recommendations).
- Concurrent administration of salmeterol with INVIRASE/ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
- The coadministration of PDE5 inhibitors and INVIRASE/ritonavir may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism.
    - The use of the PDE5 inhibitor sildenafil (Revatio®) is contraindicated when used for the treatment of pulmonary arterial hypertension (see **CONTRAINDICATIONS**).
    - Dose adjustments are recommended for use of the PDE5 inhibitors sildenafil, vardenafil, and tadalafil for erectile dysfunction and tadalafil for pulmonary arterial hypertension when used with INVIRASE/ritonavir (see Table 3 in the enclosed package label for dosage recommendations).

Important Information About INVIRASE (saquinavir mesylate)

Indication

INVIRASE in combination with ritonavir and other antiretroviral agents is indicated for the treatment of HIV-1 infection in adults (over the age of 16 years).

The following points should be considered when initiating therapy with INVIRASE:

- The twice daily administration of INVIRASE in combination with ritonavir is supported by safety data from the MaxCmin 1 study *[see Adverse Reactions (6.1)]* and pharmacokinetic data *[see Clinical Pharmacology (12.3)]*.
- The efficacy of INVIRASE with ritonavir has not been compared against the efficacy of antiretroviral regimens currently considered the standard of care.
- The number of baseline primary protease inhibitor mutations affects the virologic response to INVIRASE/ritonavir.

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Important Safety Information

Coadministration of INVIRASE/ritonavir is contraindicated with CYP3A substrates for which increased plasma levels may result in serious or life-threatening reactions, e.g., alfuzosin, amiodarone, bepridil, quinidine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, lovastatin, simvastatin, pimozide, sildenafil (Revatio®) for the treatment of pulmonary arterial hypertension, triazolam, orally administered midazolam, and trazodone.

Additionally, INVIRASE is also contraindicated with dofetilide, flecainide, lidocaine (systemic), and propafenone.

Rifampin should not be administered in patients taking INVIRASE/ritonavir due to the risk of severe hepatocellular toxicity.

INVIRASE is contraindicated in patients with clinically significant hypersensitivity (e.g., anaphylactic reaction, Stevens-Johnson syndrome) to saquinavir, saquinavir mesylate, or any of its ingredients including ritonavir.

INVIRASE, when administered with ritonavir, is contraindicated in patients with severe hepatic impairment. 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 (e.g., atorvastatin).

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 pre-existing 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. Cholesterol and triglyceride levels should be monitored prior to initiating INVIRASE/ritonavir therapy and at periodic intervals while on therapy.

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.

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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 in combination with ritonavir (1000/100 mg bid), the Grade 2, 3 and 4 adverse events (including events with unknown relationship to the study drug) occurring in >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.

Should you have any questions regarding the use of INVIRASE, please refer to the INVIRASE Product Information at **www.gene.com**, or call our Medical Information/Communications Department at 1-800-821-8590.

Healthcare professionals should report any serious adverse events suspected to be associated with the use of INVIRASE to Genentech at 1-888-835-2555. Alternatively, this information may be reported to the FDA's MedWatch reporting system online (**https://www.accessdata.fda.gov/scripts/medwatch/**), by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), or by mail using the MedWatch Form FDA 3500 (FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787).

Sincerely,

Hal Barron, MD
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Chief Medical Officer