

**IMPORTANT  
PRESCRIBING  
INFORMATION**

February 2013

**Subject: Important Changes to the INVIRASE® (saquinavir mesylate) Capsules and Tablets  
Prescribing Information: Pediatric Use and Potential for QT and PR Interval Prolongation**

Dear Healthcare Professional:

INVIRASE (saquinavir mesylate) is an inhibitor of HIV-1 protease and is indicated for use in combination with ritonavir and other antiretroviral agents for the treatment of HIV-1 infection in adults (over the age of 16 years). Genentech Inc., a member of the Roche Group, would like to inform you of new and updated important prescribing information as a result of pediatric pharmacokinetic data and observed QT and PR interval prolongation in adults associated with the use of INVIRASE (saquinavir mesylate) Capsules and Tablets. As a result of the review of available data, the INVIRASE Prescribing Information has been updated to include a number of changes described below, including an update to Section 8.4 USE IN SPECIFIC POPULATIONS: Pediatric Use, to inform prescribers that pediatric dose recommendations that are both reliably effective and below the threshold of concern with respect to QT and PR prolongation could not be determined.

## BACKGROUND

Roche conducted pediatric trials with INVIRASE boosted with ritonavir. Although no cases of QT prolongation were observed, saquinavir steady-state exposures observed in pediatric patients were substantially higher than historical data in adults where both dose- and exposure- QTc and PR prolongation was shown. Pediatric dose recommendations that are both reliably effective and below the threshold of concern with respect to QT and PR prolongation could therefore not be determined because a lower dose is likely to reduce antiviral efficacy, based on modeling and simulation work conducted by the FDA and there are no clinical efficacy data available at INVIRASE doses less than 50 mg per kg body weight in pediatric subjects.

Updated pediatric information has been included in the INVIRASE prescribing information under **Sections 8.4 and 12.3**. This important new information in the INVIRASE prescribing information is described below.

## USE IN SPECIFIC POPULATIONS (Section 8.4 Pediatric Use)

Section 8.4 of the revised prescribing information includes the results of the pediatric clinical trials conducted at INVIRASE dose of 50 mg per kg body weight. Modeling and simulation assessment

of pharmacokinetic/pharmacodynamic relationships in pediatric subjects suggest that reducing the INVIRASE dose to minimize risk of QT prolongation is likely to reduce antiviral efficacy. In addition, since no clinical efficacy data are available at INVIRASE doses less than 50 mg per kg in pediatric subjects, pediatric dose recommendations that are both reliably effective and below thresholds of concern with respect to QT and PR prolongation could not be determined.

### **CLINICAL PHARMACOLOGY (Section 12.3)**

Section 12.3 of the revised prescribing information includes the results of a pediatric pharmacokinetic trial. The observed steady-state saquinavir exposures in pediatric subjects were substantially higher than historical adult exposure and the day 3 exposures may be within the range of adult exposure associated with QT and PR prolongation.

Other sections of the INVIRASE prescribing information and medication guide have also been updated to improve clarity to the healthcare professional and patient.

**INVIRASE is not a cure for HIV-1 infection or AIDS.**

**INVIRASE does not prevent the transmission of HIV-1.**

For additional information on INVIRASE's indication, important safety information and important prescribing information, please see the INVIRASE Prescribing Information enclosed with this letter or visit [www.gene.com](http://www.gene.com).

If you have any questions or require additional information regarding the use of INVIRASE, please contact our Medical Communication/Information Department at 1-800-821-8590 from 5:30 AM to 4:00 PM Pacific Time, Monday through Friday.

As always, healthcare professionals are encouraged to report side effects associated with the use of INVIRASE to Genentech at 1-888-835-2555. Alternatively, such information may be reported to FDA's MedWatch Safety Information and Adverse Event Reporting Program, either online at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), by telephone (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 Fisher Lane, Rockville, MD 20852-9787).

Sincerely,



Hal Barron, MD  
Executive Vice President  
Head, Global Development  
Chief Medical Officer

## SUMMARY OF IMPORTANT PEDIATRIC INFORMATION ABOUT INVIRASE (saquinavir)

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dose

- Pediatric dose recommendations that are both reliably effective and below thresholds of concern for QT and PR interval prolongation could not be determined.

#### 6.2 Clinical Trial Experience in Pediatric Subjects

Limited safety data are available from two pediatric clinical trials of saquinavir hard gel capsules (approximately 50 mg per kg twice daily) used in combination with either low dose ritonavir or lopinavir/ritonavir. These trials enrolled pediatric subjects aged 4 months to 16 years old. In the HIVNAT 017 study (INVIRASE + lopinavir/ritonavir), adverse events were reported in 90% of the 50 subjects enrolled. The most commonly reported adverse events considered related to study treatment were diarrhea (18%) and vomiting (10%). In the NV20911 study (INVIRASE + ritonavir), 4 subjects (22% of 18 enrolled) experienced adverse events that were considered related to INVIRASE + ritonavir. These events (n) were vomiting (3), abdominal pain (1) and diarrhea (1). All reported adverse events were mild or moderate in intensity. The adverse reaction profile of INVIRASE in the pediatric trials is similar to that observed in adult trials.

#### 8.4 Pediatric Use

The safety and activity of saquinavir have been evaluated in 68 pediatric subjects 4 months to less than 16 years of age treated with INVIRASE boosted with either ritonavir or with lopinavir/ritonavir in two clinical trials. Data from the NV20911 trial demonstrated that saquinavir boosted with low dose ritonavir provided plasma levels of saquinavir that were significantly higher than those historically observed in adults at the approved dose [see *Clinical Pharmacology* (12.3)]. The HIVNAT 017 trial provided long term 96-week activity and safety data; however, pharmacokinetic data from this study could not be validated.

HIVNAT 017 was an open-label, single-arm trial at two centers in Thailand that evaluated the use of INVIRASE (50 mg per kg twice daily given as 200 mg capsules) with lopinavir/ritonavir (230/57.5 mg/m<sup>2</sup> twice daily) for 96 weeks. Fifty subjects 4 years to less than 16 years of age were enrolled. In this trial population, treatment resulted in HIV-1 RNA <400 copies/mL at week 96 in 78% of subjects (HIV-1 RNA <50 copies per mL at week 96 in 66%). Mean CD4 lymphocyte percentage increased from 8% at screening to 22% at week 96.

NV20911 was an open label, multinational trial that evaluated the pharmacokinetics, safety, and activity of INVIRASE (50 mg per kg twice daily as 200 mg capsules, up to the adult dose of 1000 mg twice daily) and ritonavir oral solution plus  $\geq 2$  background ARVs. Eighteen subjects 4 months to less than 6 years of age were enrolled. Treatment with INVIRASE/ritonavir resulted in HIV-1 RNA <400 copies per mL at week 48 in 72% of subjects (HIV-1 RNA <50 copies per mL at week 48 in 61%). The percentage of subjects with HIV-1 RNA <50 copies per mL at week 48 was 61%. Mean CD4 lymphocyte percentage increased from 29% at screening to 34% at week 48.

Steady state saquinavir exposures observed in pediatric trials were substantially higher than historical data in adults where dose- and exposure-dependent QTc and PR prolongation were observed [see *Warnings and Precautions* (5.3), *Clinical Pharmacology* (12.2, 12.3)]. Although electrocardiogram abnormalities were not reported in these pediatric trials, the trials were small and not designed to evaluate QT or PR intervals. Modeling and simulation assessment of pharmacokinetic/ pharmacodynamic relationships in pediatric subjects suggest that reducing the INVIRASE dose to minimize risk of QT prolongation is likely to reduce antiviral efficacy. In addition, no clinical efficacy data are available at INVIRASE doses less than 50 mg per kg in pediatric subjects. Therefore, pediatric dose recommendations that are both reliably effective and below thresholds of concern with respect to QT and PR prolongation could not be determined.

## 12.3 Pharmacokinetics

### Pediatric Subjects

Steady-state pharmacokinetic information is available from HIV-1 infected pediatric subjects from study NV20911. In this study, 5 subjects less than 2 years of age and 13 subjects between 2 and less than 6 years of age received 50 mg per kg saquinavir twice daily (not to exceed 1000 mg twice daily) boosted with ritonavir at 3 mg/kg for subjects with body weight ranging from 5 to <15 kg or 2.5 mg per kg for subjects with body weight ranging from 15 to 40 kg (not to exceed 100 mg twice daily). For subjects unable to swallow the INVIRASE capsules, the contents of INVIRASE 200 mg capsules were mixed with sugar syrup, or sorbitol syrup (for subjects with Type I diabetes or glucose intolerance), jam, or baby formula. The mean steady state saquinavir PK parameters for pediatric subjects 2 to less than 6 years of age were:  $AUC_{0-12h}$  37269  $\pm$  18232 ng·h/mL;  $C_{trough}$  1811  $\pm$  998 ng/mL;  $C_{max}$  5464  $\pm$  2782 ng/mL, and day 3 exposures may be within the range of exposure associated with QT and PR prolongation [see *Clinical Pharmacology: Pharmacodynamics (12.2)*]. The subject number was too low and the pharmacokinetic data too variable in the subjects less than 2 years to establish an appropriate dosing recommendation for this age group. Pharmacokinetic data for subjects ages 6 to 16 years were not available for comparisons with observations from NV20911 [see *Use in Specific Populations: Pediatric Use (8.4)*] as the data from HIVNAT 017 could not be validated.