



Dublin, 15 July 2010

Association of Invirase (saquinavir) with Arrhythmogenic Risk due to Prolongation of the QT and PR Intervals

Dear Healthcare Professional

Roche Products (Ireland) Limited ("Roche"), in coordination with the European Medicines Agency and the Irish Medicines Board, would like to notify you of the risk of QT prolongation associated with Invirase (saquinavir), and the subsequent important safety-related addition to the Summary of Product Characteristics (SmPC) for Invirase.

Summary

Healthcare professionals should note that:

- **Invirase is contraindicated in patients with congenital or acquired QT prolongation or other predisposing conditions for cardiac arrhythmias, including concurrent therapy with other drugs that prolong the QT and/or PR interval.**
- **The combination of Invirase with drugs known to increase the plasma level of saquinavir is not recommended and should be avoided when alternative treatment options are available.**
- **Invirase should be discontinued in case of arrhythmias, QT or PR prolongation.**

Recommendations:

- The recommended dose of Invirase should not be exceeded since the magnitude of QT and PR prolongation may increase with increased plasma levels of saquinavir.
- Baseline and follow-up electrocardiogram recording should be considered (e.g. in patients taking concomitant medication known to increase the plasma level of saquinavir).
- Patients should be warned of the arrhythmogenic risk and told to report any signs of cardiac arrhythmias (e.g. chest palpitations, syncope, presyncope) to their physician.

For detailed information on the administration and use of Invirase, please refer to the attached Summary of Product Characteristics.

Further information on the safety concern

Invirase is indicated for the treatment of HIV-1 infected adult patients. Invirase should only be given in combination with ritonavir and other antiretroviral medicinal products.

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The effects of therapeutic (1000/100 mg twice daily) and supra-therapeutic (1500/100 mg twice daily) doses of Invirase/ritonavir on the QT interval were evaluated in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg) study in healthy male and female volunteers:

- In the therapeutic and the supra-therapeutic arm 11% and 18% of subjects, respectively, had a QTcS* between 450 and 480 msec. In the moxifloxacin active control group, none of the subjects had a QTcS over 450 msec. No study subjects experienced QT prolongation > 500 msec or torsade de pointes in the study.
- PR interval prolongation of > 200 msec was observed in 40% and 47% of subjects receiving Invirase/ritonavir 1000/100 mg twice daily and 1500/100 mg twice daily, respectively, and in 3% and 5% of subjects in the moxifloxacin active control group and the placebo arm, respectively.
- Events of syncope/presyncope occurred at a higher than expected rate and were seen more frequently under treatment with Invirase/ritonavir.

Call for reporting

Healthcare professionals are reminded to continue to report serious adverse events suspected to be associated with the use of Invirase to the Roche Drug Surveillance Centre (either by mail, telephone [(01) 4690700], fax [(01) 4690793] or e-mail [Ireland.drug_surveillance_centre@roche.com]). Alternatively, adverse events may be reported to the pharmacovigilance section of the IMB in the usual manner.

Communication information

The Patient Information Leaflet will be revised in accordance with the updated Summary of Product Characteristics.

Should you have any questions or require additional information regarding the use of Invirase, please contact Medical Information at Roche (either by mail, telephone [(01) 4690700], fax [(01) 4690791] or e-mail [Ireland.druginfo@roche.com]).

Yours sincerely ,



Dr. Zirke Wiid MB ChB

Medical Advisor

Annexes:

Text of the revised Invirase Summary of Product Characteristics

* study-specific heart-rate corrected QT interval based on individual subject data (results were similar when Fredericia's or Bazett's correction formulae were used)