19th May 2014

Subject: **Direct Healthcare Professional Communication**

IMPORTANT SAFETY UPDATE OF PRESCRIBING INFORMATION FOR INVIRASE® (Saquinavir)

Dear Healthcare Provider,

F. Hoffmann-La Roche Ltd (hereafter referred to as Roche) would like to inform you about new recommendations for ECG monitoring of treatment-naïve patients receiving Invirase® (saquinavir). The new recommendations have been included in the summary of product characteristics (SmPC) for Invirase®.

Summary

- **Dose-dependent prolongations of QT and PR intervals have been previously observed in healthy volunteers receiving ritonavir-boosted Invirase.**
- **Treatment-naïve HIV-1 infected patients should continue to be started on a reduced dose of 500mg of Invirase BID for the first seven days, before increasing to the standard dose of 1000mg BID (always in conjunction with ritonavir 100mg BID and appropriate anti-retroviral agents).**
- **In addition to baseline, the ECG should now be performed for treatment-naïve patients after approximately 10 days of treatment, at the day of peaked mean maximal QTcF prolongation.**
- **For patients with ongoing Invirase/ritonavir treatment (1000/100 mg BID), the recommendations for the ECG monitoring remain unchanged (see below the section "Further Recommendation").**

This letter is being sent with the agreement of the European Medicines Agency (EMA) and the Medicines Authority.

Further information on the background of the new recommendations

This letter highlights the need for and the recommended timing of ECG-monitoring after starting therapy with saquinavir/ritonavir.

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High saquinavir plasma levels are associated with a risk of potentially severe QT-prolongation. It has been shown that saquinavir exposure is higher than was expected during the first days of therapy with saquinavir/ritonavir at a dose of 1000/100 mg twice daily. Subsequently, saquinavir levels decrease (as a consequence of gradual CYP-induction by ritonavir). It was therefore decided that saquinavir/ritonavir should be given at a dose of 500/100 mg twice daily during the first week of therapy, as described below.

Previously, an ECG was recommended 3-4 days into Invirase therapy, based on the time of maximum saquinavir-induced QT prolongation, for patients initiating therapy at the full dose regimen of 1000/100 mg BID.

A new study has shown, however, that the maximal QT-prolongation with the newly recommended regimen occurs around day 10. Therefore the recommended timing of ECG follow up has been changed.

This open-label 2-week study in 23 HIV-1 infected, treatment-naïve patients initiating Invirase/ritonavir therapy investigated the effect on QTc interval, PK, viral load and safety of the modified dosing regimen (Invirase/ritonavir 500 /100 mg twice daily in combination with 2 NRTIs for the first 7 days of treatment followed by Invirase/ritonavir 1000 /100 mg twice daily in combination with 2 NRTIs in the subsequent 7 days) . The results from this study demonstrated that the mean maximal change from dense pre-dose baseline in QTcF (ΔQTcFdense) peaked on study day 10 (Table 1). Mean peak exposure to saquinavir (C_{max}) was also greatest on day 10.

Table 1 Summary of electrocardiogram and PK parameters following administration of the modified Invirase/ritonavir regimen in treatment-naïve HIV-1 infected patients initiating treatment with Invirase/ritonavir

Parameter	**Day 3 500/100 mg (n=22)**	**Day 4 500/100 mg (n=21)**	**Day 7 500/100 mg (n=21)**	**Day 10 1000/100 mg (n=21)**	**Day 14 1000/100 mg (n=21)**
Mean Maximal $\Delta QTcF_{dense}$ ms (SD)	3.26 ± 7.01	0.52 ± 9.25	7.13 ± 7.36	**11.97 ± 11.55**	7.48 ± 8.46
Patients with maximal $\Delta QTcF_{dense} \geq 30$ ms (%)	0	0	0	**2/21 (9%)**	0
Mean C_{max} (ng/ml) (CV%)	4030 (29.1)	2960 (40.2)	1960 (53.3)	**5300 (36.0)**	4860 (46.8)

Further recommendation

Indication remains unchanged:
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.

New Safety information added in section "Warnings and Precautions" of the prescribing information:
Clinical Management
Consideration should be given for performing baseline and follow-up electrocardiograms after initiation of treatment, e.g. in patients taking concomitant medication known to increase the exposure of saquinavir (see section 4.5). If signs or symptoms suggesting cardiac arrhythmia occur, continuous monitoring of ECG should be performed. Ritonavir-boosted Invirase should be discontinued if arrhythmias are demonstrated, or if prolongation occurs in the QT or PR interval.

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Patients initiating therapy with ritonavir-boosted Invirase:

- *An ECG should be performed on all patients prior to initiation of treatment: patients with a QT interval > 450 msec should not use ritonavir-boosted Invirase. For patients with a QT interval < 450 msec, an on-treatment ECG is recommended.*
- *For treatment-naïve patients initiating treatment with Invirase/ritonavir 500/100 mg two times daily for the first 7 days of treatment followed by Invirase 1000 mg two times daily with ritonavir 100 mg two times daily after 7 days and with a baseline QT interval < 450 msec, an on-treatment ECG is suggested after approximately 10 days of therapy.*
- ~~*For patients with a baseline QT interval < 450 msec, an on-treatment ECG is suggested after approximately 3 to 4 days of therapy.*~~
- *Patients demonstrating a subsequent increase in QT-interval to > 480 msec or prolongation over pre-treatment by > 20 msec should discontinue ritonavir-boosted Invirase.*

Further Information

If you have any questions or require additional information regarding the use of Invirase, please contact Roche Medical Information by phone on +44(0)800 328 1629 or via e-mail medinfo.uk@roche.com.

Reporting Adverse Events

Health care professionals should report any serious adverse events suspected to be associated with the use of Invirase according to national reporting requirements. You can assist in monitoring the safety of Invirase by reporting suspected adverse events associated with the use of Invirase to the Medicines Authority; ADR report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and sent to postlicensing.medicinesauthority@gov.mt or sent to ADR reporting 203, level 3, Rue d'Argens Gzira/GZR 1368. In addition adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44(0)1707 367554.

Yours sincerely,

Dr Daniel Thurley MA MB BChir MRCP FFPM

Medical Director – UK

Updated Prescribing Information for Invirase® (Saquinavir) is available at www.medicines.org.uk

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