27th October 2010

Circular No. P14/2010

Dear Healthcare Professional,

Re: The European Medicines Agency concludes that benefit-risk balance of Invirase remains positive

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has reviewed all available data on Invirase (saquinavir) and the potential risk of arrhythmia and concluded that the benefit of the medicine continues to outweigh its risks. However, the Committee has recommended that treatment-naïve patients should take a reduced dose of Invirase during the first week of treatment, as a precautionary measure.

Invirase is authorised in all EU countries including Malta, and is also being marketed locally. Invirase (boosted with ritonavir) in combination with other antiretroviral medicines is indicated for the treatment of HIV-infected adult patients.

The Committee started this review following the results of a study conducted by the marketing authorisation holder of Invirase, Roche Registration Ltd, showing that Invirase prolonged the QT and PR interval in healthy volunteers. In June 2010, the CHMP recommended restrictions on the use of Invirase, including a contra-indication in patients at high risk of arrhythmia and in patients using other medicines that may cause QT or PR prolongation. Warnings for patients at moderate risk of arrhythmia, together with recommendations for electrocardiogram (ECG) monitoring, were also agreed. However, the CHMP still had concerns about the magnitude of the observed QT and PR interval changes and the potential clinical impact on the safe and effective use of the medicine and carried out a full review of the benefits and risks of Invirase.

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The Committee reviewed all available clinical and preclinical data on the cardiovascular safety of Invirase and discussed any additional measures that might be necessary to ensure its safe and effective use. The CHMP noted that the effectiveness of Invirase has been demonstrated in several clinical studies. Although the dedicated study in healthy volunteers did show QT and PR interval prolongation, this signal was not confirmed in post-marketing safety reports on Invirase with a worldwide exposure of approximately 1 million patient-years.

The risk of QT and PR interval prolongation is dose dependent, and is expected to be highest in treatment-naïve patients starting Invirase therapy. To minimise the risk of arrhythmia, a reduced dose for these patients in the first week of treatment is recommended. Also, Roche has been asked to investigate the potential risk of arrhythmia in treatment-naïve patients receiving the reduced dose of Invirase in combination with other antiretroviral medicines in a new study.

The Medicines Authority has participated in the discussions held at the EMA and is in agreement with the full **press release** issued by the EMA, attached here for your perusal. A **question-and-answer** document with more information about the outcome of this assessment is also available.

Healthcare professionals are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

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