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Questions and answers on the review of Invirase (saquinavir)

Outcome of a procedure under Article 20 of Regulation (EC) No 726/2004

The European Medicines Agency has completed a review of Invirase at the request of the European Commission, following concerns over the cardiovascular safety of the medicine. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of Invirase continue to outweigh its risks, but that a number of changes need to be introduced into the prescribing information to minimise the potential risk of heart problems.

What is Invirase?

Invirase is used to treat adults infected with human immunodeficiency virus type 1 (HIV-1), a virus that causes acquired immune deficiency syndrome (AIDS). Invirase is always used in combination with ritonavir (another anti-HIV medicine) and other anti-HIV medicines.

The active substance in Invirase, saquinavir, is a protease inhibitor. It blocks an enzyme called protease, which is involved in the reproduction of HIV. When the enzyme is blocked, the virus does not reproduce normally, slowing down the spread of infection. Invirase, taken in combination with other antiviral medicines, reduces the amount of HIV in the blood and keeps it at a low level. Invirase does not cure HIV infection or AIDS, but it may delay the damage to the immune system and the development of infections and diseases associated with AIDS.

Invirase has been authorised in the EU since 4 October 1996 and is marketed in all Member States except for the Czech Republic, Slovenia and Estonia. It is also marketed in Norway, Iceland and Liechtenstein.

Why was Invirase reviewed?

In June 2010, the CHMP finalised the review of studies carried out by the company that makes Invirase, showing that this medicine in healthy volunteers prolonged the QT and PR intervals as seen in the electrocardiogram (ECG). These indicate alterations of the electrical activity of the heart. As a result, the Committee concluded that the product information for Invirase should be amended to restrict the use of the medicine. In particular, the Committee concluded that Invirase must not be used in patients at high risk of arrhythmia (unstable heartbeat) or with medicines that may cause QT or PR

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prolongation. Warnings for patients at moderate risk and recommendations to perform ECG monitoring were also included.

However, despite the restrictions, CHMP still had concerns about the changes of the electrical activity of the heart observed, and their impact on the safe use of the medicine. Consequently, the European Commission asked the CHMP to carry out a full review of the benefit-risk balance of Invirase, and to issue an opinion on whether, on the basis of the findings, its marketing authorisation should be maintained, varied, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The Committee looked at all the available data from preclinical studies and clinical trials with Invirase that were considered relevant for the assessment of the cardiovascular safety of the medicine. The CHMP also reviewed all the side effects reported since the initial marketing authorisation of Invirase.

What are the conclusions of the CHMP?

The CHMP noted that the effectiveness of Invirase has been demonstrated in several clinical studies, and that most treatment guidelines recommend the medicine as an alternative for patients who cannot tolerate other treatments. The Committee also noticed that, although the dedicated study in healthy volunteers did show QT and PR prolongation, there have been no relevant reports of heart problems associated with the use of Invirase since the medicine was first authorised in 1996.

The risk of QT and PR prolongation has been shown to be dose dependent, and is expected to be higher in patients who have not been treated with any anti-HIV medicines before. Therefore, to minimise the risk of heart problems, the CHMP recommended a reduced dose for these patients in the first week of treatment. The Committee also requested the company to carry out a study looking at the effects of the medicine in patients who are starting treatment at a reduced dose.

Overall, based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of Invirase continue to outweigh its risks, and therefore recommended that the marketing authorisation be maintained. However, the CHMP recommended changes to the prescribing information to minimise the potential cardiovascular risk.

The full changes made to the information to doctors and patients are detailed here.

What are the recommendations for patients and prescribers?

- Patients taking Invirase should continue to do so, and should contact their doctor if they have any questions about their treatment.
- Doctors are reminded that Invirase should only be used in accordance with the updated prescribing information. When prescribing Invirase to patients who have not been treated before, a reduced dose should be used for the first week to minimise the potential risk of QT prolongation.

A European Commission decision on this opinion will be issued in due course.

The current European public assessment report for Invirase can be found on the Agency's website ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.