European Medicines Agency

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Questions and answers on the follow-up to the contamination of Viracept (*nelfinavir*) with ethyl mesilate

In 2007, batches of Viracept, a medicine used in HIV patients, were found to be contaminated with a harmful substance called ethyl mesilate. The European Medicines Agency (EMEA's) and its Committee for Medicinal Products for Human Use (CHMP) made sure that the manufacturing problems that lead to the contamination were addressed. In addition, the CHMP requested that Roche, the company that makes Viracept, investigates the toxicity of ethyl mesilate in more detail, particularly the possibility that it could lead to the development of cancer.

These investigations have now been completed and the CHMP has concluded that the patients who received contaminated Viracept are not at an increased risk of developing cancer. The Committee has therefore decided that there is no need to follow these patients up in 'registries', as was previously planned.

What is Viracept?
Viracept is an antiviral medicine, which contains nelfinavir (as nelfinavir mesilate) as its active substance. It is available as tablets and as a powder to be made up into an oral suspension. It is used in combination with other antiviral medicines to treat adults, adolescents and children over three years of age who are infected with human immunodeficiency virus (HIV-1), the virus that causes acquired immune deficiency syndrome (AIDS).

What has been happening with Viracept?[1]
During the last few months of 2006 and at the beginning of 2007, some batches of nelfinavir mesilate became contaminated with high levels of ethyl mesilate during manufacture. Ethyl mesilate is a known genotoxic substance (harmful to DNA, the genetic material in cells). The contaminated batches were used to make Viracept tablets that were distributed around the world to a total of 29 countries including six within the European Union (France, Germany, Italy, Portugal, Spain and the United Kingdom). This resulted in an estimated 20,000 to 25,000 patients being exposed to ethyl mesilate. In the worst cases, patients may have taken highly contaminated Viracept for up to three months.

The European Commission was informed by Roche of the contamination in June 2007, as the company started recalling Viracept from the market. The Commission had concerns over the exposure of patients to ethyl mesilate and it decided to suspend the marketing authorisation. Over the following months, Roche addressed the manufacturing problem that led to the contamination, the marketing authorisation was re-instated and the company is now permitted to produce Viracept again. Supply of Viracept has resumed in Belgium, France, Germany, Italy, the Netherlands, Portugal, Spain and the United Kingdom.

When the contamination was discovered, the CHMP noted that very little was known about the toxicity of ethyl mesilate. In particular, it was not possible to determine whether there was a level for ethyl mesilate in medicines below which harm would not occur. Therefore, the Committee recommended that the patients who had been exposed to the contaminated medicine should be followed up. This was to be done by setting up registries of patients who had been exposed to the

[1] The EMEA has published a number of question-and-answer documents on the issues with Viracept. These can be found on the EMEA website as published on 6 June 2007, 21 June 2007, 26 July 2007 and 20 September 2007.

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highly contaminated batches of the medicine, children who had taken the medicine, and children born to mothers who had taken Viracept during pregnancy.

What information is now available?
Roche has now completed its in-depth studies into the effects of ethyl mesilate as requested by the EMEA. These animal studies have shown that there is a threshold level below which ethyl mesilate does not have a harmful effect on the DNA (25 mg per kilogram and per day in the mouse).
Company experts have used special models that allow results from animal studies to be 'extrapolated' to humans. This has allowed them to calculate the threshold value for patients who have been exposed to ethyl mesilate (2 mg per kilogram and per day). This level has been endorsed by the experts from the CHMP's Safety Working Party.
Patients who took Viracept tablets at the highest level of contamination were exposed to levels of ethyl mesilate of about 0.05 mg per kilogram per day. As these levels are below the threshold, the CHMP concluded that patients exposed to contaminated Viracept are not at an increased risk of developing cancer, and that they do not need to be followed up as was previously planned. The CHMP has therefore concluded that the registries do not need to be set up.

What are the consequences for patients?
- Patients who have taken Viracept during the time when contaminated stock was being distributed can be reassured that they are not at an increased risk of developing cancer than HIV patients not exposed to the contaminant.
- No increased risk is expected either for children who took Viracept, or for children born to mothers who took Viracept during pregnancy.