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QUESTIONS AND ANSWERS ON THE CHMP RECOMMENDATION TO ALLOW VIRACEPT BACK ONTO THE MARKET

In August 2007, the marketing authorisation for Viracept was suspended because of contamination of the medicine due to a problem in its manufacture. Having looked at the measures put in place by the manufacturer, Roche, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) has now made a recommendation to the European Commission (EC) that the suspension be lifted and Viracept be allowed back onto the market.

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?

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, a known genotoxic substance (harmful to DNA, the genetic material in cells). The contaminated batches were used to make Viracept for all markets, except those in Canada, Japan and the United States. This led to Viracept contaminated with high levels of ethyl mesilate reaching the market from March 2007. The contamination was first noticed by some patients because the tablets had a strange smell.

Because ethyl mesilate is a harmful substance, Viracept was removed from the market (recalled) at the beginning of June, and doctors had to switch their patients to an alternative treatment. Since the recall of the medicine, Roche has begun to set up registries in order to follow up patients who were exposed to the highly contaminated batches of the medicine. The company will also follow up children who have taken the medicine, and children born to mothers who took Viracept during pregnancy. Roche also temporarily stopped the production of nelfinavir mesilate.

The company was asked to look in depth into the reason for the contamination, in order to find out why it happened, and to ensure that appropriate measures could be put in place to make sure that it would not happen again. While this was underway, the EC, on the recommendation of the CHMP and the EMA, decided to suspend Viracept's marketing authorisation. This suspension came into force on 6 August 2007.

Why is the suspension being lifted?

At its September 2007 meeting, the CHMP assessed the answers given by Roche to the Committee's questions, and looked at the report from the inspectors who visited the factory in Switzerland where nelfinavir mesilate is made. The Committee was satisfied by the actions taken by the company, and by the outcome of the inspection, which confirmed that the necessary measures had been put in place.

The CHMP noted that:

- Roche has identified the source of the contamination. The ethyl mesilate contaminant was found to have formed in a tank at the factory, which held a chemical used in the manufacture of Viracept called methane sulfonic acid. Before being filled, this tank had been cleaned using ethanol, but had not been dried out properly. This triggered a chemical reaction in the holding

tank between the remaining ethanol and the methane sulfonic acid. This resulted in the formation of ethyl mesilate at very high levels, which subsequently ended up in some batches of the finished medicine. Roche has now changed the manufacturing process so that a holding tank is no longer used.

- Roche has also introduced checks to ensure that any formation of ethyl mesilate during the manufacture of Viracept can be detected as early as possible. Strict, acceptable maximum limits for the active substance and for the finished medicine have been set. These limits have been established in accordance with current guidance on genotoxic substances¹.

Therefore, the CHMP has recommended that the suspension of marketing authorisation for Viracept be lifted: the manufacturer has satisfied the Committee that it can now resume manufacturing of nelfinavir mesilate using a process where the possibility of ethyl mesilate forming is kept to a bare minimum. The Committee was re-assured that all Viracept manufactured using nelfinavir mesilate produced with this new process would meet the required quality standards.

While the suspension was in force, Roche started to put in place other key measures requested by the CHMP. In particular, the company has started to investigate the harmful effects of ethyl mesilate in more depth using animal studies. It will also continue to monitor the patients who received the contaminated medicine to ensure that they are followed up appropriately. The CHMP will make sure that these measures are carried out and completed in a satisfactory manner. The EMEA will keep the public updated as relevant information becomes available.

What will happen next?

The EC will look at the recommendation of the CHMP and EMEA, and will issue a Decision in due course. Once a positive Decision has been issued, Roche will be able to resume supply of Viracept. As the production of nelfinavir mesilate and of Viracept had stopped completely, it may take some time before the medicine is available again for doctors to prescribe. The earliest this can be expected is the beginning of 2008.

The EMEA will make more information public once the EC has confirmed that the suspension can be lifted. In particular, the Agency will publish the report of the assessment carried out by the CHMP in order to reach its opinion on the lifting of the suspension. This will be published as part of the update of the European Public Assessment Report (EPAR)² for Viracept on the EMEA website.

¹ 'Guideline on the limits of genotoxic impurities' published on the EMEA website at the following address:
<http://www.emea.europa.eu/pdfs/human/swp/519902en.pdf>.

² The full EPAR for Viracept is available at the following address:
<http://www.emea.europa.eu/humandocs/Humans/EPAR/viracept/viracept.htm>.