SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE SUSPENSION OF THE MARKETING AUTHORISATION OF VIRACEPT PRESENTED BY THE EMEA

On the evening of 5 June 2007 the European Medicines Agency (EMEA) was made aware by Roche Registration Limited (the Marketing Authorisation Holder, MAH) of the contamination of Viracept (nelfinavir) with a genotoxic substance. As a consequence, the product was recalled from the European Union markets, with immediate effect. All packs of Viracept currently available on the market were affected, including packs that patients may have had at home. A Direct Healthcare Professional Communication (DHPC) was released by the MAH on Thursday, 7 June 2007, to inform prescribers about the incident and the need to switch patients on Viracept to other alternative antiretroviral therapies. The choice of alternatives was left to the prescriber. The EMEA issued a Press Release and Q&A document on the same day.

The MAH had identified the presence of the contaminant ethyl mesilate (also known as methane sulfonic acid ethylester or ethylmethane sulfonate, EMS) in some batches of nelfinavir mesilate (the active substance). EMS is a known genotoxic, carcinogenic and teratogenic substance in animals. The level of risk to patients resulting from this contamination is currently not known and therefore needs to be further evaluated.

In order to characterise the toxicological risk associated with EMS, an ad-hoc expert group meeting of toxicologists was held at the EMEA on Wednesday, 13 June 2007. The group concluded that there was insufficient data to quantify the risk posed by exposure to the levels of EMS present as a contaminant in the affected batches of Viracept. On Monday, 18 June 2007 the EMEA convened a Pharmacovigilance expert meeting which discussed the follow-up of patients exposed to the contaminant in Viracept and measures to be undertaken by the MAH in order to address the resulting public health concerns.

Swissmedic, in collaboration with the EMEA, organised an inspection of the Basel active substance manufacturing site on 11 and 12 June 2007, in order to further investigate the root causes leading to the contamination, other possible GMP failures, and to assess the adequacy of the MAH's CAPA (Corrective and Preventive Action) plan. The results of the inspection were presented to the CHMP on 19 June 2007.

Based on the critical GMP deficiencies found which led to contamination of the active substance, concerns were raised about the quality of Viracept and its safety under normal conditions of use.

Therefore, on 19 June 2007, the European Commission referred the matter to the CHMP in accordance with the procedure laid down in Article 20 of Regulation (EC) No 726/2004, for its Opinion on the measures necessary to ensure the quality as well as the safe use of Viracept. The CHMP, during its plenary session, drafted a list of questions, which were addressed by the MAH during an oral explanation on Wednesday, 20 June 2007.

The CHMP reviewed the data submitted by the MAH as well as the recommendations of both the toxicology and pharmacovigilance ad-hoc expert group meetings and the report from the GMP inspection and came to the following conclusions:

- The MAH is required to put measures in place to ensure that the GMP deficiencies identified are corrected and prevented from future occurrence.

- A suitable limit of EMS in nelfinavir mesilate should be introduced in the specification. This limit should reflect the capability of the process to deliver the lowest achievable level, but be in any case below the Threshold of Toxicological Concern (TTC), which translates to a maximum of not more than 0.6 ppm.

- The MAH should, in close co-operation with the CHMP perform non- clinical studies in order to better quantify the risk to patients who have been exposed to the contaminated batches.

- The MAH should, within the EU Risk Management Plan, undertake to set up a Registry for the follow-up and monitoring of patients. This registry should be in line with the CHMP's request to include
    - all patients having been exposed to Viracept contaminated with EMS at a level of 1000 ppm or above
    - all pregnant women and children (including those exposed *in utero*) who have ever been exposed to Viracept.

GROUNDS FOR SUSPENSION OF THE MARKETING AUTHORISATION OF VIRACEPT

The CHMP is of the Opinion that the Marketing Authorisations for Viracept products can no longer be maintained under normal conditions of use for the following reasons:

- The MAH, at this stage, cannot guarantee an acceptable quality of Viracept.
- Based on this, the current safe use of Viracept cannot be ensured.

Therefore, the CHMP has recommended the suspension of the Marketing Authorisations for Viracept.

Until the above has been satisfactorily addressed, the Marketing Authorisation will remain suspended.