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# Assessment report

## Tamiflu

oseltamivir

**Procedure number:** EMEA/H/C/402/A-20/0093

## Note

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# 1. Background information on the procedure

On 9 December 2011, the European Medicines Agency (EMA) was made aware by Roche of deficiencies in the quality management system at Roche's ingredients manufacturing site, Roche Carolina Inc. (RCI), Florence, in the United States of America (USA).

An internal investigation conducted by Roche from 29 November 2011 to 8 December 2011 revealed information indicating deficiencies with regard to good manufacturing practice (GMP). On 13 December 2011 the company further informed the Committee for Medicinal Products for Human Use (CHMP) on this issue during an oral explanation. The investigation raised concerns with regard to the cleaning practices, potential data integrity and GMP documentation practices at RCI. Events such as missing documentation, falsification of maintenance data sheets, inadequate cleaning, lack of documented involvement and accountability by Manufacturing and Quality leadership constitute a non-exhaustive list.

Deficiencies observed in the oversight of manufacturing and quality operations at RCI raised questions on the overall quality assurance system, which could potentially have a detrimental impact on the quality and safety of products manufactured and released by the site.

The site produces a number of ingredients (e.g. active substances, intermediates and other materials) used in the manufacturing process of six centrally authorised medicines, i.e. alli, Mircera, Pegasys, Tamiflu, Xeloda and Xenical.

Regarding the centrally authorised products, the activities at RCI include manufacture of active substance by chemical synthesis for Tamiflu and Xeloda, milling of the active substance for alli and Xenical, and manufacture of a starting material (pegylation reagent) for Mircera and Pegasys.

The MAH having considered the key issues identified in their internal audit report, their risk assessment of the medicinal products, the sourcing of the material from alternative manufacturing sites and the availability of alternative treatment options decided to put on-hold the release and further processing of any ingredients from this manufacturing site and of any finished products using these ingredients from RCI until a positive conclusion of the investigations. Corrective and preventive actions (CAPAs) were initiated at the site to ensure compliance with GMP, and a review by a third party consultant was performed.

An assessment of the impact of the issues identified at RCI and Roche's CAPAs on the quality of the ingredients and, consequently, on the quality of the finished product was considered necessary.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the CHMP on 15 December 2011 to assess the above concerns and their impact on the benefit/risk for alli, Mircera, Pegasys, Tamiflu, Xeloda and Xenical, and to give its opinion on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.

# 2. Scientific discussion

Tamiflu is a medicine that contains the active substance oseltamivir. It is available as capsules (30 mg, 45 mg, and 75 mg) and as a powder that is made up into an oral suspension (6 mg/ml and 12 mg/ml). Tamiflu is used to treat or prevent influenza (flu) in patients above one year of age. During a flu pandemic, Tamiflu can also be used to treat or prevent flu in babies below one year of age.

Product specific risk assessments were undertaken by the marketing authorisation holder (MAH) to address the concerns identified at RCI. It was noted that for Tamiflu the starting material of the active

substance (epoxide) as well as the active substance (oseltamivir) are produced at RCI. Nevertheless, the MAH informed the Committee that an alternative active substance manufacturing site is being used to supply oseltamivir in the European Union during the standard seasonal flu periods. The MAH plans to continue supply from the alternative manufacturing site approximately until end 2013. In addition, the last production of epoxide at RCI was performed in 2006. When the active substance is manufactured at RCI, production is done on shared equipment; the other substances manufactured with the same equipment include intermediates from the manufacturing process of the active substance of Xeloda (capecitabine).

The risk assessment conducted also assessed whether any contaminants could enter the process and could be carried over to the final active substance. It was concluded that the CAPAs introduced by the MAH would prevent any cross-contamination between oseltamivir and capecitabine (which synthesis is performed in the same equipment). In addition, a risk assessment was conducted for potential contaminations with e.g. cleaning agent, xylene residues, coating material. The results were reassuring and the MAH developed a control strategy relating to the above potential impurities, which the CHMP considered adequately address the concerns in relation to the above mentioned potential contaminants. The drug product is tested and released according to the authorised finished product specifications. The HPLC (high performance liquid chromatography) release testing uses the same chromatographic conditions as the active substance release method. Any impurities which were present at the level of the active substance, if existing, would also be detected at the release step of the drug product with the exception of one impurity from the active substance manufacturing process which cannot be detected by the drug product method. In addition, the CHMP pointed out that the HPLC release testing may not detect small amounts of impurities that could come from material cross-contamination. In that respect as part of the CAPAs the CHMP was satisfied that the MAH developed and validated a more sensitive and specific HPLC method for determination of impurities.

Solvents used at site were detected in the Pharma Water System and a microbiological contamination investigation was also considered. The MAH was asked to investigate the possible impact of these contaminants for oseltamivir and a product specific assessment was presented. The assessment revealed that all solvents would be removed during the manufacturing process and that no negative impact on the quality of oseltamivir was expected. In addition, microbial limit excursions were evaluated and no exceeding of microbiological alert/action limits have been reported for the unit used for the production of Tamiflu. The CAPAs in place will address satisfactorily this issue and prevent future contaminations (organic solvents or microbiological).

RCI is implementing CAPAs that address the specific actions necessary to correct product specific deficiencies as well as the system deficiencies identified. An inspection was held at RCI by the supervisory authorities in May 2012 in order to assess the extent of the issues identified by Roche and the appropriateness of the proposed corrective action plan.

Based on all available data and taking into account the CAPA plan, the CHMP considered that the identified deficiencies shall not affect the quality of the active substance. Subsequently, no impact on the quality and safety of the finished product is expected. On the basis of the proposed measures and the feedback from the inspection the CHMP was reassured that appropriate corrective actions are being implemented.

Therefore, the CHMP considers that the benefit-risk balance of Tamiflu manufactured using materials from RCI is positive and recommends the maintenance of its marketing authorisation.

# 3. Conclusion and grounds for the recommendation

Having considered the overall submitted data provided by the MAH in writing and at an oral explanation, as well as the inspection report,

Whereas:

- The manufacturing site RCI was found at an internal audit to have GMP deficiencies in relation to the production of a number of ingredients of centrally authorised products, including ingredients for Tamiflu. This investigation raised concerns such as the cleaning practices, potential data integrity and GMP documentation practices at the site;
- Appropriate corrective and preventive actions are being implemented at RCI to correct the deficiencies identified and this was confirmed by an inspection;
- Based on all available data and taking into account the CAPA plan, the CHMP considered that the identified deficiencies shall not affect the quality of the active substance. Subsequently, no impact on the quality and safety of the finished product is expected;

the CHMP considers that the benefit-risk balance of Tamiflu is positive and therefore recommends the maintenance of its marketing authorisation.