20 September 2012
EMA/568020/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xeloda

capecitabine

Procedure number: EMEA/H/C/316/A-20/0048

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

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

Xeloda is a medicine that contains the active substance capecitabine. Capecitabine is a fluoropyrimidine carbamate, which is an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). It is available as peach-coloured tablets (150 and 500 mg).

Xeloda is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer, for the treatment of metastatic colorectal cancer, for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. Xeloda in combination with docetaxel is

indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Xeloda is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

Product specific risk assessments were undertaken by the marketing authorisation holder (MAH) to address the concerns identified at RCI. It was noted that for Xeloda the starting material, intermediates and the active substance (capecitabine) are produced at RCI. The production of capecitabine is a three step process. The final step for the production of capecitabine is performed on dedicated equipment.

Capecitabine is further processed to the final drug product (Xeloda) in another manufacturing site (Roche Toluca). Before further processing of capecitabine retesting is performed at Roche Toluca where quality defects, if existing, would have been detected. It was noted that no out of specification (OOS) results have been reported at Roche Toluca site from analysis performed on capecitabine from RCI.

Additionally, 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. Therefore, 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. It was noted that no out of specification (OOS) results have been reported at Roche Toluca.

The CHMP pointed out that the current approved specifications and test methods may not be adequate to control all possible impurities resulting from the identified GMP deficiencies. The MAH was asked as part of the CAPA to develop a control strategy relating to the following potential impurities: xylene residues, coating material, two potential cross-contamination impurities that were identified as potentially capable of entering the manufacturing process, impurities created by cleaning agents reacting with process material, residual cleaning agents, potential impurities caused by missing maintenance (abrasion, rubber particles, lubricants, etc) and potential impurities caused by defect glass tanks. 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.

Solvents used at site have been detected in the Pharma Water System. The MAH was asked to investigate the possible impact of these contaminants for capecitabine and a product specific assessment was presented. The assessment revealed that all solvents would be removed during the manufacturing process and no negative impact on the quality of capecitabine was expected. The CAPAs in place will address satisfactorily this issue and prevent future contaminations.

In addition, the evaluation of the capecitabine assay/impurities method specificity was considered inadequate. Although the method appeared to be stability-indicating and scientifically sound and can separate many capecitabine related compounds, there were no solution stress studies performed to demonstrate the active substance degradation under treatment with acid base, peroxide, light and only heat treatment of the active substance powder was performed. The CHMP requested from the MAH to perform a full validation according to the current state of art for capecitabine assay/impurities. A validation plan/protocol is in place and this was considered appropriate by the CHMP.

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 Xeloda 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 Xeloda. 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 Xeloda is positive and therefore recommends the maintenance of its marketing authorisation.