



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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## Assessment report for Xenical

Review under Article 20 of **Regulation (EC) No 726/2004**

International Non-proprietary Name: orlistat

Procedure number: EMEA/H/C/154/A-20/0059

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, Mircerca, 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 Mircerca 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, Mircerca, 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

Xenical is a medicine that contains the active substance orlistat. It is available as hard capsules containing 120 mg of orlistat.

Xenical is indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a body mass index (BMI) greater or equal to 30 kg/m<sup>2</sup>, or overweight patients (BMI ≥ 28 kg/m<sup>2</sup>) with associated risk factors.

Product specific risk assessments were undertaken by the marketing authorisation holder (MAH) to address the concerns identified at RCI. It was noted that for Xenical the only manufacturing step performed at RCI is the milling of its active substance (i.e. orlistat). RCI is also registered as manufacturing site for the synthesis of orlistat (crude). However, the last production of orlistat (crude) by RCI was performed in 2001; since then only milling has been performed. The milled active substance is further processed to the final drug product (i.e. Xenical) in another manufacturing site (Roche Segrate).

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. No out of specification (OOS) results were reported at Roche Segrate site. It was noted that HPLC release testing may not detect small amounts of impurities that could come from material cross-contamination, but milling of the active substance is performed on dedicated equipment (i.e. on equipment dedicated to orlistat only).

As per the MAH's internal audit, one batch of orlistat showed an out of specifications (OOS) result for residue on ignition. Following further investigation, it was concluded that this was due to a laboratory error and all retest results of this batch passed specifications. From all lots of orlistat tested and released by RCI in the last 3 years this is the only occurrence where an out of specification result was observed for residue on ignition therefore it was considered to be an isolated case and no additional concerns were raised.

Another area of concern was that a complaint received on 24<sup>th</sup> November 2009 was managed outside of the official complaint system and was not processed and entered into the complaint system. The complaint was related to a data logger issue for the shipment of the orlistat active substance to the Drug Product Manufacturing site. The datalogger (temperature recorder) issue was fully investigated and the root cause of the data logger not working was assigned to a wrong date format entered (US format used instead of European format), so that the data logger did not start to monitor the shipment conditions. The storage conditions for the active substance are "store below 30°C and protect from humidity". It was noted that even if the data logger did not work appropriately, it is unlikely that temperatures above 30°C would have occurred during shipment in the month of November, when the complaint was reported. Appropriate CAPAs are in place to prevent reoccurrence of this event.

In addition, the external third party consultancy group performed a product specific assessment to determine if the active substance will meet specifications throughout shelf-life and to identify any potential compliance gaps. It was concluded that none of the deficiencies identified would impact the ability of orlistat to meet specifications throughout the retest period.

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