20 September 2012
EMA/568034/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mircera

methoxy polyethylene glycol-epoetin beta

Procedure number: EMEA/H/C/739/A-20/0039

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

Mircera is a solution for injection for either subcutaneous or intravenous use that contains the active substance methoxy polyethylene glycol-epoetin beta. It is available in pre-filled syringes at various strengths.

Mircera is indicated for the treatment of anaemia associated with chronic kidney disease (CKD) including patients on dialysis and patients not on dialysis. Treatment is administered once every two

weeks or once monthly for correction of anaemia in patients without previous treatment with an erythropoiesis stimulating agent (ESA) or once monthly in patients already receiving an ESA.

Product specific risk assessments were undertaken by the marketing authorisation holder (MAH) to address the concerns identified at RCI. It was noted that for Mircera, only the pegylation reagent is produced at RCI in a small scale manufacturing area which is further processed to the final drug substance (polyethylene glycol-epoetin beta) in another manufacturing site (Penzberg). Before further processing of the pegylation reagent received from RCI, several testings are performed at Penzberg site where quality defects, if existing, would have been detected. It was noted that no out of specification (OOS) results were reported at Penzberg site from analysis performed on the pegylation reagent received from RCI.

The risk assessment conducted also assessed whether any contaminants could enter the manufacturing process for the reagent and could be carried over to the final active substance. It was concluded that all potential contaminants would be consistently removed during the purification process of Mircera drug substance. Furthermore, as part of the CAPAs, dedicated equipment will be used for the peg-reagent for Mircera and will not be shared any longer with Pegasys. This measure addresses satisfactorily the potential risk of cross-contamination.

In addition, the external third party consultancy group performed a product specific assessment to determine if the pegylation reagent 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 the pegylation reagent 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 pegylation reagent and, therefore, 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 Mircera 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 Mircera. 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 pegylation reagent and, therefore, 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 Mircera is positive and therefore recommends the maintenance of its marketing authorisation.