16 September 2010
EMA/11835/2011

Assessment report for Clopidogrel Ratiopharm GmbH

International Non-proprietary Name: clopidogrel

Procedure No. EMA/H/001165/A-20/0009

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

The European Medicines Agency (EMA) was made aware on 3 March 2010 by the Supervisory Authority of Germany (Regeirung von Oberbayern) of the outcome of a Good Manufacturing Practice (GMP) inspection of an Active Pharmaceutical Ingredient (API) manufacturing site conducted from 23 to 26 February 2010 on behalf of the European Medicines Agency and requested by the CHMP in October 2009, resulting in the issue of a GMP non-compliance statement. The site is listed in the marketing authorisations as one of the API manufacturing sites for 8 centrally authorised medicinal products containing clopidogrel (Clopidogrel 1A Pharma, Clopidogrel Acino, Clopidogrel Acino Pharma, Clopidogrel Acino Pharma GmbH, Clopidogrel Hexal, Clopidogrel Ratiopharm, Clopidogrel Ratiopharm GmbH, Clopidogrel Sandoz):

Glochem Industries Ltd. (Unit II)
Survey No. 36, 37 & 46, Plot No. 77 Jawaharlal Nehru Pharmacity
Thanam Village, Visakhapatnam Dist. Andhra Pradesh
India

The inspection report, detailing the findings, identified one critical and 8 major GMP deficiencies.

The critical deficiency was related to the discovery of a minimum of 70 completed Batch Manufacturing Records (BMR) in the solid waste yard waiting for disposal. All these BMR's had been re-written and some original entries had been changed.
Practices such as re-writing batch records is contrary to basic GMP rules and the impact on the quality of the product by the tampering with source data is unknown. The amount and the variety of records discovered showed that this was not an isolated practice by the manufacturer, therefore, the possibility of data change / manipulation could not be excluded for other documents.

The 8 Major Deficiencies were related to the lack of implementation of a basic quality assurance system, non compliance with basic GMP requirements for the premises and equipment, including poor preventative maintenance and concerns relating to the handling of solvents. In addition the room and equipment cleaning procedures were found to be inadequate to guarantee the absence of contamination and cross contamination.

The Supervisory Authority issued a certificate of non-compliance with Good Manufacturing Practice on 16th March 2010.

The CHMP was informed that the manufacturing site does not comply the principles and guidelines of Good Manufacturing Practice for active substances referred to in Article 47 of Directive 2001/83/EC.

The CHMP was informed on the matter at the March 2010 plenary meeting, during which the Marketing Authorisation Holder (MAH) (Acino Pharma GmbH) was invited for an oral explanation on 17th March in order to provide further information on the root cause of the GMP non compliance as well as on the corrective actions proposed and implemented to guarantee the quality of the product and to reassure the CHMP of the credibility of the data supporting the Marketing Authorisations and documentation related to batches of finished product released to the market.

Given the explanations provided by the MAH during the Oral Explanation on 17 of March 2010 and taking into consideration the potential impact of this Good Manufacturing Practice non-compliance on the quality of the above mentioned medicinal products, the CHMP considered that appropriate provisional measures should be taken to address the identified concerns and to ensure protection of Public Health. The CHMP subsequently informed the European Commission of its concerns.

In view of the above, the European Commission (EC) initiated on 18 March 2010 a procedure under Article 20 of Regulation (EC) No 726/2004 and, referred the matter to the Committee for Medicinal Products for Human Use (CHMP). The EC requested opinion from the CHMP as to whether measures are necessary to ensure the quality of these products and specifically whether the marketing authorisations should be maintained, varied, suspended or withdrawn.

Steps taken for the assessment of this procedure:

The notification for an Article 20 procedure received from the European Commission on:	18 March 2010
The procedure started on:	18 March 2010
The CHMP, during its March 2010 plenary meeting, issued an Opinion on:	18 March 2010

2. SCIENTIFIC DISCUSSION

Clopidogrel ratiopharm GmbH 75 mg film-coated tablets is a centrally approved medicinal product containing clopidogrel as clopidogrel besilate as active substance. Clopidogrel is a non-competitive inhibitor of adenosine diphosphate (ADP) at the platelet receptors. It is indicated in adults for the prevention of atherothrombotic events in:
- Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.
- Patients suffering from acute coronary syndrome:
    - Non ST segment elevation acute coronary syndrome (unstable angina or non Q wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
    - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

Quality Aspects

The CHMP after reviewing the GMP report provided by the Supervisory Authority and the available data presented by the MAH during the Oral Explanation from the ongoing investigations on the inspection-GMP non compliance issues and its impact on the quality concluded the following:

Considering the fact that the company altered original manufacturing and quality related documents, that this was organised and supported at management level, that the quality assurance system was found to be deficient in major areas such as maintenance of premises and equipment, documentation, cleaning and validation, so that the inspectors considered that basic principles of good manufacturing practice were not applied.

Therefore the Committee concluded that it did not have confidence that the manufacturing process used to manufacture the active substance of the 8 centrally authorised medicinal products containing clopidogrel was the process assessed and described in the marketing authorisations.

The Committee further concluded that the above leads to a lack of confidence in the quality and purity of the finished product. The corrective actions proposed by the MAH cannot assure *a posteriori* the quality of the product manufactured in the absence of quality assurance and good manufacturing practice and therefore the quality of affected products cannot be guaranteed.

Conclusions on Quality
The Committee recommends that the Glochem site should be removed from the list of sites authorised for API to manufacture clopidogrel active substance and recommends the recall of all batches containing clopidogrel manufactured at the Glochem Visakhapatnam manufacturing site from the distribution chain to the pharmacy level.

The annexes I, II, and III of the Marketing Authorisation are not affected.

3. Overall Conclusion and grounds for the recommendation

The CHMP reviewed the inspection report provided by the Supervisory Authority and the available data presented by the MAH during the Oral Explanation from the ongoing investigations on the inspection-GMP non compliance issues and its impact on the quality of the medicinal product.

Given the following facts:

- The manufacturing site was found by the supervisory authority to be not in compliance with EU GMP, so that there was a lack of assurance that the active substance, has been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.
- The critical GMP deficiency was related to the discovery of re-written, altered and therefore unreliable source documents such as Batch Manufacturing Records (BMR) and cleaning reports.
- The major GMP Deficiencies further demonstrated that the quality of the API could not be assured.
- The explanations provided by the MAH during the Oral Explanation including the proposed corrective measures did not provide sufficient justification and reassurance that the manufacturing process used to manufacture the active substance of the 8 centrally authorised medicinal products containing clopidogrel was the process assessed and described in the marketing authorisation.

Therefore the Committee recommends the variation of the Marketing Authorisation to delete the Glochem Visakhapatnam site from the list of sites allowed to supply clopidogrel active substance.

In addition the CHMP also recommends, as a precautionary measure, that all batches containing clopidogrel made at the Glochem Visakhapatnam factory should be recalled from the distribution chain to pharmacy level.

The CHMP also recommends that provisional measures are taken and therefore recommends to the European Commission that the batches containing clopidogrel medicinal products as mentioned above should be recalled in all concerned EU Member States awaiting the adoption of the Commission Decision.