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Assessment report for Leflunomide Actavis (leflunomide) and associated names

Procedure number: EMEA/H/A-31/1340

Referral under Article 31 of Directive 2001/83/EC for authorised medicinal products for which studies have been carried out or analysed by Cetero Research, during the time period April 2005 to June 2010

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

1.1. Referral of the matter to the CHMP

The US Food and Drug Administration informed the European Medicines Agency that following an inspection, concerns have been raised about the conduct of bio-analytical studies performed by the Cetero Research facilities in Houston (Texas, USA) during the period from April 2005 to June 2010. The inspection identified significant instances of misconduct and violations of federal regulations, including falsification of documents and manipulation of samples. Other Cetero Research sites were not affected.

In the European Union, it was considered that this could potentially impact the marketing authorisations of a number of medicinal products. The EMA, CMD(h) and CHMP initiated a process to identify and assess all medicinal product dossiers that include studies conducted at the above mentioned facility during the identified time period.

On 01 August 2012, the United Kingdom triggered a referral under Article 31 of Directive 2001/83/EC for the identified nationally authorised products. The CHMP was requested to assess whether the deficiencies in conduct of bio-analytical studies performed by the Cetero Research facilities in Houston (Texas, USA) have impact on the benefit/risk of the concerned medicinal products and to give its opinion on whether the marketing authorisations for authorised medicinal products for which studies have been carried out or samples analysed by Cetero Research, during the identified time period, should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC was applicable.

2. Scientific discussion

2.1. Introduction

Leflunomide Actavis contains leflunomide, a pyrimidine synthesis inhibitor belonging to the DMARD (disease-modifying antirheumatic drug) class of drugs, which are chemically and pharmacologically very heterogeneous. It is indicated for the treatment of adults with active moderate to severe rheumatoid arthritis and psoriatic arthritis. The single pivotal bioequivalence study 125-07 was conducted in May 2008 at the Cetero Research facilities in Houston. Leflunomide Actavis is available as 10 mg, 20 mg and 100 mg film-coated tablets.

2.2. Clinical aspects

In response to the CHMP list of questions, the MAH declared that the medicinal product Leflunomide Actavis was never marketed and is currently not available on any market. The MAH is currently in the process of withdrawing the marketing authorisations in all EU member states and did therefore not provide any responses to the CHMP list of questions.

In conclusion, the CHMP considered that the potential deficiencies in the conduct of bio-analytical studies by the Cetero Research facilities invalidate the pivotal bioequivalence study. Therefore, given the serious doubts regarding the reliability and the correctness of the data from the critical pivotal bioequivalence study 125-07, submitted in support of the marketing authorisation, and in the absence of a reliable bioequivalence study specifically designed to establish the bioequivalence Leflunomide Actavis to its EU reference product, the CHMP was unable to conclude on the bioequivalence of Leflunomide Actavis. The CHMP was of the opinion that the previous conclusions regarding bioequivalence will need to be confirmed by repeating the bioequivalence study.

3. Overall discussion and benefit/risk assessment

As no data has been submitted by the MAH in response to the CHMP List of Questions, the CHMP retained serious doubts due to the findings of the inspection of the Cetero Research facilities in Houston (Texas, USA), regarding the reliability and the correctness of the data from the critical pivotal bioequivalence study submitted in support of the marketing authorisation. Therefore, and in the absence of a reliable bioequivalence study specifically designed to establish the bioequivalence of

Leflunomide Actavis to its EU reference product, the benefit-risk balance of Leflunomide Actavis cannot be considered to be favourable. The CHMP therefore recommended the suspension of the marketing authorisations until adequate bioequivalence data is made available.

4. Conclusion and grounds for recommendation

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for Leflunomide Actavis and associated names.
- The Committee considered that the available data gave rise to serious doubts as to the evidence of the bioequivalence of Leflunomide Actavis and associated names with the EU reference product in view of concerns on the reliability of the data, due to the findings of the inspection of the Cetero Research facilities.
- The Committee is of the opinion that considering the serious doubts in respect of the evidence of bioequivalence, the benefit-risk of Leflunomide Actavis and associated names cannot be confirmed.

The Committee, as a consequence, recommended the suspension of the marketing authorisations for Leflunomide Actavis and associated names, pursuant to Article 116 of Directive 2001/83/EC; as

a. the risk-benefit balance cannot be considered favourable and

b. the particulars supporting the application as provided in Article 10 of Directive 2001/83/EC cannot be considered correct

The conditions for the lifting of the suspension of the Marketing Authorisations are set out in Annex III of the CHMP opinion.

5. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.