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Assessment report for Leflunomide Apotex (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.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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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or samples analysed by Cetero Research, during the identified time period, should be maintained, varied, suspended or withdrawn.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 Apotex 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 used in the treatment of adults with active moderate to severe rheumatoid arthritis and psoriatic arthritis. The single pivotal bioequivalence study B050309 conducted to support the marketing authorization application was a comparative, parallel, three arm study to compare the relative bioavailability of Leflunomide Apotex 20 mg tablets with that of the EU reference product Arava 20 mg tablets in healthy, adult volunteers under fasting conditions. The clinical phase of the study was performed in January and February 2006 at Gateway Medical Research Inc. in St. Charles (USA) while the analytical phase was performed at BA Research International LP in Houston (USA) and the statistical phase was performed at BA Research International LP in Austin (USA) in February and March 2006. All three facilities became part of Cetero Research. Leflunomide Apotex is available as 10 mg and 20 mg tablets.

2.2. Clinical aspects

In response to the CHMP list of questions, the MAH submitted a review of the benefit-risk balance of Leflunomide Apotex. The results of the pivotal bioequivalence study showed that the 90% confidence intervals were within the 80% to 125% limits for AUC0-72 and Cmax and the pharmacokinetic data was therefore considered to demonstrate that the Leflunomide Apotex 20 mg tablets and the reference product 20 mg tablets were bioequivalent under fasting conditions. The MAH stated that plasma samples are no longer available and that there is therefore no possibility to reanalyse the data. As further evidence of the bioequivalence of Leflunomide Apotex with the reference product, the MAH provided an overview of the qualitative and quantitative composition of its 10 and 20 mg tablets intended for the US, Canadian and European market, considering them to be identical. In addition, all Leflunomide Apotex products for these markets are manufactured at the same manufacturing site, Apotex Inc., Toronto (Canada), according to the same manufacturing process. The MAH also provided details of 4 bio-equivalence studies, conducted to support the marketing authorisation application in the United States and Canada, comparing Leflunomide Apotex with their reference product, under fasting and fed conditions. The studies had a cross-over design with 2 weeks wash-out in between the study periods. In all 4 studies, the 90% confidence intervals for AUC0-72 and Cmax were within the 80% to 125% limits. The MAH therefore considered that the pharmacokinetic data demonstrate that

the EU Leflunomide Apotex is bioequivalent to both the US and Canadian reference products under fasting and fed conditions. The studies with the US and Canadian products were performed by Apotex Research Inc., Toronto, Canada. As the results from the bioequivalence study for the European product are in line with the results for US and Canadian products, in particular with regard to the blood plasma level results, the MAH considered the US and Canadian bio-equivalence data to support the data from the questioned EU bio-equivalence study.

Finally, the MAH provided comparative dissolution profiles between Leflunomide Apotex 10 and 20 mg, tablets and reference product 10 and 20 mg tablets from various markets, supporting the MAH view that the dissolution profiles of Leflunomide Apotex and the reference product are similar.

Regarding the safety profile of Leflunomide Apotex, the MAH performed a search for lack of effect / drug ineffectiveness in all case reports for leflunomide in the MAH's global pharmacovigilance database, from the date of first authorization of Leflunomide Apotex (08 September 2004) to 08 August 2012. 102 case reports related to leflunomide were identified, out of which 10 could be identified as lack of effect /drug ineffective case reports, all related to Leflunomide Apotex. 5 were from Canada and 5 from the USA, with no reports coming from Europe. One case report reported lack of efficacy, where the product was used for lupus mixed connective tissue disease, which is not an approved indication. For six of the reports, quality assurance investigations were conducted by the MAH and no problems were identified with Leflunomide Apotex. The annual PSUR (data lock point 27 October 2011) submitted to the European authorities did not identify any lack of efficacy cases reported globally and the MAH therefore concluded that there was no change to the benefit risk ratio of Leflunomide Apotex. The MAH considered that the data described in this PSUR did not change the benefit-risk balance of Leflunomide Apotex.

In conclusion, the MAH was of the opinion that the results from the pivotal bioequivalence study supporting the marketing authorisation application are confirmed by the other studies not conducted at, or analysed by, Cetero Research, which all showed a high degree of similarity between Leflunomide Apotex and the US and Canadian reference product. The MAH therefore concluded that the deficiencies identified at the Cetero Research Houston facility do not impact the benefit-risk balance of Leflunomide Apotex.

The CHMP noted the data from the bioequivalence studies performed with the US and Canadian product and identified some minor protocol violations. The CHMP agreed that the generic formulation is qualitative and quantitatively the same for the markets referred to and that the products are manufactured in the same manufacturing site, via the same manufacturing process. It is therefore plausible that the same quality active substance and excipients are used, although these bioequivalence studies were conducted using different sources of the reference product and no evidence was presented to confirm whether the reference product is indeed the same in all the studies. The AUC, Cmax and Tmax of the US and Canadian fasting studies were comparable to the values obtained in the European study, which was also performed in fasting state. However, the CHMP stated that bioequivalence studies performed with a non-EU reference products cannot be accepted as evidence of bioequivalence and that any evidence of product similarity between EU and non-EU products can only be considered as supportive.

Regarding the comparative dissolution testing, the CHMP was of the view that bioequivalence studies are pivotal to demonstrate bioequivalence for oral tablets. According to the bioequivalence guideline, dissolution studies to compare the proposed product with the reference product can be submitted as supportive of the results of bioequivalence studies, to evaluate whether there may still be differences between the formulations that might be relevant for efficacy and safety. The CHMP noted that although f2 calculations were not provided, the MAH conclusion was supported based on the studies in the two media. However, according to the new bioequivalence guideline, such studies should be performed without the addition of surfactants and in media pH 1.2, 4.5, 6.8 and with the quality control method. The CHMP noted that such dissolution results were not provided.

The CHMP also noted the safety assessment carried out by the MAH but carried out a separate search of EudraVigilance, identifying 14 cases of lack of efficacy specifically for generic products. For ten of these cases, the potential involvement of Leflunomide Apotex was ruled out. Of the four remaining cases potentially attributable to Leflunomide Apotex, two involved arthralgia and swollen joints not related to rheumatoid arthritis (RA) while one was confounded by the concomitant use of other drugs while the last suggested concomitant use of TNF-alpha inhibitors. Based on the available safety data, the CHMP was therefore of the view that no signal of lack of efficacy was identified. Although the company did not discuss any other potential safety signals, the CHMP acknowledged that there are no

signals of increased adverse events when compared to the reference product, based on the data in the last PSUR (reporting period 28-10-2010 until 27-10-2011).

Finally, the CHMP noted that the MAH did not plan to perform a new bioequivalence study, as it considered the provided additional data sufficient to confirm the validity of the studies for the EU applications in which Cetero Research was involved.

Overall, the CHMP stated that bioequivalence studies performed with a non-EU reference products cannot be accepted as evidence of bioequivalence and that any evidence of product similarity between EU and non-EU products can only be considered as supportive. Therefore, the CHMP did not consider the available data to be sufficient to support the bioequivalence of the EU formulation of Leflunomide Apotex to the EU reference product. The dissolution testing data submitted was not considered complete as it was performed with a surfactant and only done in water and was therefore considered to be only of limited value. The fact that the qualitative compositions of the EU and non-EU Leflunomide Apotex products are fully identical and that the products are manufactured at the same manufacturing facility via the same manufacturing process can only be considered as supportive evidence. The CHMP also noted that due to the lack of availability of samples, it was not possible to reanalyse the samples from the clinical study in order to check the validity of the original findings. The CHMP also noted the PSUR data, which did not indicate any safety concerns; however this is insufficient to confirm the bioequivalence of the product.

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 B050309, submitted in support of the marketing authorisation, and in the absence of a reliable bioequivalence study specifically designed to establish the bioequivalence of Leflunomide Apotex to its EU reference product, the CHMP was unable to conclude on the bioequivalence of Leflunomide Apotex. 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

Having assessed the available data, 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 Apotex to its EU reference product, the benefit-risk balance of Leflunomide Apotex 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 Apotex and associated names.
- The Committee considered that the available data gave rise to serious doubts as to the evidence of the bioequivalence of Leflunomide Apotex 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 considered that the responses of the MAH are not adequate to refute the serious doubts as to the evidence of the bioequivalence of Leflunomide Apotex and associated names with the EU reference product.
- The Committee is of the opinion that considering the serious doubts in respect of the evidence of bioequivalence, the benefit-risk of Leflunomide Apotex and associated names cannot be confirmed.

The Committee, as a consequence, recommended the suspension of the marketing authorisations for Leflunomide Apotex 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.