20 February 2013
EMA/20843/2013

Assessment report for Fenofibrato Pensa and Fenofibrato Ranbaxy (fenofibrate)

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or samples analysed by Cetero Research, during the identified time period, should be maintained, varied, suspended or withdrawn.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

Fenofibrato Pensa and Fenofibrato Ranbaxy contain fenofibrate, a drug of the fibrate class. It is used to reduce cholesterol levels in patients at risk of cardiovascular disease. It is used alone or in conjunction with statins in the treatment of hypercholesterolemia and hypertriglyceridemia. The single pivotal bioequivalence study 10540314 using the 160 mg tablets was conducted by the Cetero Research facilities in Houston in 2005. Fenofibrato Pensa and Fenofibrato Ranbaxy are both available as 160mg tablets.

2.2. Clinical aspects

In response to the CHMP list of questions, the MAHs stated that no samples were available to carry out a re-analysis. The MAHs therefore stated their intention to repeat the study, with a study report expected to be available by 15th November 2012.

The CHMP noted the absence of samples from the critical pivotal bioequivalence study 10540314 and that there is therefore no possibility to reanalyse the data.

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 10540314, submitted in support of the marketing authorisations, and in the absence of a reliable bioequivalence study specifically designed to establish the bioequivalence of Fenofibrato Pensa and Fenofibrato Ranbaxy to their EU reference product, the CHMP was unable to conclude on the bioequivalence of Fenofibrato Pensa and Fenofibrato Ranbaxy. The CHMP was of the opinion that the previous conclusions regarding bioequivalence will need to be confirmed by repeating the bioequivalence study.

2.3. Re-examination procedure

Following the adoption of the CHMP opinion during the September 2012 CHMP meeting, a request for re-examination was received from the MAH. The MAH submitted grounds for the re-examination, which consisted of a new bioequivalence study (study 2016_FENOF_11), carried out to replace the pivotal

bioequivalence study (study 10540314), for which serious doubts were raised regarding the reliability and the correctness of the data.

Following the assessment of the grounds for the re-examination, the CHMP noted that the results from the new bioequivalence study became available after the CHMP adopted its opinion and were therefore not available to the CHMP during its initial assessment. According to Article 62(1) of Regulation (EC) 726/2004, such new data cannot be considered in the context of the re-examination. In light thereof, the CHMP therefore confirmed its previous conclusions.

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 authorisations. Therefore, and in the absence of a reliable bioequivalence study specifically designed to establish the bioequivalence of Fenofibrato Pensa and Fenofibrato Ranbaxy to their EU reference product, the benefit-risk balance of Fenofibrato Pensa and Fenofibrato Ranbaxy 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 Fenofibrato Pensa and Fenofibrato Ranbaxy.
- The Committee considered that the available data gave rise to serious doubts as to the evidence of the bioequivalence of Fenofibrato Pensa and Fenofibrato Ranbaxy 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 Fenofibrato Pensa and Fenofibrato Ranbaxy 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 Fenofibrato Pensa and Fenofibrato Ranbaxy cannot be confirmed.

The Committee, as a consequence, recommended the suspension of the marketing authorisations for Fenofibrato Pensa and Fenofibrato Ranbaxy, 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.

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.