

Annex II

Scientific conclusions and grounds for suspension of the marketing authorisations

Scientific conclusions

Overall summary of the scientific evaluation of Cilazapril Teva and associated names (see Annex I)

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or samples analysed by Cetero Research, during the identified time period, should be maintained, varied, suspended or withdrawn.

Cilazapril Teva contains cilazapril, a pyridazine angiotensin-converting enzyme inhibitor (ACE inhibitor) used for the treatment of hypertension and congestive heart failure. The initial marketing authorisations applications for the Cilazapril Teva tablets were supported by a single pivotal bioequivalence study (Study 2005-980), comparing Cilazapril Teva with the EU reference product Vaspace, for which samples were analysed by BA Research International (now Cetero Research) between May 26th 2005 and December 20th 2005. Cilazapril Teva is available as 0.5 mg, 1 mg and 2.5 mg and 5 mg tablets.

In response to the CHMP list of questions, the MAH stated that the pivotal bioequivalence study 2005-980 conducted for Cilazapril Teva met the bioequivalence criteria (point estimates of 93.4% and 100% for AUC_{0-4h} and C_{max}, respectively) with respect to the Guideline on the Investigation of Bioequivalence. The quality of the bio-analytical report was checked internally by the MAH and was considered to be of good quality, based on the guideline applicable at that time ("Guideline for Industry - Bioanalytical Method Validation", May 2001). Only minor deficiencies were identified, which were not considered to influence the outcome of the clinical bioequivalence (e.g. exact EDTA matrix not specified, validated batch size not given, no influence of haemolytic or lipidaemic plasma shown, matrix effect in 4 different plasma batches shown).

In addition, the MAH stated that it had already carried out a number of repeats or re-assays of bio-analytical studies potentially affected by the Cetero Research findings for other Teva products in response to the concerns raised by the FDA. The MAH considered that the satisfactory results of these re-analyses suggest that the final outcome of the Cilazapril Teva study was not influenced by the bio-analytical analyses carried out at Cetero Research, Houston. However, for Cilazapril Teva, the MAH stated that no study samples were available for study 2005-980 and that there is therefore no possibility to reanalyse the data. The study will therefore be repeated, with the final results expected to be ready by the end of June 2013.

The MAH also referred to comparative dissolution data for the Cilazapril Teva tablets and the reference product, using three different dissolution media (0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer). In all three media, both products released more than 85% or close to 85% of the drug substance within 15 minutes and more than 95% in 20 minutes. The MAH stated that the calculated f₂ values indicated dissolution similarity between the drug products in all three media, and therefore considered the probability of the drug being released in the stomach to be high. The resulting solution is not expected to precipitate at higher pH values later in the intestine, due to the good aqueous solubility of the compound. The MAH was therefore of the view that the formulation of this immediate-release product will have only little influence on the bioavailability, which is supported by good point estimates for AUC and C_{max} in study 2005-980.

Finally the MAH noted that the periodic safety update report (PSUR) no. 383/01/12, dated February 13th 2012, reported no increased number of safety concerns with cilazapril. The report covers the period 1st January 2009 to 31st December 2011 and identified two case reports, both of which were

medically confirmed reports describing non-serious adverse reactions. The MAH considered that the data described in this PSUR did not impact the benefit-risk balance of Cilazapril Teva.

The CHMP assessed the MAH responses and noted that the MAH had repeated a number of studies, producing data in line with that obtained by Cetero Research, although no details of these studies were included in the response documentation to support this. The CHMP considered that these results could not be extrapolated to confirm the reliability of the pivotal bioequivalence study 2005-980. The CHMP also noted the MAH review of study 2005-980 and the quality of the bio-analytical report and the reported similarity between the results generated by Cetero Research and those found from repeated studies/analysis for other drug products. The highly soluble nature of the drug substance over the physiological pH range and the dissolution similarity between Cilazapril Teva and the reference product was also acknowledged. However, the CHMP did not consider these general data to be sufficient to provide re-assurances specifically regarding the bioequivalence of Cilazapril Teva to its EU reference product. The CHMP also noted that due to the lack of availability of samples, it was not possible to re-analyse the samples from the clinical study in order to check the validity of the original findings, but the CHMP acknowledged the MAH intention to repeat the study, with final results expected to be available by the end of June 2013. 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 2005-980, submitted in support of the marketing authorisation, and in the absence of a reliable bioequivalence study specifically designed to establish the bioequivalence of Cilazapril Teva to its EU reference product, the CHMP was unable to conclude on the bioequivalence of Cilazapril Teva. The CHMP was of the opinion that the previous conclusions regarding bioequivalence will need to be confirmed by repeating the bioequivalence study.

Overall conclusion and benefit-risk balance

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 Cilazapril Teva to its EU reference product, the benefit-risk balance of Cilazapril Teva cannot be considered to be favourable.

The CHMP therefore recommended the suspension of the marketing authorisations until adequate bioequivalence data is made available.

Grounds for suspension of the marketing authorisations

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for Cilazapril Teva and associated names.
- The Committee considered that the available data gave rise to serious doubts as to the evidence of the bioequivalence of Cilazapril Teva 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 Cilazapril Teva 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 Cilazapril Teva and associated names cannot be confirmed.

The Committee, as a consequence, recommended the suspension of the marketing authorisations for Cilazapril Teva 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.