06 December 2012
EMA/12875/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ribavirin Teva

ribavirin

Procedure number: EMEA/H/C/001018/A-20/0008

Note

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 7418 8416
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

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 identified that this could potentially impact the marketing authorisation of Ribavirin Teva.

On 16 November 2011 the European Medicines Agency (EMA) informed relevant MAHs that the Food and Drug Administration had raised concerns, following its inspection of Cetero Research facilities in Houston (Texas, USA), on the conduct of bio-analytical studies in the period between April 2005 and June 2010. The EMA asked MAH of all centrally authorised medicinal products to identify the products for which the marketing authorisation dossier included studies conducted at the above-mentioned facility.

The MAH for Ribavirin Teva provided responses on 15 December 2011.

On 2 May 2012, the FDA informed the EMA of a letter sent to Cetero confirming that, based on the final results of the inspection, the period of concern for which data generated by Cetero was considered potentially unreliable and for which the FDA recommended actions to be taken is from April 2005 to August 2009.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 16 July 2012 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 balance of Ribavirin Teva, and to give its opinion on whether measures are necessary to ensure the safe use of the product and specifically on whether the marketing authorisation for Ribavirin Teva should be maintained, varied, suspended or withdrawn

2. Scientific discussion

Ribavirin Teva contains ribavirin, a purine nucleoside analogue which is active against a number of DNA and RNA viruses. There are a number of proposed mechanisms of action for ribavirin. These include indirect effects such as inhibition of inosine monophosphate and immunomodulatory effects and direct effects such as polymerase inhibition and interference with viral RNA capping. Ribavirin Teva is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with interferon alfa-2b (adults) or interferon alfa-2b (adults and children of 3-years of age or older). Ribavirin Teva was approved via centralised procedure in 2009 under Article 10(1) of Directive 2001/83/EC supported by a single pivotal bioequivalence study R07-1285, which was a single dose study in parallel design under fed conditions using the 200 mg strength, conducted to determine bioequivalence with the EU reference product Rebetol. The samples were analysed at Cetero Research facilities in Houston (Texas), during the period of concern. Ribavirin Teva is available as 200 mg capsules.

2.1. Clinical aspects

In response to the CHMP list of questions, the MAH stated that it had carried out a critical analysis of study R07-1285 which supports the marketing authorisation, in light of the Cetero Research inspection findings. Only minor deficiencies were found, which were not considered to influence the result of the studies. The studies complied with the bioanalytical standards valid at the time when they were performed. The point estimates for AUC_{0-T} (106%), AUC_{∞} (103%) and C_{max} (101) were close to 100% and the 90% confidence interval was well within the acceptance range (AUC_{0-T} (91.1 to 123), AUC_{∞} (88.3 to 120) and C_{max} (91.8 to 110)). Therefore, the MAH assumed that even if there were small discrepancies generated by the Cetero Research bioanalytical studies, the influence on the positive outcome of this study should be minor. The MAH also confirmed that an electronic data audit has been initiated at Cetero Research to further analyse the risk with regard to the bioanalytical results produced for study R07-1285, with final results expected by the last quarter of 2012.

The MAH also 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 Ribavirin Teva study was not influenced by the bio-analytical analyses carried out at Cetero Research, Houston. However, for Ribavirin Teva, no plasma samples are available for the questioned study and there is therefore no possibility to reanalyse the data. The MAH therefore agreed to repeat the bioequivalence study, with final results expected by the last quarter of 2012.

The MAH also provided bioequivalence criteria from further fasted and fed studies conducted to support the US approval of Ribavirin Teva capsules, which had the same composition those as in the questioned study R07-1285. Based on the fasted study 10928, conducted in 2001 on lot K-27001 and on the fed study 10929, conducted in 2001 on lot K-27900, the capsules were approved by the FDA in 2004. Both studies were performed at MDS Pharma, Quebec, Canada. As the studies comparing Ribavirin Teva to the EU reference product and to the US reference product all demonstrated equivalence, the MAH considered it unlikely that the bioanalytical results produced at Cetero Research for study R07-1285 were incorrect.

An initial study was conducted prior to study R07-1285, by the CRO Anapharm Inc., Canada (project no. 02105, report dated October 29th 2002), comparing the Ribavirin Teva 200mg capsules to the EU reference product. The Ribavirin Teva capsules had the same formulation as those used in study R07-1285 and the study demonstrated bioequivalence between the two products. The MAH considered that this further supported the argument that it is unlikely that the bioanalytical data from study R07-1285 was strongly influenced by any bad laboratory practice at Cetero Research.

With regard to safety, the periodic safety update report no. 32 (7/08/11) dated August 25th 2011, identified no new safety concerns with ribavirin. The report covers the period August 1st 2010 to July 31st 2011. Overall, 42 case reports were received from countries where the MAH ribavirin products are authorised. 24 of these were medically confirmed reports describing serious adverse reactions and non-serious unlisted adverse reactions, 12 cases were non-serious listed reports from healthcare professionals and the remaining 6 cases were reported by non-healthcare professionals. The MAH considered that the data described in this safety update report did not impact the benefit-risk balance of ribavirin.

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 S08-0152.
The CHMP agreed that the initial results of study R07-1285 showed satisfactory bioequivalence of the test and the EU reference product with point estimates for study R07-1285 reported to be close to 100% (AUC0-T (106%), AUC0-∞ (103%) and Cmax (101%)) which suggests that the Teva product is comparable with the reference product.

The CHMP also noted that information provided by the MAH from other pharmacokinetic studies which were conducted in 2001 to support the bioequivalence of the Teva capsule formulation against the US reference product, as well as the 2002 study by the CRO Anapharm Inc., Canada. The CHMP acknowledged the MAH claim that the EU reference product and US reference product are equivalent in the quantity of active substance, are manufactured by the same company and have the same qualitative composition with regard to the excipients, while the US formulation and the EU formulation of Ribavirin Teva were said to have identical compositions, but noted that no data was submitted to support this.

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. Therefore, the CHMP did not consider the available data to be sufficient to support the bioequivalence of the EU formulation of Ribavirin Teva to the EU reference product. 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, but the CHMP acknowledged the MAH intention to repeat the study, with final results expected to be available by the last quarter of 2012. 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 raise serious doubts with regard to the reliability and the correctness of the data from the critical pivotal bioequivalence study. Therefore, given the serious doubts regarding the reliability and the correctness of the data from the critical pivotal bioequivalence study R07-1285, submitted in support of the marketing authorisation, and in the absence of a reliable bioequivalence study specifically designed to establish the bioequivalence of Ribavirin Teva to its EU reference product, the CHMP was unable to conclude on the bioequivalence of Ribavirin Teva. The CHMP was of the opinion that the previous conclusions regarding bioequivalence will need to be confirmed by repeating the bioequivalence study and noted that the MAH agreed to repeat the bioequivalence study, with results expected to be available by the last quarter of 2012.

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 Ribavirin Teva to its EU reference product, the benefit-risk balance of Ribavirin Teva cannot be considered to be positive under normal conditions of use.

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

4. Conclusion and grounds for the recommendation

Whereas

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Ribavirin Teva initiated by the European Commission.
- The Committee considered that the available data gave rise to serious doubts as to the evidence of the bioequivalence of Ribavirin Teva 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 Ribavirin Teva 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 Ribavirin Teva cannot be confirmed.

The Committee, as a consequence, recommended the suspension of the marketing authorisations for Ribavirin Teva, pursuant to Article 116 of Directive 2001/83/EC; as

a. the risk benefit balance cannot be considered positive under normal conditions of use 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 II of the CHMP opinion.