



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 February 2013
EMA/796016/2012 rev.1

Questions and answers on the review of medicines for which studies have been conducted at Texas-based Cetero Research facility

Outcome of four procedures under Article 20 of Regulation (EC) No 726/2004 and of one procedure under Article 31 of Directive 2001/83/EC as amended¹

On 20 September 2012, the European Medicines Agency completed a review of nine centrally and nationally authorised medicines², following concerns over the conduct of laboratory analyses of certain studies submitted as part of their marketing authorisation applications. The studies concerned were all conducted at the Cetero Research facility in Houston, Texas, USA.

The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that for seven medicines (Cilazapril Teva, Fenofibrato Pensa, Fenofibrato Ranbaxy, Leflunomide Actavis, Leflunomide Apotex, Ribavirin Teva and Ribavirin Teva Pharma B.V.) some of the studies that supported their authorisation could not be considered reliable. In the absence of reliable data, the CHMP recommended that their marketing authorisation should be suspended until adequate data are provided. For Temodal and Tygacil the findings have no impact on the benefit-risk balance of these medicines and no further action is needed.

At the request of the company that markets Fenofibrato Pensa and Fenofibrato Ranbaxy, the CHMP re-examined the initial opinion for these medicines, and confirmed its previous recommendation on 13 December 2012.

Which medicines are affected by the Agency's review?

The Agency's review covers the following centrally authorised medicines, whose marketing authorisation applications included studies conducted at the Cetero Research facility in Houston, Texas, USA:

- Ribavirin Teva and Ribavirin Teva Pharma B.V., generic medicines containing ribavirin, used for the treatment of hepatitis C (a disease of the liver due to an infection with the hepatitis C virus);

¹ Procedure numbers: EMEA/H/C/001018/A-20/0008, EMEA/H/C/001064/A-20/0007, EMEA/H/C/000229/A-20/0060, EMEA/H/C/000644/A-20/0072, EMEA/H/A-31/001340.

² This review was initiated by the European Commission for the centrally authorised medicines and by the UK Medicines Regulatory Agency for the nationally authorised medicines.



- Temodal, anticancer medicine containing temozolomide, used for the treatment of malignant glioma (brain tumours);
- Tygacil, an antibiotic containing tigecycline, used for the treatment of complicated infections of the skin and soft tissue (the tissue below the skin), and complicated infections in the abdomen.

More information on these medicines can be found on the EMA website: ema.europa.eu/Find/medicine/Human_medicines/European_Public_Assessment_Reports.

In addition, the Agency reviewed the following nationally authorised medicines, whose marketing authorisation applications also included studies conducted at this Cetero Research facility:

- Cilazapril Teva, a generic medicine containing cilazapril, used for the treatment of hypertension (high blood pressure) and heart failure (when the heart does not work as well as it should);
- Fenofibrato Pensa and Fenofibrato Ranbaxy, generic medicines containing fenofibrate, used to control the levels of cholesterol and other lipids (fats) in the blood;
- Leflunomide Actavis and Leflunomide Apotex, generic medicines containing the active substance leflunomide, used for the treatment of rheumatoid arthritis (an immune system disease causing damage and inflammation in the joints).

In July 2012, the CHMP had concluded a similar review for three other concerned centrally authorised medicines: Conbriza, PecFent and Torisel.³

Why were these medicines reviewed?

The EMA was made aware that recent inspections of the Texas-based Cetero Research facility by the US Food and Drug Administration had raised concerns over the way laboratory analyses of certain studies, called 'bio-analytical' studies, were conducted at this facility in the period from April 2005 to June 2010. Hence, the results of the studies concerned could not be considered reliable.

In total, seven centrally authorised medicines and five nationally authorised medicines were identified, whose marketing authorisation applications included data from studies conducted at this Cetero Research facility.

Consequently, the European Commission asked the CHMP to assess whether the identified issues have an impact on the benefit-risk balance of the centrally authorised medicines concerned, and to issue an opinion on whether the marketing authorisation for these medicines should be maintained, varied, suspended or withdrawn across the EU. In addition, the UK Medicines Regulatory Agency requested the CHMP to carry out the same assessment for the concerned nationally authorised medicines.

Which data has the CHMP reviewed?

The CHMP reviewed the bio-analytical studies performed at Texas-based Cetero Research facility that had been submitted as part of the marketing authorisation applications of the medicines concerned.

The Committee considered the importance of the data from these studies in the context of the overall data submitted in the applications. The CHMP also requested the companies to provide any additional relevant data, which had not been submitted as part of the initial applications.

³ For more information, see:

http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2012/07/WC500130159.pdf

What are the conclusions of the CHMP?

Cilazapril Teva, Fenofibrato Pensa, Fenofibrato Ranbaxy, Leflunomide Actavis, Leflunomide Apotex, Ribavirin Teva and Ribavirin Teva Pharma B.V.

For these generic medicines, the studies conducted at the Texas-based Cetero Research facility were bioequivalence studies, to demonstrate that they produce the same levels of the active substance in the body as their reference medicines. Although the Committee noted that no problems have been identified with the products currently on the market, bioequivalence studies are a mandatory part of the marketing authorisation application for generic medicines. As the results of these studies could not be considered reliable, the CHMP concluded that the marketing authorisation of these medicines should be suspended until the companies provide adequate data.

During a re-examination procedure for Fenofibrato Pensa and Fenofibrato Ranbaxy, the company submitted new data, which is not permitted in the context of a re-examination. The CHMP confirmed its previous conclusions on these medicines.

Temodal

The CHMP noted that the studies conducted at this facility were two studies submitted in support of the approval of Temodal solution for infusion. The Committee concluded that the data from these studies were confirmed by other studies conducted elsewhere, and therefore that there is no impact on the benefit-risk balance of Temodal and no further action is needed.

Tygacil

The Committee noted that the studies conducted at this facility do not support any indication or prescribing recommendation for Tygacil. One of the studies is a 'pharmacokinetic' study in children, whose results are included in the product information. However, as Tygacil is not approved for use in this population, no specific action was considered necessary. Nevertheless the CHMP requested the company to update the product information with revised data.

In July 2012, the CHMP had already completed a similar review of three other medicines (Conbriza, PecFent and Torisel) and concluded that there is no impact on the benefit-risk balance of these medicines and that the marketing authorisation should be maintained.

What are the recommendations for patients and prescribers?

- Patients and prescribers should note that there are no safety concerns with any of these medicines currently on the market.
- Patients who are taking any of the generic medicines that have been suspended should be aware that alternative treatments are available.
- Patients who have any questions should speak to their doctor or pharmacist.

The European Commission issued a decision on:

- Temodal: 26 November 2012
- Leflunomide Actavis and associated names: 30 November 2012
- Leflunomide Apotex and associated names: 30 November 2012
- Tygacil: 30 November 2012
- Ribavirin Teva: 06 December 2012

- Ribavirin Teva Pharma B.V: 06 December 2012
- Cilazapril Teva and associated names: 10 December 2012
- Fenofibrato Pensa and Fenofibrato Ranbaxy: 20 February 2013

Medicinal product no longer authorised