NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

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This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by Germany (BfArM):

Details on the products concerned are listed in Annex I (pending and finalized) to this notification.

The Federal Institute of Drugs and Medical Devices (BfArM), Germany, and the Health Care Inspectorate (IGZ), Ministry of Health of the Netherlands performed a joint GCP inspection from 9 - 12 March 2015 at Alkem Laboratories Limited, Department of Bioequivalence, C-17/7, MIDC Industrial Estate, Taloja, Dist. Raigad - 410 208, India (Inspection references: BfArM: 2015_03_D / 2015_05_D, NL: VGR-1005124). Three bioequivalence trials, two performed in 2013 and one performed in 2014, were inspected.

The findings reported during this inspection cast doubts on the reliability of the data of bioequivalence studies conducted between 2013 and 2014 at the site inspected.

The following critical observations were made in relation to the ECGs performed for two of the three inspected trials:

- For one of the inspected trials (performed in 2013) an ECG printout was used as source data for two different subjects. As the subject's identifier and date of birth must have been actively changed, this is considered by the inspection team as intentional misrepresentation of study data.
- For the other inspected trial (performed in 2014) in at least one case the ECGs ascribed to two different individuals and having been recorded at consecutive time points, were judged by the experts as having been recorded from one/the same individual. The observation has to be seen as intentional misrepresentation of study data. Furthermore, for the same day wrongly assigned ECGs for blocks of successive subjects, displacement or 'inversion' of leads during ECGs, wrong subjects details (DOB) on an ECG and inaccurate assessment of an ECG by the physician was identified.
- In the response to the inspection report, the inspected site acknowledged that there were severe errors with the ECGs which were recorded by contractual technicians and acknowledged carelessness and non-compliance of the quality system by these users.

Intentional misrepresentation of data happened at the site in two different trials performed in 2013 and 2014. This was neither avoided nor detected by the quality management system, which was in place during this time period. There was one general quality management system implemented at the site which included a quality assurance unit which was responsible for the clinical and the bioanalytical part of the trial and which reported to the CEO of the facility.

As the quality management system was a general one covering all parts of the trial and as a failure of the system in relation to the ECGs was acknowledged by the site, this system is considered highly insufficient and severe failures in other areas of the trial which were not yet detected cannot be excluded.

This affects the trustworthiness of the data generated by the site (clinical and bioanalytical) in the time period from the beginning of the first study in March 2013 until the inspection took place in March 2015 as it must be assumed, that the critical deficiencies were not identified by the site in the meantime, because CAPAs were only implemented after the inspection.

The findings are detailed in the BfArM/IGZ inspection report, dated 08 September 2015, to which Alkem Laboratories Ltd. responded on 29 October 2015, and in the final evaluation of the responses by the inspection team, which was issued on 01 December 2015.

In view of the elements described above and the fact that based on the inspection findings applications for marketing authorizations have already been refused, there is the necessity to take an action at EU level. Germany considers, that it is in the interest of the Union to refer the matter to the CHMP and requests, that it assesses the potential impact of the findings mentioned above on the benefit-risk balance of the medicinal products, which have been authorized by the Member States on the basis of relevant trials performed at the inspected site as well as for pending procedures based on trials in the period between March 2013-March 2015. It should in particular provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorizations of these products should be maintained, varied, suspended, or withdrawn.

Signed 

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