Annex II

Scientific conclusions

Scientific conclusions

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 of the above mentioned inspection cast doubts on the reliability of the data of bioequivalence studies conducted between 2013 and 2014 at the site inspected. 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 at the site 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 parts of the trial and which reported to the CEO of the facility.

As the quality management system covered all parts of the trial and a failure of the system in particular in relation to the ECGs monitoring was detected and acknowledged by the site, this system was considered by BfArM to be insufficient and severe failures in other areas of the trial could not be excluded even if not detected.

Therefore BfArM considered that 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 date when the inspection took place in March 2015, as it must be assumed that critical deficiencies could not be detected by the quality management system at the site in the meantime, because corrective actions and preventive actions (CAPAs) were only implemented after the inspection.

In view of the elements described above, BfArM considered that there was a need to take action at EU level. On 8 March 2016 the BfArM initiated a referral under Article 31 of Directive 2001/83/EC, and asked the CHMP to assess the potential impact of the above findings on the benefit-risk balance of marketing authorisation applications and medicinal products authorised on the basis of relevant trials performed at the inspected site between March 2013-March 2015, and issue a recommendation on whether the marketing authorisations should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

Where the bioequivalence is not established, safety and efficacy cannot be extrapolated from the EU reference medicinal product to the generic medicinal product as the bioavailability of the active substance between the two medicinal products may differ. If the bioavailability of the generic product is higher than the bioavailability of the reference medicinal product, this may result in a higher than intended exposure of patients to the active substance, leading potentially to an increase in the incidence or severity of adverse effects. If the bioavailability of the generic product is lower than the bioavailability of the reference medicinal product, this may result in a lower than intended exposure to the active substance, leading potentially to a decrease in efficacy, a delay or even a lack of therapeutic effect.

Taking the above into account, the benefit-risk balance of medicinal products for which bioequivalence is not established cannot be considered positive, as the possibility of safety/tolerability or efficacy issues cannot be excluded.

Marketing authorisation holders (MAHs) have argued that pharmacovigilance data collected on their medicinal products have not indicated any problems which could be attributed to non-bioequivalence, such as reduced efficacy or worsened safety and tolerability. However, the CHMP is of the opinion that

the absence of the identification of any pharmacovigilance signals does not provide sufficient reassurance because it is not established that the pharmacovigilance activities may be designed to detect such a signal.

It has been highlighted that all the CAPAs agreed after the BfArM/IGZ inspection have been either implemented (for critical observations) or committed to (for other observations). A later MHRA inspection (March 2016) has also resulted in one critical and 2 major observations, for which CAPAs have already been agreed with the inspectors. Although Alkem agreed to the CAPAs and committed to implement them following the joint GCP inspection in March 2015, the fact that a second inspection in March 2016 by the MHRA identified critical/major findings during the period of concern further demonstrates that the quality management system in place during the period concerned by the procedure was suboptimal. The data generated at the site can therefore not be relied upon to establish bioequivalence of products to the EU reference medicinal product.

Cefuroxime

For cefuroxime-containing products affected by this review (Cefuroxime Alkem, Cefuroxime Krka and Cefuroxime Ingen Pharma), bioequivalence to the EU reference medicinal product was established based on an alternative bioequivalence study conducted at a different facility (study 0258-16, Lambda therapeutic Research Inc.). Having assessed the alternative study, the CHMP considered that it supports bioequivalence of these medicinal products to the reference medicinal product Zinnat.

Riluzole

For the riluzole-containing medicinal product affected by the review (Riluzole Alkem), the MAH provided some comparative dissolution data to claim that, as the multi-media dissolution profiles of cefuroxime and riluzole are similar to those of the reference products, the probability of the products being bioequivalent is high. The CHMP considered these data, however a conclusion on bioequivalence cannot be drawn from a simple comparison of dissolution profiles.

The MAH also submitted an expert report with a reassessment of the original bioequivalence study performed by Alkem, concluding that no abnormalities were observed with the ECG data. In view of the inspection findings and the conclusion that there was a failure of the overall quality management system in place at the site, even of the ECG data for this particular study has no abnormalities, severe failures in other parts of the trial could not be excluded and all the data generated by the site during the period from March 2013 to March 2015 cannot be relied upon.

In addition, the MAH presented data to demonstrate that the US and Australian reference medicinal products are similar to the EU reference medicinal product, and that bioequivalence studies comparing the riluzole generic product under discussion to the US and Australian originators concluded in bioequivalence, therefore it is very likely that the product is also bioequivalent to the EU reference medicinal product.

The arguments of the MAH were considered, including the results of the studies with the US and Australian originator medicines, the data submitted do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as required by Article 10 of Directive 2001/83/EC. Therefore CHMP concluded that bioequivalence to the EU reference medicinal product is not established for Riluzole Alkem.

Ibuprofen

The applicant for the ibuprofen-containing medicinal product affected by the review (Ibuprofen Orion) did not submit alternative data to establish bioequivalence vis-à-vis an EU reference medicinal product. The bioequivalence to the EU reference medicinal product is therefore not established.

Conclusions

In the absence of the demonstration of bioequivalence vis-à-vis the EU reference medicinal product, the requirements of Article 10 of Directive 2001/83/EC cannot be considered fulfilled, the efficacy and safety of the concerned medicinal products cannot be established, hence the benefit-risk balance of these medicinal products cannot be considered positive.

The CHMP therefore recommends the suspension of the marketing authorisation for Riluzole Alkem.

As regards the marketing authorisation application for Ibuprofen Orion, the CHMP considers that the applicant did not establish bioequivalence to the EU reference medicinal product and therefore the marketing authorisation application does not currently fulfil the criteria for authorisation.

Alternative data were submitted to demonstrate the bioequivalence of Cefuroxime Alkem, Cefuroxime Krka and Cefuroxime Ingen Pharma to an EU reference medicinal product. Having assessed the alternative data, the CHMP recommends the maintenance of the marketing authorisations for Cefuroxime Alkem and Cefuroxime Krka and concludes that, with regards to the Cefuroxime Ingen Pharma marketing authorisation application, bioequivalence has been demonstrated vis-à-vis the EU reference medicinal product using alternative data.

Grounds for CHMP opinion

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for marketing authorisations and marketing authorisation applications for medicinal products for which the clinical and/or bioanalytical parts of the bioequivalence studies were performed at Alkem Laboratories Limited during the period between March 2013 and March 2015;
- The Committee reviewed all available data and information provided by the MAHs/applicants, as well as information provided by Alkem Laboratories;
- The Committee concluded that the particulars supporting the marketing authorisation/marketing authorisation application are incorrect and that the benefit-risk balance is considered not favourable for:
  - Authorised medicinal products for which alternative bioequivalence data or a justification was submitted but considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product (annex IB);
  - Marketing authorisation applications for which no alternative bioequivalence data or a justification was submitted (annex IB).
- The Committee concluded that, for both marketing authorisations and marketing authorisation applications referred to in annex IA, there was alternative data to establish bioequivalence vis-à-vis the EU reference medicinal product.

Therefore, in accordance with Articles 31 and 32 of Directive 2001/83/EC, the CHMP concludes that:

a. Marketing authorisations for medicinal products for which bioequivalence data or justification were not submitted or considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product (annex IB) should be suspended, as the particulars supporting the marketing authorisations are incorrect and the benefit-risk balance of these marketing authorisation is considered not favourable pursuant to Article 116 of Directive 2001/83/EC.

The condition for the lifting of the suspension of the Marketing Authorisations, as applicable, is set out in Annex III.

b. Marketing authorisation applications for which bioequivalence data or justification were not submitted or considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product (annex IB) do not satisfy the criteria for authorisation, as the particulars supporting the marketing authorisations are incorrect and the benefit-risk balance of these marketing authorisation is considered not favourable pursuant to Article 26 of Directive 2001/83/EC.

c. Marketing authorisations for medicinal products for which the bioequivalence vis-à-vis the EU reference medicinal product has been established (annex IA) should be maintained, as the benefit risk balance of these marketing authorisation is considered favourable.

d. Bioequivalence vis-à-vis the EU reference medicinal product has been established for marketing authorisation applications listed in annex IA.

The conditions imposed to lift the suspension of the marketing authorisation are set out in section 4 of this report.