Annex II

Scientific conclusions

Scientific conclusions

Bioequivalence (BE) is required for the conclusion that efficacy and safety are similar to those of the reference medicinal product for a medicinal product with a marketing authorisation or marketing authorisation application under Article 10(1) of Directive 2001/83/EC.

Micro Therapeutic Research Labs Ltd is a contract research organisation (CRO) which conducts the analytical and clinical parts of bioequivalence studies, some of which have been used to support marketing authorisation applications of medicines in the EU.

Critical findings were identified following inspections to check compliance with Good clinical practice (GCP) by the Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) in February 2016 at Micro Therapeutic Research Labs Pvt. Ltd, Chennai, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore was inspected. Both the Chennai site and the Coimbatore site follow the same provisions.

In view of the critical inspection findings and the necessity to protect public health in the EU, several Member States considered that it is in the interest of the Union to refer the matter to the CHMP and request that it assesses the impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at these sites between June 2012 and June 2016 and also that of pending marketing authorisation applications (MAA) that include such studies.

The CHMP was requested in particular to provide its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked and whether marketing authorisations applications should be authorised.

Overall summary of the scientific evaluation

The findings of the Austrian and Dutch inspections raise serious concerns relating to the suitability of the quality management system in place at Micro Therapeutics Research LTd, India. Data from bioequivalence studies submitted to the Competent Authorities to demonstrate bioequivalence of medicinal products with their originator is considered unreliable. Therefore, for those products bioequivalence is not established.

Based on the submitted data during the procedure, the medicinal products Tadalafil Mylan 2.5 mg, 5 mg, 10 mg and 20 mg; Paracetamol DAWA 1000 mg film-coated tablets; Memantine Pharmascope 10 mg and 20 mg; Memantine DAWA 10 mg and 20 mg; Morysa 10 mg and 20 mg – SVUS Pharma a.s.; Bendroflumetiazid Alternova 2.5 mg and 5 mg tablets; the CHMP concluded that bioequivalence has been demonstrated vis-à-vis the EU reference medicinal product and recommended the maintenance of these marketing authorisations. For the Hydrokortison Alternova (Orifarm) and Hydrokortison BBS marketing authorisation applications, the CHMP concluded that the Member State(s) will have to consider whether the bridging between the proposed product and the medicinal products described in the literature as par Annex I of Directive 2001/83/EC is sufficiently established as the applications relate to Article 10a of Directive 2001/83/EC (‘Well-established use’).

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 cannot be considered positive. The CHMP therefore recommended the suspension of the marketing authorisations for all remaining medicinal products concerned by this referral procedure, as bioequivalence vis-à-vis the EU reference medicinal products has not been demonstrated.

Furthermore, the Committee recommends that the concerned marketing authorisations should be suspended unless the medicinal product is considered critical by the relevant national competent authorities.

An authorised medicinal product may be considered critical by the EU Member States based on the evaluation of the potential unmet medical need, considering the availability of suitable alternative medicinal products in the respective EU Member States and, as appropriate, the nature of the disease to be treated.

For marketing authorisations of a medicinal product considered critical, the suspension may be deferred in the relevant EU Member States for a period which shall not exceed twenty-four (24) months from the Commission Decision. Should during this period the EU Member State(s) consider a medicinal product not critical anymore, the suspension of the concerned marketing authorisation shall apply.

For all other marketing authorisation applications subject to this referral the CHMP considers that the applicants did not submit information which allows establishing bioequivalence to the EU reference medicinal product, and therefore the marketing authorisation applications do not currently fulfil the criteria for authorisation.

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 Micro Therapeutic Research Labs Limited during the period between June 2012 and June 2016;
- The Committee reviewed all available data and information provided by the MAHs/applicants, as well as information provided by Micro Therapeutic Research Labs Limited;
- The Committee concluded that the particulars supporting the marketing authorisations and marketing authorisation applications are incorrect and that the benefit-risk balance is considered not favourable for:
  - Authorised medicinal products for which alternative data or a justification was submitted but considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product;
  - Marketing authorisation applications for which no alternative data or a justification was submitted.
- The Committee concluded that, for both marketing authorisations and marketing authorisation applications where there was alternative data to establish bioequivalence vis-à-vis the EU reference medicinal product the benefit-risk balance is considered favourable.

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 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.

Some of these authorised medicinal products may be considered critical by the individual EU Member States on the evaluation of the potential unmet medical need, considering the availability of suitable alternative medicinal products in the respective EU Member State(s) and, as appropriate, the nature of the disease to be treated. Where on the basis of these criteria the relevant national competent authorities of the EU Member States consider that a medicinal product is critical, the suspension of the concerned marketing authorisation(s) may be deferred by the period for which the medicinal product is considered critical. This period of deferral shall not exceed twenty-four months from the Commission Decision. Should during this period the EU Member State(s) consider a medicinal product not critical anymore, the suspension of the concerned marketing authorisation(s) shall apply. For these medicinal products considered critical by EU Member State(s), the marketing authorisations holders shall submit a bioequivalence study conducted vis-à-vis the EU Reference Medicinal Product within 12 months from the Commission Decision.

For the suspension of the marketing authorisations to be lifted the MAH shall demonstrate bioequivalence data vis-à-vis a valid EU reference medicinal product based on relevant data, in accordance with the requirements of Article 10 of Directive 2001/83/EC (e.g. a bioequivalence study conducted vis-à-vis the EU reference medicinal product).

b. Marketing authorisation applications for which data or justification were not submitted or considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product 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 should be maintained, as the benefit risk balance of these marketing authorisation is considered favourable.

d. Bioequivalence vis-à-vis a valid EU reference medicinal product has been established for marketing authorisation applications listed in Annex Ia of the CHMP Opinion.