EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Medicinal products which have been authorised or are pending approval based on clinical trials performed at Panexcell Clinical Laboratories Priv. Ltd.

Procedure number: EMEA/H/A-31/1494

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

The Federal Office for Safety in Health Care (BASG), Austria, and the Federal Institute of Drugs and Medical Devices (BfArM), Germany, performed a joint GCP inspection from 14 – 17 October 2019 at the contract research organisation (CRO) Panexcell Clinical Laboratories Priv. Ltd., located in Navi Mumbai 400 701, India. This inspection focussed on a bioequivalence trial performed by this CRO in 2018 and 2019 for the substance doxorubicin. The following critical observations were made during the inspection which cast serious doubts on the reliability of the data of this bioequivalence study:

- The reported PK profiles for free doxorubicin and doxorubicinol of several subjects were found to be exceptionally similar. From the verification done during inspection it was apparent that study samples could not have been mixed-up accidentally. The similarities of the profiles were of such extent that they could not be explained and there were serious doubts whether the reported concentrations of the subjects originated from these.
- During the inspection, study personnel intentionally documented the wrong room temperature in order to pretend that room temperature in the sample processing area was within the acceptance range.

The severity and the extent of the findings of the inspection of BASG and BfArM raise serious concerns relating to the suitability of the quality management system at Panexcell Clinical Laboratories Priv. Ltd. and about the overall reliability of the data generated by this CRO since the set-up of the site under the name Panexcell Clinical Laboratories Priv. Ltd., and submitted to support the marketing authorisation applications for medicinal products in the EU.

On 19 February 2020 Germany (BfArM) therefore triggered a referral under Article 31 of Directive 2001/83/EC and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of products which have been authorised in the EU on the basis of clinical trials performed at Panexcell Clinical Laboratories Priv. Ltd. since the set-up of the site under the name Panexcell Clinical Laboratories Priv. Ltd., or pending approval, and issue a recommendation as to whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

In applications for generic medicinal products under Article 10(1) of Directive 2001/83/EC, the concept of bioequivalence is fundamental. The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a reference medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product.

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 of patients to the active substance, leading potentially to a decrease in efficacy, a delay or even a lack of therapeutic effect.

In view of the severity and the extent of the findings of the joint GCP inspection of BASG and BfArM at Panexcell Clinical Laboratories Priv. Ltd. casting serious concerns about the suitability of the quality management system at Panexcell Clinical Laboratories Priv. Ltd. and the overall reliability of the data generated by this CRO and submitted to support the marketing authorisation applications for medicinal products in the EU, the data from all bioequivalence studies performed at Panexcell Clinical Laboratories Priv. Ltd. and submitted to the Competent Authorities to demonstrate bioequivalence of medicinal products with their originator are considered unreliable.

In the absence of reliable data demonstrating bioequivalence with an EU reference medicinal product, the benefit-risk balance of the products either authorised or seeking a marketing authorisation based only on data generated at Panexcell Clinical Laboratories Priv. Ltd. to demonstrate the bioequivalence could not be considered positive, as the possibility of safety/tolerability or efficacy issues cannot be excluded.

2.2. Clinical aspects

In order to demonstrate a positive benefit-risk balance of the concerned medicinal products, the marketing authorisation holders (MAHs) and applicants of the products concerned by this procedure were invited to comment on the impact of the above on their marketing authorisation(s) or application(s) and provide evidence of bioequivalence (e.g. bioequivalence trials) with the EU reference medicinal product using alternative data.

The submissions received from the MAHs and applicants for products are summarised below per INN.

2.2.1. Iron Sucrose

Baxter, the MAH of iron sucrose medicinal products listed in Annex I (FER BAXTER 20 mg/mL, Eisen Sucrose Baxter 20 mg/mL, Iron sucrose 20 mg/mL), conducted a detailed reanalysis of the study data of the bioequivalence study performed at Panexcell to support the marketing authorisation of iron sucrose. The MAH did not detect any pattern of repeating values (descriptive statistics, regression analysis, cluster analysis, discrete uniform distribution test, comparison of PK parameters, pharmacokinetic and statistical analyses of serum concentrations versus time profiles) and was of the view that the findings regarding Panexcell related to doxorubicin should not give rise to questions concerning the continuing validity of Baxter´s iron sucrose marketing authorisations. Moreover, the MAH argued that quality and non-clinical data which were not performed by Panexcell showed essential similarity of test and reference product. In addition, the MAH claimed that the data analysis techniques employed for fraud detection were unable to detect any clear anomalies in the data and that their investigations did not reveal any indications of fraud or misconduct by Panexcell Clinical Laboratories Priv. Ltd.

Moreover, the MAH submitted data on a recent bioequivalence study conducted in the US with the US reference product according to FDA requirements.

The arguments of the MAH were carefully considered. It is acknowledged that the quality data, namely characterization studies, and the non-clinical data provided to support the similarity of iron sucrose to the reference product did not originate from Panexcell. However, the clinical study submitted to demonstrate bioequivalence vis-à-vis the EU reference product was conducted utilizing the services of Panexcell. In light of the nature, the seriousness and extent of the inspection findings identified during the joint BASG and BfArM inspection, all data generated at Panexcell Clinical Laboratories Priv. Ltd. is considered unreliable and no review or audit of unreliable data can be used to address the concerns. In addition, results from bioequivalence studies using non-EU reference medicinal products cannot be accepted for demonstrating said bioequivalence.

In conclusion, the data submitted to support the marketing authorisation do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product foreseen in Article 10 of Directive 2001/83/EC and, in the absence of demonstration of the bioequivalence, the efficacy and safety of the medicinal product of iron sucrose has not been established. Therefore, the benefit-risk balance cannot be considered positive.

2.2.2. Amoxicillin

Based on the review of the study, performed at Panexcell Clinical Laboratories Priv. Ltd., which was submitted to support the marketing authorisation of their amoxicillin 500 mg capsule product, the MAH, Almus, claimed that the said study was satisfactory and provided evidence of the bioequivalence of their product with the EU reference medicinal product. The MAH did not present any alternative bioequivalence data generated elsewhere than at Panexcell Clinical Laboratories Priv. Ltd..

The MAH also highlighted that the observations made by the Austrian and German competent authorities in the 2019 joint inspection had not been observed in another inspection carried out at the same CRO by another EU Competent Authority in 2017. Therefore, the MAH claims that the bioequivalence study conducted at Panexcell Clinical Laboratories Priv. Ltd. could be relied upon to support the marketing authorisation of their product.

The arguments of the MAH were carefully considered. However, the findings observed during the BfArM and BASG 2019 joint inspection are considered to reflect broader serious concerns regarding corporate culture and quality management. These can affect all areas of trial conduct and are, because of their nature, either difficult to identify or not possible to detect during an inspection. Considering the nature, the severity and the extent of the joint inspection findings, it is considered that any other inspection performed in the past at the site would not provide sufficient reassurance since they may not have detected serious GCP violations, even if present.

Hence, the CHMP cannot rule out beyond reasonable doubt that critical GCP violations at the site have affected the said studies and is of the opinion that the studies cannot be relied upon to establish bioequivalence vis-à-vis the EU reference medicinal product. Therefore, the arguments presented by Almus do not demonstrate that the study performed at Panexcell Clinical Laboratories Priv. Ltd., submitted to support the marketing authorisation of their amoxicillin 500 mg capsule product, can be relied upon.

In conclusion, the data submitted to support the marketing authorisation do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product foreseen in Article 10 of Directive 2001/83/EC and, in the absence of demonstration of the bioequivalence, the efficacy and safety of the medicinal product has not been established. Therefore, the benefit-risk balance cannot be considered positive.

2.2.3. Other products

For the rest of products (i.e. atazanavir, azithromycin, carbocisteine, trimethoprim) included in the referral, the MAHs and applicants have not responded to the request of the CHMP to provide evidence of bioequivalence with the EU reference medicinal product based on data generated elsewhere than at Panexcell Clinical Laboratories Priv. Ltd..

In light of the nature, the seriousness and extent of the inspection findings identified during the joint BASG and BfArM inspection, the CHMP considers that the data generated at Panexcell Clinical Laboratories Priv. Ltd., do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product foreseen in Article 10 of Directive 2001/83/EC. Therefore, in the absence

of demonstration of bioequivalence, the CHMP considers that the efficacy and safety of the medicinal products concerned cannot be established and hence the benefit-risk balance cannot be considered positive.

2.3. Response from the contract research organisation (CRO)

The CRO Panexcell Clinical Laboratories Priv. Ltd. was invited to submit any relevant and substantiated information to be considered by the CHMP when determining the impact of the inspection findings on the benefit-risk balance of medicinal products authorised, as well as for pending marketing authorisation applications, on the basis of trials performed since the set-up of the site under the name Panexcell Clinical Laboratories Priv. Ltd..

In response to the CHMP questions, the CRO provided additional information on the two critical findings identified during the inspection.

Panexcell Clinical Laboratories Priv. Ltd. acknowledged that the reported PK profiles of several subjects were exceptionally similar and argued that there was not enough plasma available at Panexcell Bioanalytical Laboratory to perform additional analyses and hypothesized that the root cause could lie with the subcontractor CRO/investigator sites.

However, according to the clinical study report and to the method validation protocols, and considering the ISR analysis, even if a sample analysis was to be repeated, there would have been enough plasma available at the bioanalytical laboratory to perform several further analyses. Based on the above, the conclusion drawn by the CRO that the samples could, due to a lack of remaining plasma, not be additionally analysed/be wrongly assigned at Panexcell/Bioanalytical Laboratory is not accepted. The hypothesis that the subcontractor CRO/investigator sites mixed up/relocated the samples is also not supported as the affected investigator sites were geographically located away from each other and the samples directly shipped from the sites to Panexcell Clinical Laboratories Priv. Ltd..

Regarding the finding that a study personnel intentionally documenting the wrong room temperature in order to pretend that room temperature in the sample processing area was within the acceptance range, Panexcell argued that this represented a failure of a single person and provided information regarding corrective and preventive actions, including re-training on the standard operating procedure and installation of an online recording system.

In this regard, the CHMP considered that, as reflected in the inspection report, the deliberate documentation of wrong data during the inspection raises serious concerns on the corporate culture and the quality management system of the CRO, and that any corrective and preventive actions (CAPAs) implemented after the Austrian and German inspection could not retrospectively correct the quality system failures observed during this inspection.

The CRO also referred to previous inspections performed by other EU competent authorities.

However, the CHMP noted that, according to the inspection report, the findings observed during the BfArM and BASG 2019 joint inspection are considered to reflect broader serious concerns regarding corporate culture and quality management. These can affect all areas of trial conduct and are, because of their nature, either difficult to identify or not possible to detect during an inspection. Considering the nature, the severity and the extent of the joint inspection findings, it is considered that any other inspection performed at the site would not provide sufficient reassurance since they may not have detected serious GCP violations, even if present.

Overall, the CRO did not provide any new information that changed the conclusions drawn by the inspection teams.

3. Conclusions

The severity and the extent of the findings of the inspection of BASG and BfArM raise serious concerns about the suitability of the quality management system at Panexcell Clinical Laboratories Priv. Ltd. and the overall reliability of the data generated by this CRO and submitted to support the marketing authorisation applications for medicinal products in the EU. The data from all bioequivalence studies performed at Panexcell Clinical Laboratories Priv. Ltd. since the set-up of the site under the name Panexcell Clinical Laboratories Priv. Ltd. and submitted to the Competent Authorities to demonstrate bioequivalence of medicinal products with their originator are considered unreliable.

In the absence of reliable data demonstrating bioequivalence with a EU reference medicinal product, the benefit-risk balance of the products either authorised or seeking a marketing authorisation based only on data generated at Panexcell Clinical Laboratories Priv. Ltd. to demonstrate bioequivalence could not be considered positive, as the possibility of safety/tolerability or efficacy issues cannot be excluded.

Although it is acknowledged that audits or inspections carried out in the past at Panexcell Clinical Laboratories Priv. Ltd., India, may have had positive outcomes, the findings observed during the BfArM and BASG 2019 joint inspection are considered to reflect broader problems concerning corporate culture and quality management. These can affect all areas of trial conduct and are, because of their nature, either difficult to identify or not possible to detect during an inspection. Considering the nature, the severity and the extent of the joint inspection findings, any other inspection performed at the site would not provide enough reassurance since they may not have detected serious GCP violations, even if present. Therefore, it is considered that these arguments do not demonstrate that the said studies can be relied upon. The CHMP cannot rule out beyond reasonable doubt that critical GCP violations at the site have affected the said studies and is of the opinion that the studies cannot be relied upon to establish bioequivalence vis-à-vis the EU reference medicinal product.

Results of a bioequivalence study conducted in the US with the US reference product have been provided. According to Article 10 of Directive 2001/83/EC, the bioequivalence needs to be established vis-à-vis an EU reference medicinal product. Results from bioequivalence studies using non-EU reference medicinal products can therefore not be accepted for demonstrating said bioequivalence.

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 and therefore, the benefit-risk balance cannot be considered positive. The CHMP therefore recommends the suspension of the marketing authorisations for all medicinal products concerned by this referral procedure.

For marketing authorisation applications included in this review, the CHMP considers that, for the reasons explain above, the applicants did not submit information which allows to establish bioequivalence to the EU reference medicinal product, and therefore the marketing authorisation applications do not currently fulfil the criteria for authorisation.

4. Condition for lifting the suspension of the marketing authorisations

For the suspension of the marketing authorisations referred to in Annex I to be lifted, the competent authorities of the EU Member States shall ensure that the below condition has been completed by the marketing authorisation holder(s):

- Bioequivalence vis-à-vis an EU reference medicinal product has been demonstrated, 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).

5. Grounds for opinion

Whereas,

- The CHMP 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 Panexcell Clinical Laboratories Priv. Ltd., located in Navi Mumbai, India, since the set-up of the site under the name Panexcell Clinical Laboratories Priv. Ltd.;
- The CHMP reviewed available data and information provided by the MAHs and applicants, as well as information provided by Panexcell Clinical Laboratories Priv. Ltd.;
- The CHMP considered that the alternative bioequivalence data or justifications submitted in support of the marketing authorisations for iron sucrose or amoxicillin were insufficient to establish bioequivalence vis-à-vis the EU reference medicinal product. In addition, the CHMP considered that Panexcell Clinical Laboratories Priv. Ltd. did not provide any new information that changed the conclusions drawn by the inspection teams;
- The CHMP 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 all authorised medicinal products and marketing authorisation applications listed in Annex I;
- 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 I) should be suspended, as the particulars supporting the marketing authorisations are incorrect and the benefit-risk balance of these marketing authorisations 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 is set out in section 4 of this report.

    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 I) 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.