EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2017
EMA/420215/2017
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Referral under Article 31 of Directive 2001/83/EC

Medicinal products for which clinical and bioanalytical parts of the bioequivalence studies were performed at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6, Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India and Micro Therapeutic Research Labs Pvt. Ltd, No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India

Procedure number(s): EMEA/H/A31/1450
Tadalafil Mylan EMEA/H/A31/1450/C/003787/0005

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

Critical findings were identified following GCP inspections by the Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) from 8-12 February 2016 at Micro Therapeutic Research Labs Pvt. Ltd Rajam Bhavanam, No. 6 , Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059, India.

In addition, a study performed at the Micro Therapeutic Research Labs Pvt. Ltd site in Coimbatore (No. 29 A, Krishna Madhuravanam, Vellokinar Pirivu, Thudiyalur, Coimbatore-641029, Tamil Nadu, India) was inspected. Both the Chennai site and the Coimbatore site follow the same provisions and QA activities and are headed by the same supervisor.

The findings reported during the inspection cast serious doubts on the reliability of the data of bioequivalence studies (clinical and bioanalytical part) conducted at the sites inspected:

- The ECG-recordings in a number of independent studies showed inconsistencies which are concluded to be intentional misrepresentation of (study) data (critical finding).
- GCP non-compliant documentation practices have been observed for different study data including the practice to generate source data retrospectively, documentation of incorrect information, overwriting and changing raw data without ensuring the readability of the initial entry and the practice to apply implausible changes without giving a sound justification.
- Other aspects on which GCP non-compliant issues were detected included the procedures on verification of subject identity, the insufficient validation of the computerised system used by the site to capture volunteer information, non-completeness of the TMF/SMF, IMP (shipped to site before approval) and the QMS e.g. standard procedures on (re-)archiving and the process of reconciliation of (QA-issued) study forms, leading to used forms ending up in the unused-forms section and thus not taken into account in clinical study report (CSR) writing.

The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016 (submission of corrective and preventive actions (CAPAs)).

Between 1st and 14th December 2016 the National Competent Authorities of Austria, Bulgaria, Croatia, Denmark, Estonia, Finland, Germany, Hungary, Iceland, Latvia, Norway, Romania, Slovakia, Slovenia, Spain, Sweden, The Netherlands and United Kingdom requested the initiation of 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 medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended, revoked or the applications not to be granted.

# 2. Scientific discussion

## *2.1. Introduction*

Bioequivalence (BE) is crucial 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.

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.

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

Circumstantial evidence has been submitted and considered that could potentially support the positive benefit-risk balance of a product even in the absence of convincing biowaiver data or data from a bioequivalence study with an EU Reference Medicinal conducted according to Good clinical practice (GCP) standards. This included a number of audits and inspections carried out at Micro Therapeutic Research Labs Ltd.; plausibility of results and controls of data integrity by MAHs; pharmacovigilance data on specific products included in this procedure.

For some medicinal products, results from bioequivalence data using non-EU Reference Medicinal Products are available. Under Article 10(1) of Directive 2001/83/EC, these data are not acceptable to support a positive benefit-risk balance for the concerned products and cannot substitute for the requirement of showing bioequivalence between test product and a suitable EU reference product.

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 concerns cannot be excluded.

The submissions from the MAHs/applicants for medicinal products affected by this procedure are summarised below per active substance or combination of active substances in alphabetical order.

### 2.1.1. Amlodipine / Valsartane

The MAHs who responded decided to immediately repeat the bioequivalence study at another CRO after reading the critical inspection findings of the February 2016 audit as well as the response provided by Micro Therapeutic Research Labs Ltd, for the study in question, against each observation cited by the Dutch and Austrian authorities. The MAHs acknowledge that the routine monitoring of the clinical phase of the said study conducted by them did not encompass thorough evaluation of all the aspects cited in the observations. As a precaution, the MAHs decided to repeat the BE study. It has to be noted that the use of a non-EU reference (and test) product is not considered acceptable to draw

conclusions regarding bioequivalence versus the EU reference medicinal product. Presently, neither a timetable for the new bioequivalence study has been provided nor have data of this new bioequivalence study yet been submitted. As such, it is still not proven that the concerned medicinal products are bioequivalent to the EU reference medicinal product. Therefore, the efficacy and safety of medicinal products within the scope of this procedure containing Amlodipine/Valsartan 5mg/80mg, 5mg/160mg, 10mg/160 mg, film-coated tablets are considered questionable and cannot be regarded as established. As long as bioequivalence has not been established based on new convincing and reliable bioequivalence data, the marketing authorisations should be suspended and marketing authorisation applications cannot be granted.

For other amlodipine/valsartan-containing medicinal products within the scope of this procedure and for which no response by the MAHs/Applicants has been submitted, the bioequivalence to the EU reference medicinal product is therefore not considered as established. Hence, the marketing authorisation should be suspended and marketing authorisation applications based on these studies cannot be granted.

### 2.1.2. Bendroflumethiazid

The MAH is of the opinion that the study in question was performed in accordance with GCP, Good laboratory practice (GLP) and all applicable local and EU regulatory guidelines and ethical guidelines and that the validity of the study is still upheld. They also refer to their own monitoring of the study in which no inconsistencies were found and to the response of the Micro Therapeutic Research Labs, a study specific assessment of the impact of the EMA inspection findings on the benefit-risk balance of the product Bendroflumetiazid Alternova. Based on that analysis, the MAH concludes that the integrity of the study is still upheld.

Furthermore, the MAH states that for confirmation of the positive risk-benefit balance of the product, another bioequivalence study was submitted to EMA in December 2014 during the Article 31 Referral on GVK Biosciences. This study confirmed bioequivalence between Bendroflumetiazid Alternova 2.5 mg tablets and the European reference medicinal product, and was accepted by EMA and the Medical Products Agency of Sweden. It was acknowledged that the results of this study could be extrapolated to the 5 mg strength due to linear pharmacokinetics of bendroflumethiazide in the 2.5 - 5 mg dose range.

Nevertheless, the MAH commits to perform a new bioequivalence study depending on the outcome of this referral in order to confirm beyond doubt the bioequivalence (and therefore substitutability) between the products Bendroflumetiazid Alternova and EU reference medicinal product.

The Medical Products Agency of Sweden has confirmed that the information from the MAH is correct: the MTR bioequivalence study is not considered pivotal, but was submitted only in order to obtain generic substitution in Sweden. The other bioequivalence study that the MAH referred to has been assessed during the Article 31 Referral for GVK Biosciences and was concluded to be acceptable. Therefore no further regulatory action is recommended and the MA is maintained.

### 2.1.3. Betahistine

The information submitted by the MAHs/Applicants, is considered insufficient to establish a positive benefit-risk balance of the medicinal product in the absence of the demonstration of bioequivalence with the EU reference medicinal product. Therefore, efficacy and safety of the betahistine tablets are

considered questionable and cannot be regarded as established. The MAHs/Applicants should provide convincing and reliable bioequivalence data; until then the marketing authorisation should be suspended and marketing authorisation applications based on these studies cannot be granted.

For other betahistine-containing medicinal products within the scope of this procedure, no response has been submitted. Bioequivalence to the EU reference medicinal product is therefore not considered established. Hence, the marketing authorisation should be suspended and marketing authorisation applications based on these studies cannot be granted.

### 2.1.4. Bupropion

The MAH Sandoz decided to perform new bioequivalence studies at a CRO, which is qualified and audited according to GCP current guidelines and has a proven positive recent inspection history. The process is ongoing and according to the MAH/Applicant Sandoz the new BE studies are scheduled for the last quarter 2017 at latest. It is acknowledged that the MAH/Applicant Sandoz decided to repeat the BE study. In addition other MAHs than Sandoz informed that these tablets have not been launched on the market. However, as long as no new convincing and reliable bioequivalence data are provided, marketing authorisations of all these products should be suspended, as efficacy and safety of these tablets are considered questionable and cannot be regarded as established. The current MAA in Luxembourg submitted by Sandoz cannot also be granted based on the studies performed at the affected sites during the concerned time period.

For other bupropion hydrochloride-containing medicinal products for which no response has been submitted, bioequivalence to the EU reference medicinal product is not considered as established. Hence, the marketing authorisations should be suspended.

### *2.1.5.* Carbimazole

One Applicant is still considering their study as valid. This is mainly based on an impact analysis prepared by MTR labs in which MTR responds to the critical findings observed at the inspection in February 2016 by the Dutch and Austrian authorities coming to the conclusion that the noticed deficiencies were not applicable for the study in question. In addition, the Applicant points out that only the clinical part was conducted at Micro Therapeutic Research Lab.

The Applicant's statement is not supported by the CHMP. The performed impact assessment has only focussed on the findings regarding ECG-recording, documentation practices and the procedures on verification of subject identity. However a complete review of all activities (e.g. incl. bioanalytical and statistical part) is considered necessary, to ensure the quality and integrity of data generated by MTR.

Due to the fact that the whole quality management system of the MTR site is considered to be not reliable, also a BE study with only the clinical part of the study conducted at MTR cannot be accepted as a valid proof of bioequivalence.

Therefore, in the absence of reliably proven bioequivalence, currently the efficacy and safety of the medicinal product have not been established. BE has to be adequately before a positive decision can be taken on the marketing authorisation applications.

### 2.1.6. Carbocisteine

The Applicant informed the EMA and member states that they withdrew their national applications. No further action is required.

### 2.1.7. Clindamycin

The MAH argued that the integrity of the BE study is upheld as it was performed, in its opinion, in accordance with GCP, GLP and all applicable local and EU regulatory guidelines and ethical guidelines. Furthermore, no inconsistencies were found during their own monitoring of the study. Nevertheless, the MAH commits to take proper action depending on the outcome of this referral. The information submitted by the MAH does not allow establishing bioequivalence versus the EU reference medicinal product and therefore the positive benefit risk balance of the medicinal product is unfavourable. The MAH should establish bioequivalence by providing convincing and reliable bioequivalence data; until then the marketing authorisation should be suspended.

### 2.1.8. Dicloxacillin

Orifarm Generics A/S is of the opinion that the study was performed in accordance with GCP, GLP and all applicable local and EU regulatory guidelines and ethical guidelines and hence, they conclude that the integrity of the study in question is still upheld. Nevertheless, Orifarm Generics A/S commits to have a new bioequivalence study performed depending on the outcome of this referral.

The MAH neither submitted new bioequivalence data to an EU reference Medicinal Product nor provided a rationale for a Biopharmaceutics Classification System (BCS)-based waiver, if applicable. The information submitted by the MAH is considered insufficient to maintain a positive benefit-risk balance of the medicinal product. As long as the bioequivalence is not established by providing convincing and reliable new bioequivalence data, marketing authorizations for Diclocacillin Alternova 250 and 500 mg hard capsules should be suspended.

### 2.1.9. Dutasteride

No response was submitted for dutasteride. The bioequivalence of the dutasteride-containing medicinal products within the scope of this procedure versus an EU reference medicinal product cannot be established and therefore the MA cannot be granted.

### 2.1.10. Etodolac

In 2014 the clinical and bioanalytical phase of the Study ETOD 1968-14 was performed at Micro Therapeutic Research Labs Private Limited, No.6, India. Nevertheless, the Applicant is of the opinion that the study was performed in accordance with GCP, GLP and all applicable local and EU regulatory guidelines and ethical guidelines concluding that the integrity of the study in question is still upheld.

Nevertheless, the Applicant committed to have a new bioequivalence study performed depending on the outcome of this referral. The current information submitted by the Applicant is considered

insufficient to establish bioequivalence versus the EU reference medicinal product and therefore for establishing a positive benefit risk balance of the medicinal product. The applications cannot be granted.

### 2.1.11. Gliclazide

Due to the concerns of the Dutch and Austrian Authorities the Applicant (Medreich) would repeat the bioequivalence study for their pending national MAA at a different CRO and submit a full study report once the study is completed. As long as no bioequivalence versus the EU reference medicinal product has been established by providing new convincing and reliable bioequivalence data, no marketing authorisation for the Gliclazide 40 and 80mg tablets should be granted.

For a different application, no response was provided. Bioequivalence to the EU reference medicinal product is therefore not considered as established for all these applications. Hence, the marketing authorisation should not be granted.

### 2.1.12. Hydrocortisone

The Applicants confirmed that the MTR study was only performed for the purpose of obtaining generic substitution. The overall risk-benefit balance of the product is therefore considered positive regardless of the validity of the bioequivalence study performed by MTR. The applications relate to Article 10a of Directive 2001/83/EC ('Well-established use').

The MTR study is not considered pivotal however 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.

### 2.1.13. Hydroxyzine

Summarizing the responses of the MAHs who replied, the concerns raised by the Austrian and Dutch authorities have been taken into account and therefore, the MAHs have decided to perform a new bioequivalence study at a new CRO. This new BE study is scheduled for the last quarter 2017 at latest. One MAH further submitted an additional evaluation and review of the bioequivalence data in question, concluding that the data integrity of the study is upheld and hence, that no market actions are deemed necessary at the current stage. In this context, bioequivalence versus the EU reference medicinal product cannot be considered demonstrated until the full clinical study report is available and assessed by the relevant competent authorities.

In the absence of having established bioequivalence versus the EU reference medicinal product, the marketing authorizations for the above-mentioned Hydroxyzine-containing medicinal products should be suspended.

For the medicinal products where no response was submitted the bioequivalence to the EU reference medicinal product is not established. Hence, the marketing authorisations should be suspended.

### 2.1.14. Ibuprofen

Addressing the concerns raised by the Austrian and Dutch authorities the MAHs carried out own investigations and study specific audits to investigate whether the studies used for the marketing authorisations suffered from inconsistencies, namely signs of intentional misrepresentation or signs of duplicated ECG's or manipulated chromatograms. The auditors did not find any signs of such inconsistencies. Therefore, the MAH/Applicant is of the opinion that the studies performed were in accordance with GCP, GLP and all applicable local and EU regulatory guidelines and ethical guidelines.

The CHMP did not consider that the above argumentation allow establishing bioequivalence versus the EU reference medicinal product and therefore concluded that the benefit-risk balance of these medicinal products is unfavourable.

Therefore, efficacy and safety of these ibuprofen 200, 400 and 600 mg film coated tablets are considered questionable and cannot be regarded as established any longer. The MAH should establish bioequivalence versus EU reference medicinal product by providing convincing and reliable bioequivalence data; until then the marketing authorisations should be suspended.

### 2.1.15. Irbesartan

HEC Pharm (Neuraxpharm Arzneimittel GmbH in Germany) submitted a GCP compliance assessment report regarding their study in question. Based on this the MAH still considers the BE data generated for this study as reliable. In view of the nature, the seriousness and extent of the critical GCP findings identified by the inspections of the Dutch and Austrian authorities, all data generated at Micro Therapeutic Research Labs Private Ltd, No. 6, India, during the concerned period are considered unreliable and no review or audit of unreliable data can be used to address and alleviate the concerns.

Therefore it is concluded that bioequivalence to the EU reference medicinal product for these irbesartan-containing medicinal products is not established. Establishment of bioequivalence versus the EU reference medicinal product should be established by providing convincing and reliable bioequivalence data; until then the marketing authorisations should be suspended.

### 2.1.16. Ethinylestradiol/Levonorgestrel

Some MAHs responses for these products did not include any bioequivalence studies, so BE to the EU reference medicinal product is not considered as established and the marketing authorisations should be suspended.

One different MAH provided *in vivo* results of a pilot study in order to support their claim of upholding the bioequivalence of their test product despite the concerns raised by the Dutch and Austrian authorities. However, the number of subjects (n=9) is too small for the pilot study to be accepted as support for bioequivalence, and no information on 90% CI is available. Meanwhile they perform a new BE study and they will submit the results from the new study as soon are these become available. Until that is done BE to the EU reference medicinal product is not considered as established and the marketing authorisations should be suspended and MA applications not granted.

## 2.1.17. Loperamide Hydrochloride

Based on a review of the study in question the Applicants are of the opinion that the integrity of the bioequivalence study is upheld.

The Applicants commit to take proper action during the national assessment depending on the outcome of this referral. The Applicants should provide new convincing and reliable bioequivalence data during the national procedures; no marketing authorisation can be granted on the basis of the MTR studies subject to the referral procedure.

One other Applicant did not provide responses. The bioequivalence to the EU reference medicinal product is therefore not considered as established. Hence, the marketing authorisation cannot be granted.

## 2.1.18. Memantine

The MAHs have submitted identical supporting data for the application of a BCS-based biowaiver. Their evaluation of the biowaiver is therefore applicable to all these biowaiver applications.

The MAHs acknowledged the inspection findings and hence would like to propose for a biowaiver request for memantine 10 and 20 mg Film-coated Tablets based on BCS-classification.

Based on solubility data and absorption/permeability characteristics, memantine meets all criteria for classification as BCS-class I since it exhibits high solubility and high permeability. Additionally, memantine is not considered to be a narrow therapeutic index drug. All requirements described in the Guideline on the Investigation of Bioequivalence[1] can be considered fulfilled for the 10 and 20 mg tablets. Thus, a BCS-based biowaiver approach for memantine 10 and 20 mg Film coated tablets is acceptable and marketing authorisations can be maintained.

## 2.1.19. Metformine hydrochloride

No response has been submitted by the Applicants. The bioequivalence to the EU reference medicinal product is therefore not considered as established. Hence, the marketing authorisation applications cannot be granted.

## 2.1.20. Metoclopramide

The MAH was of the opinion that the study was performed in accordance with GCP, GLP and all applicable local and EU regulatory guidelines and ethical guidelines and hence considers the integrity of the study in question still upheld. Nevertheless, the MAH commits to take proper action depending on the outcome of this referral.

In this context, bioequivalence cannot be considered demonstrated until the full clinical study report is available and assessed by the relevant competent authorities. As long as bioequivalence versus the EU reference medicinal product is established by means of convincing and reliable bioequivalence data, the marketing authorization for metoclopramide tablets should be suspended.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

### 2.1.21. Naproxen

In their response the MAHs confirmed that they have decided to repeat the bioequivalence study at another CRO after reading the critical inspection findings of the Dutch and Austrian authorities.

In this context, bioequivalence cannot be considered demonstrated until the full clinical study report is available and assessed by the relevant competent authorities. As long as bioequivalence versus the EU reference medicinal product is established by means of convincing and reliable bioequivalence data, the marketing authorizations for naproxen tablets should be suspended.

### 2.1.22. Olanzapine

The MAH submitted a GCP compliance assessment report regarding the BE study in question. Summarizing the response of the MAH, they still consider the BE data generated for this study as reliable.

The CHMP did not agree with the argumentation of the MAH and considered that bioequivalence versus the EU reference medicinal product is not established. The marketing authorisations should be suspended.

### 2.1.23. Omega-3-acid-ethyl esters 90

No response was submitted from the MAH and Applicant. The bioequivalence to the EU reference medicinal product is therefore not considered as established. Hence, the marketing authorisations should be suspended.

### 2.1.24. Paracetamol

The MAH Dawa Ltd. applied for a BCS-based biowaiver for these paracetamol-containing medicinal products concerned by this procedure.

The data submitted by this MAH indicate high solubility related to the maximum dose of 1000 mg. The proposed BCS classification in terms of absorption is sufficiently demonstrated.

The composition of the paracetamol 1000 mg test tablet was qualitatively compared with the reference medicinal product 1000 mg tablet. No relevant differences in excipients are noted. The lack of a quantitative comparison of the composition can be accepted, since paracetamol is a BCS class I product, no critical excipients potentially affecting paracetamol absorption are present in the formulations. Based on the review of the data on the BCS-based biowaiver and considering the data provided, bioequivalence of paracetamol 1000 mg film-coated tablets can be concluded and the marketing authorisations be maintained.

For the 500 mg tablet comparative dissolution data are lacking and a BCS-class biowaiver for the 500 mg test formulation cannot be granted. The provided data are considered insufficient to support a BCS-biowaiver for the 500 mg strength, as comparative dissolution data are lacking. As such, it is still not

proven that the 500 mg paracetamol medicinal product is bioequivalent to the EU reference medicinal product. Therefore, the efficacy and safety of the 500 mg paracetamol tablets are considered questionable and cannot be regarded as established any longer. The marketing authorisation holder should provide convincing and reliable bioequivalence data, otherwise the marketing authorisation should be suspended. Another MAH marketing paracetamol 500 and 1000 mg tablets did not provide data. As no response was submitted, the bioequivalence to the EU reference medicinal product is therefore not considered as established. Hence, the marketing authorisation should be suspended.

No response has been submitted by the Applicants. The bioequivalence to the EU reference medicinal product is therefore not considered as established. Hence, the marketing authorisation applications cannot be granted..

### 2.1.25. Perindopril/Indapamide

The MAHs committed to perform a new complete BE study report as per current EMA guidelines[1] for Perindopril/Indapamide Marketing Authorisations.

In this context, bioequivalence cannot be considered demonstrated until the full clinical study report is available and assessed by the relevant competent authorities. As long as bioequivalence versus the EU reference medicinal product is not established by providing convincing and reliable bioequivalence data, the marketing authorizations for Perindopril/Indapamida Combix tablets should be suspended.

Different MAHs did not submit any responses. As the bioequivalence to the EU reference medicinal product is not considered established, the marketing authorisations should be suspended.

### 2.1.26. Prednisolone

Based on a review of the study the MAH Alternova was of the opinion that the study was performed in accordance with GCP, GLP and all applicable local and EU regulatory guidelines and ethical guidelines. Thus, the MAH considers the integrity of the study in question still upheld. Nevertheless the MAH committed to take proper action after the outcome of this referral.

The CHMP concluded that the bioequivalence versus the EU reference medicinal product was not established. Hence, the marketing authorisation should be suspended.

### 2.1.27. Sodium cromoglicate

The MAH refers to an earlier conducted BE study, which was repeated because of a large number of drop-out/withdrawal of subjects. This study is acknowledged but based on the outcome of the study, failing the acceptance criterion for $C_{max}$, it cannot be accepted.

The MAH further states that only the clinical phase of new BE study was conducted at Micro Therapeutic Research Labs. However, due to the fact that the whole quality management system of the MTR site is considered to be not reliable, also a BE study with only the clinical part of the study conducted at MTR cannot be accepted as a valid proof of bioequivalence.

In addition, they point out that their product is the only generic product available on the market.

As long as bioequivalence versus the EU reference medicinal product is not established by providing convincing and reliable data, the marketing authorisation should be suspended.

The suspension of the marketing authorisation may be deferred by the concerned Member States if the medicinal product is considered critical, in accordance with the terms laid down in the CHMP opinion.

## 2.1.28. Tadalafil

For Tadalafil Mylan (EU procedure, centrally authorised product) two new bioequivalence studies (under fasting and fed conditions) for Tadalafil 20 mg Film-coated tablet were initiated which have been conducted at another CRO. The final study reports have been submitted. Based on the submitted bioequivalence studies, Tadalafil 20 mg Film-coated tablets and EU reference product are considered bioequivalent under fasting and fed conditions and the marketing authorisation should be maintained.

For all other tadalafil MAHs new convincing and reliable bioequivalence data need to be provided; until then the marketing authorisation for those Tadalafil 2.5 /5 /10 /20 mg film coated tablets should be suspended.

## 2.1.29. Tianeptine

Zydus France has informed the EMA that Tianeptine Zydus 12.5 mg, coated tablet is currently not marketed and has no intention to market this product in the future.

The CHMP took note of this statement. As no bioequivalence versus the EU reference medicinal product has been established, the MA should be suspended.

## 2.1.30. Ursodeoxycholic acid

The applicant Substipharm development submitted a monitoring report and an expert assessment and is of the opinion that the integrity of their bioequivalence study is upheld.

However, the CHMP concluded that the Applicant did not establish bioequivalence versus the ER reference medicinal product by providing new convincing and reliable data. As a consequence the marketing authorisations should not be granted based on these MTR studies.

## 2.1.31. Voriconazole

Some of the MAHs/Applicants decided to repeat the bioequivalence study at another CRO after reading the critical inspection findings of the Dutch and Austrian authorities.

In this context, bioequivalence cannot be considered demonstrated until the full clinical study report is available and assessed by the relevant competent authorities. As long as no bioequivalence versus the EU reference medicinal product is established by providing convincing and reliable data, the marketing authorization of voriconazole 50 and 200mg film-coated tablets should be suspended and marketing authorisation applications should not be granted.

A different MAH did not submit response. As bioequivalence versus the EU reference medicinal product is not established their marketing authorisation(s) should be suspended.

### 2.1.32. Other products

For all other products included in the referral, no data or justification was submitted. The CHMP considered that the bioequivalence to the EU reference medicinal product is therefore not established.

# 3. Responses from contract research organisation (CRO)

In their response to the CHMP List of Questions, the CRO MTR argued that studies performed after January 2015 should not be included in the Article 31 procedure.

This request is based on the fact that the first on site procedural changes have been implemented in January 2015. However, since corrective and preventive actions (CAPAs) were not completely implemented before July 2016 and MTR did not provide any new documented evidence and so the conclusions drawn by the inspection teams are not changed.

The implementation of corrective actions to ensure consistent GCP compliant recording of ECGs was completed in early 2016. The demonstrated decrease in documentation errors since 2015 doesn't mitigate other deficient documentation practices, like the practice of retrospective generation of raw data and the documentation of incorrect information. Relevant trainings were done by MTR only in May and July 2016. The software update of the volunteer management system done in 2015 was insufficient and the software was updated again in June 2016.

The CAPAs initiated are triggered by the single findings described in the inspection reports and are focussed on the relevant aspects of the clinical operations. However a complete review of all activities (e.g. incl. bioanalytical and statistical part) is considered necessary to ensure the quality and integrity of data generated by MTR. As the main non-compliances to GCP were caused by a lack of management oversight and by absence of adequate quality assurance, MTR should ensure an adequate quality management system at all levels.

# 4. Conclusions and Benefit-risk balance

Bioequivalence (BE) is required for establishing 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 Good clinical practice (GCP) inspections 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.

Based on the submitted data during the procedure, for the medicinal products Tadalafil Mylan 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablets; Paracetamol DAWA 1000 mg film-coated tablets; Memantine Pharmascope 10 mg and 20 mg film-coated tablets; Memantine DAWA 10 mg and 20 mg film-coated tablets; Morysa 10 mg and 20 mg film-coated tablets (SVUS Pharma a.s.); Bendroflumetiazid Alternova 2.5 mg and 5 mg tablets; Sulfamethizole Alternova 500 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 MTR study is not considered pivotal – the concerned Member States will need to check that the requirements of Directive 2001/83/EC are fulfilled to grant or not a marketing authorisation.

The CHMP concluded that the bridging between the proposed medicinal product and the medicinal products described in the literature will not be compromised if the MTR bioequivalence study can no longer be used.

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 State(s) based 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.

For marketing authorisations of a medicinal product considered critical, the suspension may be deferred in the relevant EU Member State(s) 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.

# 5. Condition for lifting the suspension of the marketing authorisations

For the suspension of the marketing authorisations to be lifted, the competent authorities shall ensure that the below conditions have been completed by the marketing authorisation holders

- Bioequivalence vis-à-vis a valid 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).

# 6. Grounds for 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.

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