15 September 2022
EMA/878177/2022
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 studies performed at Synchron Research Services, a contract research organisation (CRO) located in Ahmedabad, Gujarat, India

Procedure number: EMEA/H/A-31/1515

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 United States (US) Food and Drug Administration (FDA) concluded in 2021 that all clinical and bioanalytical studies conducted by Synchron Research Services, a contract research organisation (CRO) located in Ahmedabad, Gujarat, India, were "not acceptable because of data integrity concerns", and that "the studies must be repeated", on the ground that inspections and analyses of study data indicated that the company was "responsible for the creation of false data" and that all studies conducted at that CRO were therefore "unacceptable"[1]. More concretely, the US-FDA recommendation is based on combination of the following:

- Outcome of US-FDA GCP inspection (18-22 November 2019):
  - The site failed to demonstrate that the analytical method used in an in vivo bioavailability or bioequivalence study, is accurate and of sufficient sensitivity to measure the actual concentration of the active drug in the body.
  - Significant pharmacokinetic (PK) data anomalies were observed across multiple studies conducted at the site.
- Analysis of study data generated at Synchron (pre- and post- GCP inspection):
  - multiple pairs of subjects with overlapping time-concentration profiles;
  - distinct groups of subjects where the T/R ratio for Cmax, AUC0-t, or AUC0-∞, among other parameters, for most subjects in the subgroups is above or below 1; or
  - study data having both the above concerns.
- Lack of adequate CRO responses to explain the study data and observations.

Similar concerns have been previously identified further to two EU inspections in 2005 and 2009, which, at the time, were treated as isolated non-compliance and data from the studies concerned were rejected.

The available information and data raise serious concerns related to the suitability of the quality management system and the overall reliability of data generated at Synchron and submitted to support marketing authorisation (applications) in EU Member States (MS).

Between 11th and 14th January 2022 Belgium, Denmark, Finland, The Netherlands, and Sweden 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 the medicinal products which have been authorised by the EU Member States on the basis of relevant trials performed at Synchron Research Services sites, as well as for pending procedures, and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

[1] Further information about FDA's action, including letters sent to Synchron are available on FDA's website.

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 not be within acceptable predefined limits. These limits are set to ensure comparable *in-vivo* performance, i.e. similarity in terms of safety and efficacy. If the bioavailability of the generic product is higher than the predefined upper limit, the bioavailability of the reference medicinal product 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 predefined lower limit, the bioavailability of the reference medicinal product 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.

In applications for hybrid medicinal products under Article 10(3) of Directive 2001/83/EC and for well established-used medicinal products under Article 10a of Directive 2001/83/EC, the need for bioequivalence studies is determined on a case-by-case basis. However, where it was considered to be fundamental to demonstrate equivalence with a reference medicinal product or with the medicinal product referred in the scientific literature submitted in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product or of the scientific literature submitted, the same principles apply.

In the absence of reliable data demonstrating bioequivalence with an EU reference medicinal product, or, for well-established use products, with the medicinal product referred in the scientific literature, the benefit-risk balance of the products either authorised or seeking a marketing authorisation based only on data generated at Synchron Research Services 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 serious concerns raised in relation to the suitability of the quality management system and the overall reliability of the data generated at Synchron 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.

Information received from the MAHs and applicants for their products and applications are summarised below per INN.

2.2.1. Alfacalcidol

The MAHs of Alfacalcidol 1 A Pharma/Sandoz and Alfacalcidol Hexal did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The MAH noted that a

marketing authorisation was granted for the same formulation under Article 10a of Directive No 2001/83/EC, and offered to provide the corresponding supportive documentation (i.e. literature data).

The CHMP noted that the present MAs were granted under Article 10(1) of Directive No 2001/83/EC, for which bioequivalence against the EU reference medicinal product must be demonstrated. It is not possible to switch legal basis for a marketing authorisation. The data mentioned would not be sufficient to demonstrate bioequivalence for the purpose of this marketing authorisation.

The MAH of Alfacalcidol Orifarm did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The MAH highlighted that only the clinical part and biostatistical evaluation were conducted by Synchron, whereas the bioanalysis was performed by another CRO. The MAH provided a GCP compliance statement regarding the study done at Synchron, and a summary of past inspections including positive outcomes. Therefore, the MAH claims that the bioequivalence study conducted at Synchron could be relied upon to support the marketing authorisation of their product.

The CHMP considered the information submitted by the MAH, i.e. reference to positive inspections, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services. Indeed, although the findings relate to the bioanalytical part of the studies, given the failure of the quality management system to prevent and detect their occurrences, failures in other areas of the trials (including clinical parts) cannot be excluded. It should also be noted that upper management is common to clinical and bioanalytical activities. Because of their nature, these issues either difficult to identify or not possible to detect during an inspection. 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 of the MAH do not demonstrate that the study performed at Synchron submitted to support the marketing authorisation of their alfacalcidol product can be relied upon.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for the alfacalcidol-containing products.

2.2.2. Amlodipine

The MAH Accord Healthcare referred to an alternative bioequivalence study conducted at a different facility (study 635-14, Lambda Therapeutic Research Ltd., No.), which has already been used to establish bioequivalence to the EU reference medicinal product for Almiden and some of their Amlodipine products further to a change in manufacturing site.

Having assessed the alternative study, the CHMP considered that it supports bioequivalence of these medicinal products to the EU reference medicinal product.

The MAH Wockhardt UK Limited did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The MAH highlighted that their product is authorised under Article 10(1) of Directive No 2001/83/EC, as an informed consent duplicate of the Jubilant Pharmaceuticals NV Amlodipine 5mg and 10mg Tablets which used to be authorised nationally in the United Kingdom.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for their amlodipine-containing products.

The MAH of Amlodipin Jubilant authorised under mutual recognition in Sweden and the Netherland referred to an alternative bioequivalence study conducted at a different facility (study AMLO/06/018,

Jubilant Clinsys Ltd), which was already used to establish bioequivalence to the EU reference medicinal product of their concerned products, in replacement of the study conducted at Synchron.

The CHMP concluded that the benefit-risk balance of this product was not affected by the concerns related to the studies performed by Synchron.

No information was provided by the MAH Strandhaven Limited (see also section on "other products").

2.2.3. Amoxicillin

The MAH Medreich PLC did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The MAH provided a summary of past inspections including positive outcomes and a letter from Synchron giving assurance that the study had been conducted to GCP and GLP standard as well as audited independently by their quality assurance team. Therefore, the MAH claims that the bioequivalence study conducted at Synchron could be relied upon to support the marketing authorisation of their product.

The CHMP considered the information submitted by the MAH, i.e. reference to positive inspections, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services. These issues 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. 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 of the MAH do not demonstrate that the study performed at Synchron submitted to support the marketing authorisation of their amoxicillin product can be relied upon.

Additionally, the MAH indicated that a BCS biowaiver may be applicable for amoxicillin, however the MAH is in the process of generating the data to substantiate this claim. While the active substance may be eligible for biowaiver, no formal request was submitted and the detailed information necessary to assess the appropriateness of a biowaiver was not made available. Finally, the MAH provided a bioequivalence study against the Australian reference medicinal product, performed at another CRO. The MAH stated that the reference product in the EU and Australia are similar, as they share the same qualitative composition and show similar dissolution profiles in various media.

The arguments of the MAH were considered, however the BE study provided does not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as per Article 10 of Directive 2001/83/EC. Therefore, CHMP concluded that bioequivalence to the EU reference medicinal product is not established for their amoxicillin-containing products concerned by this referral procedure.

No information was provided by the MAH Accord Healthcare Limited (see also section on "other products").

2.2.4. Amoxicillin/clavulanic acid

For the Bluefish Pharmaceuticals AB product, only the Co-amoxiclav Bluefish 500 mg/125 mg film-coated tablets strength is concerned by this procedure, as the bioequivalence of the higher strength (875mg/125mg) relies on data from another CRO.

The MAH Bluefish Pharmaceuticals AB did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The MAH provided a summary of past inspections including positive outcomes and a letter from Synchron giving assurance that the study had been conducted to GCP and GLP standard as well as audited independently by their quality assurance team. Therefore, the MAH claims that the bioequivalence study conducted at Synchron could be relied upon to support the marketing authorisation of their product.

The CHMP considered the information submitted by the MAH, i.e. reference to positive inspections, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services. These issues 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. 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 of the MAH do not demonstrate that the study performed at Synchron submitted to support the marketing authorisation of their amoxicillin/clavulanic acid product can be relied upon.

Further, the MAH provided a bioequivalence study between their product and the Australian reference medicinal product conducted at another CRO, based on which they consider their product to be bioequivalent to the Australian reference medicinal product.

The arguments of the MAH were considered, however the BE study provided does not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as per Article 10 of Directive 2001/83/EC. Therefore, CHMP concluded that bioequivalence to the EU reference medicinal product is not established for Co-amoxiclav Bluefish 500 mg/125 mg.

The MAH Medreich PLC did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The MAH provided a summary of past inspections including positive outcomes and a letter from Synchron giving assurance that the study had been conducted to GCP and GLP standard as well as audited independently by their quality assurance team. Therefore, the MAH claims that the bioequivalence study conducted at Synchron could be relied upon to support the marketing authorisation of their product.

The CHMP considered the information submitted by the MAH, i.e. reference to positive inspections, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services. These issues 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. 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 of the MAH do not demonstrate that the study performed at Synchron submitted to support the marketing authorisation of their amoxicillin product can be relied upon.

Additionally, the MAH indicated that a BCS biowaiver may be applicable for amoxicillin, however the MAH is in the process of generating the data to substantiate this claim. While the active substances may be eligible for biowaiver, no formal request was submitted and the detailed information necessary to assess the appropriateness of a biowaiver was not made available.

Finally, the MAH provided a bioequivalence study against the Australian reference medicinal product. The MAH stated that the reference product in the EU and Australia are similar, as they share the same qualitative composition and show similar dissolution profiles in various media.

The arguments of the MAH were considered, however the BE study provided does not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as per Article 10 of Directive 2001/83/EC. Therefore, CHMP concluded that bioequivalence to the EU reference medicinal product is not established for their amoxicillin-containing products concerned by this referral procedure.

The MAH Stewart Italia S.r.l. did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for Stemox.

No information was provided by the MAH Laboratórios Basi - Indústria Farmacêutica, S.A (see also section on "other products").

2.2.5. Atorvastatin

Two alternative bioequivalence studies from different CROs than Synchron have been submitted by the MAHs Mylan/McDermott Laboratories/Generics and Pensa Pharma AB:

- Study ATO/CR/249/11-12, used for the registration of the atorvastatin film coated tablets in the US using the reference product Lipitor Tablets (Pfizer Inc.). The MAH stated that the formulations of their product and of the reference medicinal product in the EU and the US were the same, therefore they consider that this study demonstrated bioequivalence to the EU RMP.
- Study C17412 performed against the EU reference medicinal product, but with a different test formulation. No information was provided on similarity of this formulation to the current authorised formulation (e.g. comparison of the quantitative and qualitative compositions or comparative in vitro dissolution profiles).

The arguments of the MAH were considered, however the BE studies provided do not address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as per Article 10 of Directive 2001/83/EC for their authorised products. Therefore, CHMP concluded that bioequivalence to the EU reference medicinal product is not established for their atorvastatin-containing products concerned by this referral procedure.

The MAH Pinewood Laboratories provided reports of past inspections including positive outcomes and a letter from Synchron giving assurance that their studies had been conducted to GCP and GLP standard as well as audited independently by their quality assurance team. Further, the MAH performed an in-depth for-cause audit review of all data associated with their Synchron BE studies. Additionally, a commissioned independent for-cause audit found the data of these two studies to be in compliance with GxP and data integrity expectations. The MAH also provided a bioequivalence study against the Brazilian reference medicinal product performed at another CRO. The MAH stated that the reference product in the EU and Brazil are similar, as they share the same qualitative composition, description, dimensions and average mass. According to the MAH this study, whilst not addressing the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as per Article 10 of Directive 2001/83/EC, further mitigates the data integrity or compliance concerns identified at Synchron and therefore provides confidence in their bioequivalence studies performed there. Overall, the MAH claims that the studies conducted at Synchron could be relied upon to support the marketing authorisation of their product.

Additionally, the MAH has 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, overdose or worsened safety and tolerability.

The CHMP considered the information submitted in writing and orally by the MAH, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the suitability of the quality management system and the overall reliability of all data generated at Synchron and no review or audit of unreliable data can be used to address the concerns. Indeed, although the findings relate to the bioanalytical part of the studies, given the failure of the quality management system to prevent and detect their occurrences, failures in other areas of the trials (including clinical parts) cannot be excluded. It should also be noted that upper management is common to clinical and bioanalytical activities. Because of their nature, these issues are either difficult to identify or not possible to detect during an inspection. 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. Considering that the concerns raised by the FDA, taken together with the observations in previous EU inspections of the site (2005 and 2009 inspections, which led to the rejection of the concerned studies), point towards a CRO system issue rather than isolated findings/cases, an at-risk period could not be defined. Likewise, a comparison between the EU and Brazilian products does 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, nor can provide reassurance regarding the conduct of another study. 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. In addition, 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. Therefore, the arguments of the MAH do not demonstrate that the studies performed at Synchron submitted to support the marketing authorisation of their atorvastatin product can be relied upon and the CHMP concluded that bioequivalence to the EU reference medicinal product is not established.

No information was provided by the MAHs Artespharm Sp. z o.o. and Amarox (see also section on "other products").

2.2.6. Azithromycin

The MAH referred to an alternative bioequivalence study conducted at a different facility (study BLCL-AZT-EU-01, Blueclinical), which was already used to establish bioequivalence of Azithromycin Heumann to the EU reference medicinal product in replacement of the study conducted at Synchron, further to a change in formulation.

The CHMP concluded that the benefit-risk balance of this product was not affected by the concerns related to the studies performed by Synchron.

2.2.7. Cinacalcet

The MAH of Cencipral did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for Cencipral.

2.2.8. Clobazam

The MAH of Clobazam Sandoz informed the CHMP that they did not have alternative bioequivalence data generated elsewhere than at Synchron Research Services.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for this clobazam-containing product.

No information was provided by the MAH TioFarma B.V. (see also section on "other products").

2.2.9. Clonazepam

The MAH of Clonazepam Sandoz informed the CHMP that they did not have alternative bioequivalence data generated elsewhere than at Synchron Research Services.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for this clonazepam-containing product.

No information was provided by the MAH TioFarma B.V. (see also section on "other products").

2.2.10. Dexamethasone

The MAH of Rexazon and Varcodes referred to an alternative bioequivalence study conducted with a 20mg strength at a different facility (study 19-VIN-0048, Veeda Research Ltd) which establishes bioequivalence to the EU reference medicinal product. The concerned authorised strength 2, 4 and 8 mg are manufactured by the same manufacturing process and the qualitative composition is the same. Appropriate in vitro dissolution data have been provided and the product can be classified as very rapidly dissolving, with more than 85% of the active substance dissolved within 15 minutes. The pharmacokinetics of dexamethasone can be considered dose-linear between 2 mg and 20 mg. However, the composition between the 2, 4, 8 mg and 20 mg strengths is not quantitatively proportional, and therefore this condition for a biowaiver of strengths is not fulfilled according to the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr. A BCS-based biowaiver is not applicable for an effervescent/soluble tablet, which is an oral solution at the time of administration. Waiving studies for oral solutions does not apply either since the reference medicinal product is not an oral solution. However, it is considered that this difference in quantitative composition between the 2, 4, 8 mg and 20 mg strengths will not cause differences in bioavailability as dexamethasone sodium phosphate is a BCS Class I substance exhibiting high solubility and complete absorption, the dosage system is rapidly dissolved prior to administration and the excipients are known to not affect bioavailability. The results of study 19-VIN-0048 with the 20 mg formulation can be extrapolated to the concerned authorised strengths of 2, 4 and 8 mg.

Therefore, CHMP concluded that bioequivalence to the EU reference medicinal product is established for the Rexazon and Varcodes 2, 4 and 8 mg products concerned by this referral procedure.

2.2.11. Dextromethorphan

The MAH of Bronchosedal Dextromethorphan and Iniston Tusiv did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The MAH preformed a retrospective review of the studies data and a review of post-marketing safety data which did not identify any patterns of events involving lack of efficacy. Therefore, the MAH claims that the bioequivalence study conducted at Synchron could be relied upon to support the marketing authorisation of their product.

The CHMP considered the information submitted by the MAH, i.e. retrospective study review and a review of pharmacovigilance data, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services and no review of unreliable data can be used to address the concerns. In addition, 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. Therefore, the arguments of the MAH do not demonstrate that the studies performed at Synchron submitted to support the marketing authorisation of their Bronchosedal Dextromethorphan and Iniston Tusiv products can be relied upon.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for their Bronchosedal Dextromethorphan and Iniston Tusiv products concerned by this referral procedure.

2.2.12. Dorzolamide

The MAHs Heumann Pharma GmbH & Co. Generica KG and Delorbis Pharmaceutica LS LTD referred to an alternative bioequivalence study conducted at a different facility (study DOR/2008, Department of Ophthalmology at Johannes Gutenberg-University Mainz), which was the sole basis to establish therapeutic equivalence to the EU reference medicinal product of their concerned products, for its initial marketing authorisation. The bioequivalence study performed at Synchron had failed to establish therapeutic equivalence.

The CHMP concluded that the benefit-risk balance of Dorzolamid Heumann and Zormid was not affected by the concerns related to the studies performed by Synchron.

2.2.13. Efavirenz

The MAH of Efavirenz Mylan provided a bioequivalence study against the Australian reference medicinal product performed at another CRO. Based on composition information and dissolution data, the MAH claims that both test and reference products are similar in the EU and Australia. Further, the MAH performed a risk assessment, noted that only the clinical part of their study was performed at Synchron and considers that the study could be relied upon to support the marketing authorisation of their product. The MAH intends nonetheless to perform a new bioequivalence study at another CRO.

The CHMP considered the information submitted by the MAH, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services and no review of unreliable data can be used to address the concerns. Indeed, although the findings relate to the bioanalytical part of the studies, given the failure of the quality management system to prevent and detect their occurrences, failures in other areas of the trials (including clinical parts) cannot be excluded. It should also be noted that upper management is common to clinical and bioanalytical activities. Because of their nature these issues are either difficult to identify or not possible to detect during an inspection. 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 of the MAH do not demonstrate that the studies performed at Synchron submitted to support the marketing authorisation of their efavirenz-containing product can be relied upon, nor address the requirement to demonstrate bioequivalence vis-à-vis an EU reference medicinal product as per Article 10 of Directive 2001/83/EC.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for Efavirenz Mylan.

2.2.14. Ethambutol

The MAH Brown & Burk UK Limited of the concerned Ethambutol film-coated tablets, did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The MAH highlighted that only the clinical part of the study was conducted at Synchron whereas analytical part of the study was conducted at another CRO. Considering that the findings at Synchron were primarily related to the analytical part, the MAH claims that the bioequivalence study conducted at Synchron could be relied upon to support the marketing authorisation of their product.

The CHMP considered the information submitted by the MAH, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services. Indeed, although the findings relate to the bioanalytical part of the studies, given the failure of the quality management system to prevent and detect their occurrences, failures in other areas of the trials (including clinical parts) cannot be excluded. It should also be noted that upper management is common to clinical and bioanalytical activities. 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 of the MAH do not demonstrate that the study performed at Synchron submitted to support the marketing authorisation of their product can be relied upon.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for the ethambutol-containing products.

2.2.15. Etodolac

The MAH of Etolyn did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The MAH provided reports of past inspections including positive outcomes, and monitoring reports. Further, the MAH did not identify report of ineffectiveness in a review of post-marketing safety data. Therefore, the MAH claims that the bioequivalence study conducted at Synchron could be relied upon to support the marketing authorisation of their products.

The CHMP considered the information submitted by the MAH, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services and no review of unreliable data can be used to address the concerns. These issues 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. 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. In addition, 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. Therefore, the arguments of the MAH do not demonstrate that the studies performed at Synchron submitted to support the marketing authorisation of their Etolyn products can be relied upon.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for these Etolyn products concerned by this referral procedure.

2.2.16. Flucloxacillin

The MAH Sandoz A/S informed the CHMP that they did not have alternative bioequivalence data generated elsewhere than at Synchron Research Services.

The MAH Medreich PLC did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The MAH provided a summary of past inspections including positive outcomes and a letter from Synchron giving assurance that the study had been conducted to GCP and GLP standard as well as audited independently by their quality assurance team. Therefore, the MAH claims that the bioequivalence study conducted at Synchron could be relied upon to support the marketing authorisation of their product. The MAH nevertheless intends to perform a new bioequivalence study at another CRO.

The CHMP considered the information submitted by the MAH, i.e. reference to positive inspections, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services. These issues 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. 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 of the MAH do not demonstrate that the study performed at Synchron submitted to support the marketing authorisation of their amoxicillin product can be relied upon.

Therefore, CHMP concluded that bioequivalence to the EU reference medicinal product is not established for flucloxacillin-containing products concerned by this referral procedure.

2.2.17. Gliclazide

The MAH Brown & Burk UK Limited, did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services. The MAH highlighted that only the clinical part of their six studies was conducted at Synchron whereas analytical parts of the studies were conducted at another CRO. Considering that the findings at Synchron were primarily related to the analytical part, the MAH claims that the bioequivalence studies conducted at Synchron could be relied upon to support the marketing authorisation of their product.

The CHMP considered the information submitted by the MAH, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services. Indeed, although the findings relate to the bioanalytical part of the studies, given the failure of the quality management system to prevent and detect their occurrences, failures in other areas of the trials (including clinical parts) cannot be excluded. It should also be noted that upper management is common to clinical and bioanalytical activities. 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 of the MAH do not demonstrate that the studies performed at Synchron submitted to support the marketing authorisation of their product can be relied upon.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for the gliclazide-containing products.

2.2.18. Hydrocortisone

For Hydrokortison Orifarm authorised under Article 10a of Directive 2001/83/EC ('Well-established use'), the study performed at Synchron with the 10 mg tablet was submitted in the post-authorisation phase to allow generic substitution in Sweden. An additional study was performed at a different CRO for the substitution of the 20mg tablet.

The CHMP concluded that the benefit-risk balance of this product was not affected by the concerns related to the studies performed by Synchron.

No information was provided by the applicant Blackrock Pharmaceuticals Limited and MAH Silicon Pharma Limited (see also section on "other products").

2.2.19. Ibuprofen

The MAH US Pharmacia Sp. z o.o. did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services but informed of their intention to conduct a new bioequivalence study at another CRO. The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for this ibuprofen-containing product.

The MAH of Ibuprofen Bril and Ibuprofen BrillPharma referred to two studies assessed during the initial marketing authorisation application. A study performed at a different CRO (study UK/05/012, Accutest Lab), which had not been considered to provide adequate evidence of bioequivalence, as well as a study performed at Synchron, with stereospecific analysis, to address the requirements of the guideline in force at the time. Based on two independent reviews of the pharmacokinetic and statistical data generated at Synchron, the MAH claimed that bioequivalence is demonstrated. Reference was also made to ibuprofen being a BCS class II substance and the MAH claims that in-vitro dissolution data demonstrate that ibuprofen is rapidly dissolved which would give confidence to the outcome of the study performed at Synchron. The MAH highlighted that the study preformed at Synchron has been previously inspected with a positive outcome and claims that it could be relied upon to support the marketing authorisation of their products.

Further, the MAH did not identify any new trend in reporting of cases pertaining to lack of efficacy in a review of post-marketing safety data.

The CHMP considered the information submitted by the MAH, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services and no review of unreliable data can be used to address the concerns. These issues 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. 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. In addition, 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. Therefore, the arguments of the MAH do not demonstrate that the studies performed at Synchron submitted to support the marketing authorisation of their ibuprofen products can be relied upon.

Further, the concerns identified by the NCA at time of the initial marketing authorisation regarding the Accutest Lab study remained. The t_{max} of the test and reference medicinal products was not similar

enough, and thus the study does not allow to exclude that the active S-enantiomer would be non-bioequivalent. An assessment of matrix effect and incurred sample analysis were also not provided.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for Ibuprofen Bril and Ibuprofen BrillPharma.

No information was provided by the applicants PharmConsul s.r.o., Strides Pharma (Cyprus) Limited, Fair-med Healthcare GmbH and Strides Pharma UK Limited (see also section on "other products").

2.2.20. Ibuprofen/paracetamol

The applicants Socium Pharma B.V., Stada Arzneimittel AG, Pharmamatch BV and Interdos Pharma B.V. did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services but informed of their intention to conduct a new bioequivalence study at another CRO.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for all ibuprofen/paracetamol applications concerned by this procedure.

2.2.21. Ibuprofen/pseudoephedrine

The applicants Socium Pharma B.V., PharmaMatch B.V. and the MAH Stada Arzneimittel AG as well as the MAHs for BoxaGrippal and Ibuprom Zatoki Sprint did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services but informed of their intention to conduct a new bioequivalence study at another CRO.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for those applications and authorised products.

No information was provided by the applicants Clonmel Healthcare Ltd and Synoptis Pharma Sp. z o.o. (see also section on "other products").

2.2.22. Isosorbide mononitrate

For Farmidur, only the 30 mg prolonged release tablets are concerned by the procedure as the bioequivalence of the 60 mg strength was supported by studies performed at another CRO.

The MAHs of did not present alternative bioequivalence data generated elsewhere than at Synchron Research Service for the Farmidur 30 mg strength, or Isonova. The MAH provided a summary of past inspections including positive outcomes and noted that no significant inconsistencies were observed through study monitoring at the time of its conduct. Therefore, the MAH claims that the bioequivalence study conducted at Synchron could be relied upon to support the marketing authorisation of their products.

The CHMP considered the information submitted by the MAH, i.e. reference to positive inspections, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services. These issues 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. 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 of the MAH do not demonstrate that the study performed at Synchron submitted to support the marketing authorisation of their Farmidur 30 mg or Isonova product can be relied upon.

Therefore, CHMP concluded that bioequivalence to the EU reference medicinal product is neither established for Farmidur 30 mg prolonged release tablets nor for Isonova.

2.2.23. Memantine

The Memaben and Memantine hydrochloride are soluble tablets, which may be administered as an oral solution after dissolution in water or, at least in United Kingdom (Northern Ireland), as solid immediate release tablet. At time of initial marketing authorisation, the dissolved tablet bioequivalence relied on a study performed at Synchron, whereas a BCS biowaiver had been accepted in the UK for the solid immediate release tablet, relying on the BE study performed at Synchron with the dissolved tablet to demonstrate that differences in excipients did not affect the efficacy.

The MAH of Memaben and Memantine hydrochloride requested biowaivers for both administration methods of their product:

- For the solid immediate release tablet, the principles of BCS biowaiver based on similar dissolution profiles and based on categorisation of memantine to the class BCS I,
- For the dissolved tablet, a biowaiver concept based on aqueous oral solution (reference product available as an oral solution Ebixa 5 mg/pump actuation oral solution).

The CHMP agreed that memantine can be classified as BCS I class substance (highly soluble substance with high permeability), further the data provided shows similarity in dissolution profiles. However, a comparison of the compositions of the concerned product and the reference products shows that the formulations contain different excipients including substances that might affect the gastrointestinal absorption e.g. mannitol, sorbitol.

Whereas for BCS class I substance biowaivers, excipients that may affect absorption should be qualitatively the same and quantitatively similar, i.e., within ± 10% of the amount of excipient in the reference product. Additionally, the cumulative difference for excipients that may affect absorption should be within ± 10% as per in ICH M9 guideline on biopharmaceutics classification system-based biowaivers (EMA/CHMP/ICH/493213/2018).

Further, for the biowaiver concept as aqueous oral solution for memantine, the need for a bioequivalence study for the solution may be waived if the same amount of sorbitol is used as in the reference product. as per the product specific guideline on memantine (EMA/CHMP/315243/2014).

According to the MAH based on literature data any impact on the rate and extent of memantine absorption is unlikely, considering the small amounts of excipients. However, CHMP considered this data insufficient to demonstrate that the differences in excipients composition have no effect on PK parameters. A bioequivalence study would be needed to that effect.

In conclusion, the CHMP considers that neither biowaivers can be accepted, and bioequivalence to the EU reference medicinal product is not established for Memaben and Memantine hydrochloride.

2.2.24. Metformin

Taking into account the biowaiver concept as aqueous oral solution described in the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), the MAHs of MetfoLiquid Geriasan, Lycis and Metformin Colonis Oral Solution request a biowaiver.

The Guideline on the investigation of bioequivalence states that if the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. However, if the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol), absorption (e.g. surfactants or excipients that may affect transport proteins), *in-vivo* solubility (e.g. co-solvents) or *in-vivo* stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. The same requirements for similarity in excipients apply for oral solutions as for biowaivers. According to the MAH, based on literature data, none of the excipients used in the formulations is considered to have any clinically relevant impact on the rate or extent of metformin hydrochloride absorption or the gastrointestinal transit time. The CHMP considered that while the excipients may not be expected to impact on the rate and extent of metformin absorption, *in vivo* data were needed to demonstrate that it is the case.

The CHMP further noted that from the documentation provided by the MAH, metformin may qualify as BCS class III substance (i.e. high solubility and low permeability), however as per ICH M9 "for BCS Class III drugs, all of the excipients should be qualitatively the same" for a biowaiver to be applied, whereas difference are noted in the qualitative composition.

In conclusion, the CHMP considers that no biowaiver can be accepted, and bioequivalence to the EU reference medicinal product is not established for MetfoLiquid Geriasan, Lycis and Metformin Colonis Oral Solution.

2.2.25. Nefopam

The MAH RIA Generics did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services in support of Nefopam Hydrochloride film coated tablets. The MAH performed a retrospective review of their Synchron study, based on which they concluded that it was compliant with GCP and showed no anomaly.

The CHMP considered the information submitted by the MAH, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services and no review of unreliable data can be used to address the concerns. Therefore, the arguments of the MAH do not demonstrate that the studies performed at Synchron submitted to support the marketing authorisation of Nefopam Hydrochloride film coated tablets can be relied upon.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for Nefopam Hydrochloride film coated tablets concerned by this referral procedure.

2.2.26. Nevirapine

The MAH Zentiva Pharma UK Limited informed the CHMP that they did not have alternative bioequivalence data generated elsewhere than at Synchron Research Services to support the bioequivalence of their prolonged-release tablet. The initial marketing authorisation was supported data from a fasting, a fed and a multiple-dose study. It is only the bio-analysis part of the multiple-dose study which was performed by Synchron Research Services. According to the MAH this implies that the bio-analytical site was blinded to the sequence of administration of test and reference formulations and the statistical analysis was done at another CRO. The MAH performed a reanalysis of study data which did not identify distinct groups of subject where key parameters were above or below 1. Therefore, the MAH claims that the multiple-dose study conducted at Synchron could be relied upon to support the marketing authorisation of their product.

The CHMP considered the information submitted by the MAH, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services, and no analysis of unreliable data can be used to address the concerns. 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 of the MAH do not demonstrate that the study performed at Synchron submitted to support the marketing authorisation of their nevirapine product can be relied upon.

Further, as this is a prolonged release formulation and accumulation is observed, the CHMP considered that a multiple dose study was required.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for the nevirapine-containing.

2.2.27. Nortriptyline

The MAH RIA Generics did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services in support of Nortriptyline tablets. The MAH performed a retrospective review of their Synchron study, based on which they concluded that it was compliant with GCP and showed no anomaly.

The CHMP considered the information submitted by the MAH, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services and no review of unreliable data can be used to address the concerns. Therefore, the arguments of the MAH do not demonstrate that the studies performed at Synchron submitted to support the marketing authorisation of Nortriptyline tablets can be relied upon.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for Nortriptyline tablets concerned by this referral procedure.

2.2.28. Paracetamol

The applicant Pharmamatch BV and the MAHs Clonmel Healthcare Ltd, Stada and Healthypharm B.V. did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services but informed of their intention to conduct a new bioequivalence study at another CRO.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for those applications and authorised products.

2.2.29. Pioglitazone

The MAH Mylan/Generics informed of its intention to conduct a new bioequivalence study at another CRO.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for the pioglitazone-containing product.

2.2.30. Progesterone

The applicants Theramex Ireland Limited and PharmaMatch B.V. did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services but informed of their intention to conduct a new bioequivalence study at another CRO.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for either progesterone-containing product applications concerned by this procedure.

2.2.31. Rosuvastatin

The MAH for Zircos and Rosuvastatin/Velka submitted a request for biowaiver based on the Biopharmaceutics Classification System (BCS, class III).

The CHMP sought the advice of the pharmacovigilance working party (PKWP) on whether there is reasonable evidence to consider that rosuvastatin maybe be classified as a BCS class III substance (see also section on PKWP consultation). The PKWP advised that rosuvastatin can be classified as a BCS class III substance based on the data submitted by the MAH and that very rapid dissolution had been demonstrated for test and reference product. However, the PKWP considered that a BCS class III biowaiver for the rosuvastatin test formulation cannot be granted due to differences in composition and that the MAH should submit a bioequivalence study in order to demonstrate that the test and reference are bioequivalent in terms of rate and extent of absorption regardless the difference in excipients.

According to the MAH, based on literature data, the difference in excipients between formulations has no impact on the metabolising enzymes nor on the transporter systems involved in the absorption process of rosuvastatin.

The CHMP endorsed the PKWP advice and considered the justification submitted to support that the difference in excipients between formulations has no impact is not sufficient, as in vivo data are needed to this effect.

In conclusion, the CHMP considers that the biowaiver cannot be accepted, and bioequivalence to the EU reference medicinal product is not established for Zircos and Rosuvastatin/Velka.

The applicant and MAH of Rosuvastatin Micro Labs and the MAH Brown & Burk UK Limited did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services but informed of their intention to conduct a new bioequivalence study at another CRO.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for this application and those authorised products.

No information was provided by the MAHs Nassington LTD, Medicair Bioscience Laboratories CY LTD and Lavipharm AE (see also section on "other products").

2.2.32. Rosuvastatin/ezetimibe

The MAH of Rozemib and Aurozeb referred to alternative bioequivalence studies conducted at a different facility (study 17-VIN-0839 and study 18-VIN-0313, Veeda clinical research Pvt. Ltd.), which are the pivotal studies supporting their marketing authorisation, whereas the studies performed at Synchron were pilot studies.

The CHMP concluded that the benefit-risk balance of Rozemib and Aurozeb was not affected by the concerns related to the studies performed by Synchron.

The applicant of Arrox plus and rosuvastatina/ezetimiba Alter referred to alternative bioequivalence studies conducted at a different facility (study 17-VIN-0839 and study 18-VIN-0313, Veeda clinical research Pvt. Ltd.), which are the pivotal studies supporting their marketing authorisation applications, whereas the studies performed at Synchron were pilot studies.

The CHMP concluded that the benefit-risk balance of Arrox plus and rosuvastatina/ezetimiba Alter was not affected by the concerns related to the studies performed by Synchron.

No information was provided by the MAHs Alter, S.A., Farmalter (see also section on "other products").

2.2.33. Sertraline

The MAH RIA Generics did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services in support of Sertraline RIA. The MAH performed a retrospective review of their Synchron study, based on which they concluded that it was compliant with GCP and showed no anomaly.

The CHMP considered the information submitted by the MAH, however in light of the nature and extent of the findings identified, serious concerns have been raised regarding the overall reliability of all data generated at Synchron Research Services and no review of unreliable data can be used to address the concerns. Therefore, the arguments of the MAH do not demonstrate that the studies performed at Synchron submitted to support the marketing authorisation of Sertraline RIA can be relied upon.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for Sertraline RIA.

2.2.34. Tianeptine

The applicant Hormosan Pharma and the MAHs Mylan, Lupin Europe GmbH, Antibiotice S.A highlighted that study TIA2009/551, performed under fasting conditions at Synchron Research Services in India, was the sole pivotal study underlying the marketing authorisations while for the ongoing marketing authorisation application (DE/H/6786/001/DC) a study under fed condition constituted a second pivotal study (study TIA.12.5/329, Triumpharma) was also submitted in the dossier.

As the recommended mode of administration for the reference product used in the fed study is "at the beginning of main meals", i.e. with food, and taking into account that food effect is not expected to impact bioequivalence of test and reference products even if administered in a fasted state, the CHMP considered that a single bioequivalence study under fed conditions could be considered sufficient in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**).

Having assessed the study performed under standardised fed condition in line with the Guideline on the Investigation of Bioequivalence, the CHMP considered that it supports bioequivalence of Tianeptine Mylan, Tianesan, Neluptin and Nobixal.

2.2.35. Torasemide

Laboratorio STADA, S.L. referred to an alternative bioequivalence study conducted at a different facility (study B034601, Gateway Medical Research), which was the sole basis to establish bioequivalence to the EU reference medicinal product of their concerned products, for its initial marketing authorisation. The bioequivalence study performed at Synchron was not considered suitable.

The CHMP concluded that the benefit-risk balance of Torasemida Stada was not affected by the concerns related to the studies performed by Synchron.

For the other torasemide-containing products, including the product authorised under Article 10a of Directive 2001/83/EC ('Well-established use'), the bioequivalence study performed at Synchron (study TOR/2001/027) was pivotal to support the marketing authorisations. The MAHs referred to an alternative bioequivalence study conducted at a different facility (study B034601, Gateway Medical Research). Having assessed the study, the CHMP noted that the study did not meet the current requirements and could therefore not be accepted nowadays as sufficient evidence of bioequivalence. Namely several shortcomings were noted to the bioanalysis with regard to the current standards of the

Guideline on bioanalytical method validation (EMEA/CHMP/EWP/ 192217/2009 Rev. 1 Corr. 2**), which could not be satisfactorily addressed. The following were either not investigated or not appropriately investigated: within- and between-run precision and accuracy, the matrix effect, the effect of any haemolysed samples (it is not known whether or how many samples were haemolysed), the influence of co-medication (ibuprofen was used), selectivity. The following were either not performed or not adequately performed: incurred sample reanalysis, the stability experiments, autosampler stability (on-instrument) testing/demonstration, working solution stability testing/demonstration. Finally, it is not reported whether K2- or K3-EDTA was used which would impact the need for additional matrix-anticoagulant testing to detect potential differences.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for those torasemide-containing products (i.e. apart from Torasemida Stada).

2.2.36. Tramadol/paracetamol

The MAHs of Tramadol/Paracetamol Mylan, Tramadol/Paracetamol EG, Tramadol/Paracetamol Stada, Tramylpa, Xymel and Tramadol/Paracetamol Alter referred to an alternative bioequivalence study conducted at a different facility (study 360-12, Lambda Therapeutic Research Ltd., No.), to comply with the new recommendations further to the revision of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/L4O7/98 Rev. 1).

Having assessed the alternative study, the CHMP considered that it supports bioequivalence of Tramadol/Paracetamol Mylan, Tramadol/Paracetamol EG, Tramadol/Paracetamol Stada, Tramylpa, Xymel and Tramadol/Paracetamol Alter to the EU reference medicinal product.

The MAHs of Foxis and Tramadol/paracetamol aurovitas spain did not present alternative bioequivalence data generated elsewhere than at Synchron Research Services but informed of their intention to submit an alternative bioequivalence study conducted at a different facility (study 360-12, Lambda Therapeutic Research Ltd., No.) to the relevant national competent authorities in a type II variation.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for Foxis and Tramadol/paracetamol aurovitas spain until submission and evaluation of the mentioned alternative bioequivalence study.

2.2.37. Zolmitriptan

The MAH Mylan informed of its intention to conduct a new bioequivalence study at another CRO.

The CHMP concluded that bioequivalence to the EU reference medicinal product is not established for the zolmitriptan-containing products.

2.2.38. Other products

In addition the MAHs and applicants specified above as not having provided information (Strandhaven Limited, Accord Healthcare Limited, Laboratórios Basi - Indústria Farmacêutica, S.A, Artespharm Sp. z o.o., Amarox, TioFarma B.V., Blackrock Pharmaceuticals Limited, Silicon Pharma Limited, PharmConsul s.r.o., Strides Pharma (Cyprus) Limited, Fair-med Healthcare GmbH, Strides Pharma UK Limited, Clonmel Healthcare Ltd, Synoptis Pharma Sp. z o.o., Nassington LTD, Medicair Bioscience Laboratories CY LTD, Lavipharm AE, Alter, S.A. and Farmalter), for the rest of applications and products (i.e. clonidine, ezetimibe/simvastatin, levothyroxine sodium liothyronine, nebivolol oxybutynin, paliperidone, paracetamol/pseudoephedrine, quetiapine, sitagliptin/metformin, vildagliptin/metformin,

zopiclone) 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 Synchron Research Services.

In light of the nature and extent of the findings identified in relation to data generated at Synchron, and of the serious concerns raised in consequence regarding the overall reliability of all data generated at that CRO, the CHMP considers that the data generated at Synchron Research Services, 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.

2.3. Response from the contract research organisation (CRO)

The CRO Synchron Research Services was invited to provide any relevant and substantiated information to be considered by the CHMP when determining the impact of the findings on the benefit-risk balance of medicinal products authorised, as well as for pending marketing authorisation applications, on the basis of studies performed since the set-up of the CRO.

In response to the CHMP questions, the CRO provided an overview of past inspections, including some positive inspections, and referred to the fact that extensive quality control and quality assurance measures were carried out for all the studies conducted at their facilities. The CRO did not give additional information on the 'creation of false data' as observed by the US FDA, nor attempted to explain or resolve the FDA's findings or analyse their impact on the benefit-risk balance of authorised medicinal products or pending marketing authorisation applications.

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. Indeed because of their nature, the findings which led to the initiation of this review are either difficult to identify or not possible to detect during an inspection. Considering that the concerns raised by the FDA, taken together with the observations in previous EU inspections of the site (2005 and 2009 inspections, which led to the rejection of the concerned studies), point towards a CRO system issue rather than isolated findings/cases, an at-risk period could not be defined. Hence, the CHMP cannot rule out beyond reasonable doubt that critical GCP violations at the site have affected all studies conducted and is of the opinion that they cannot be relied upon to establish bioequivalence vis-à-vis the EU reference medicinal product.

Overall, the CRO did not provide any new information that changed the conclusions drawn by the inspection teams and highlighted in the notification for this procedure.

3. Pharmacokinetic Working Party (PKWP) consultation

The CHMP consulted the PKWP which provided advice on the BCS classification of rosuvastatin.

The PKWP highlighted that as described in the ICH M9 guideline for biopharmaceutics classification system-based biowaivers, the requirements of a medicinal product to be eligible for a BCS Class III biowaiver are:

1. High solubility of the active substance
2. If high permeability is not demonstrated, the drug substance is considered to have low permeability for BCS classification purposes
3. Drug substances (both test and reference product) should have very rapid (≥ 85% dissolved in ≤ 15 minutes) *in vitro* dissolution characteristics in pHs 1.2, 4.5 and 6.8

4. All the excipients should be qualitatively the same and quantitatively similar. Excipients that may affect absorption as mannitol, sorbitol and surfactants should be within ± 10% of the amount of excipient in the reference product and the cumulative difference for these excipients should be within ± 10%.

The PKWP considered that the MAH has demonstrated that rosuvastatin can be classified as a BCS Class III substance regarding bullet points 1-2 described above (high solubility, low permeability).

The PKWP further noted that for the BCS Class III waiver, point 3 has been fulfilled (very rapid dissolution), however, point 4 is not fulfilled as in this particular case there exists a qualitative difference in tablet core excipients between the test and reference products, which precludes a waiver for an *in vivo* bioequivalence study. No *in vivo* experimental data in humans with the MAH's formulation, showing no impact on bioavailability applying the observed differences in compositions, have been submitted. Also, no other *in vivo* data in humans demonstrating that these particular excipients do not affect the absorption of rosuvastatin have been submitted. Therefore, in this case the PKWP a BCS Class III biowaiver for the rosuvastatin test formulation cannot be granted and the MAH should submit a bioequivalence study in order to demonstrate that the test and reference are bioequivalent in terms of rate and extent of absorption regardless the difference in excipients.

4. Benefit-risk balance

4.1. Initial benefit-risk balance assessment

The severity and the extent of the findings identified in relation to data generated at Synchron, raised serious concerns related to the suitability of the quality management system and the overall reliability of data generated at Synchron and submitted to support marketing authorisation (applications) in EU MS.

In the absence of reliable data demonstrating bioequivalence with a EU reference medicinal product or, where applicable, with the medicinal product referred in the scientific literature demonstrating that the active substance of the medicinal product concerned has been in well-established medicinal use, the benefit-risk balance of the products either authorised or seeking a marketing authorisation based only on data generated at Synchron Research Services to demonstrate the 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 Synchron Research Services, India, may have had positive outcomes, the findings identified in relation to data generated at Synchron are considered to reflect broader problems concerning the suitability of the quality management system and the overall reliability of all data generated at Synchron and no review or audit of unreliable data can be used to address the concerns. Indeed, although the findings relate to the bioanalytical part of the studies, given the failure of the quality management system to prevent and detect their occurrences, failures in other areas of the trials (including clinical parts) cannot be excluded. It should also be noted that upper management is common to clinical and bioanalytical activities. Because of their nature, these issues are either difficult to identify or not possible to detect during an inspection. It is considered that any other inspection performed at the site would not provide enough reassurance since they may not have detected serious GCP violations, even if present. Considering that the concerns raised by the FDA, taken together with the observations in previous EU inspections of the site (2005 and 2009 inspections, which led to the rejection of the concerned studies), point towards a CRO system issue rather than isolated findings/cases, an at-risk period could not be defined. Therefore, it is considered that those arguments do not demonstrate that the said studies can be relied upon. In addition, 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. 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.

Alternative data were submitted to demonstrate the bioequivalence of Almiden, Amlodipine Accord, Rexazon, Varcodes, Tianeptine Mylan, Tianesan, Neluptin, Nobixal, Tramadol / Paracetamol Mylan, Tramadol/Paracetamol EG, Tramadol/Paracetamol Stada, Tramylpa, Xymel and Tramadol/Paracetamol Alter to an EU reference medicinal product. Having assessed the alternative study, the CHMP recommends the maintenance of the marketing authorisations for Almiden, Amlodipine Accord, Rexazon, Varcodes, Tianeptine Mylan, Neluptin, Nobixal, Tramadol / Paracetamol Mylan, Tramadol/Paracetamol EG, Tramadol/Paracetamol Stada, Tramylpa, Xymel and Tramadol/Paracetamol Alter, and concludes that, with regards to the Tianesan marketing authorisation application, bioequivalence has been demonstrated vis-à-vis the EU reference medicinal product using alternative data.

Alternative bioequivalence studies were referred to as the pivotal evidence to demonstrate the bioequivalence of Amlodipin Jubilant, Azithromycin Heumann, Dorzolamid Heumann, Zormid, Rozemib, Aurozeb and Torasemida Stada, and of the ongoing marketing authorisation application for Arrox plus and rosuvastatina/ezetimiba Alter to an EU reference medicinal product, and not the studies performed at Synchron. Having assessed the information provided, the CHMP concluded that the benefit-risk balance of Amlodipin Jubilant, Azithromycin Heumann, Dorzolamid Heumann, Zormid, Rozemib, Aurozeb and Torasemida Stada were not affected by the concerns related to the studies performed by Synchron and recommended the maintenance of the marketing authorisations. Likewise, the CHMP concluded that the benefit-risk balance of Hydrokortison Orifarm was not affected by the concerns related to the studies performed by Synchron and recommended the maintenance of the marketing authorisation. Having assessed the information provided, the CHMP also concluded that the benefit-risk balance of Arrox plus and rosuvastatina/ezetimiba Alter was not affected by the concerns related to the studies performed by Synchron and recommended that the evaluation of this application may continue at national level.

Results of bioequivalence studies conducted outside the EU, with non-EU reference products 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, or in the absence of demonstration that the active substance of the medicinal product has been in well-established medicinal use, the requirements of Article 10 or 10a 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 considers that all concerned marketing authorisation applications not listed in the above paragraph of this section do not currently fulfil the criteria for authorisation and recommended the suspension of the marketing authorisations for all concerned medicinal products not listed in the above paragraph of this section (those concerned marketing authorisation applications and marketing authorisations are listed in annex IB).

The Committee recommends that these marketing authorisations (annex IB) should be suspended unless the medicinal product is considered critical by the relevant national competent authorities.

For marketing authorisation(s) 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 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 these medicinal products considered critical by EU Member States, the marketing authorisation holders shall submit a bioequivalence study conducted vis-à-vis the EU reference medicinal product within 12 months following Commission Decision. An authorised medicinal product listed in Annex IB 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.

4.2. Re-examination procedure

Following the adoption of the CHMP opinion in May 2022, the MAHs AbZ Pharma GmbH, Pliva, Teva and Ratiopharm requested a re-examination of the CHMP opinion on the Article 31 referral for Synchron Research Services according to Article 32(4) of Directive 2001/83/EC for their affected torasemide-containing products (i.e. Diuver, Torasemide Teva, Torasemid-ratiopharm, Torasemide and Torasemide Teva Italia).

It is noted that the CHMP is a scientific committee and that while it operates within the framework of the Union legislation regulating medicinal products, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the CHMP, and therefore the re-examination of the referral procedure under Article 31 of Directive 2001/83/EC focuses only on the scientific grounds for re-examination.

4.2.1. Detailed grounds for re-examination submitted by the MAH

Detailed grounds for re-examination of the CHMP recommendation have been submitted by the MAHs on 18 July 2022 and are summarised below:

The MAHs consider the bioequivalence of their products demonstrated based on the study performed at Synchron and the alternative bioequivalence study conducted at a different facility (study B034601, Gateway Medical Research) on the following basis:

1. CHMP recommended in its initial opinion the maintenance of the MA for Torasemida Stada, which was first authorised based on study B034601. Furthermore, the formulation and manufacturers of Torasemida Stada and of products of the MAHs concerned by the re-examination procedure are the same. Study B034601 was also accepted as evidence of bioequivalence in 2010 by a national competent authority for the authorisation of another torasemide-containing product, not concerned by the present procedure.
2. No concerns were identified through pharmacovigilance reporting, over nearly 20 years for which the products have been marketed in the EU.
3. The MAHs suggested that the conduct of a third BE study, to confirm bioequivalence vis-à-vis an EU reference medicinal product, could be imposed on the marketing authorisation of their products, whilst the MAs should be maintained, in view of the above-mentioned arguments.
4. The MAHs provided a scientific justification for the lack of incurred sample reanalysis (ISR – in line with point 1.3 of the EMA Q&A on Clinical pharmacology and pharmacokinetics) to confirm the reliability of the results and to address the concerns expressed by the CHMP on the bioanalysis of

study B034601 with regard to the current standards of the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/ 192217/2009 Rev. 1 Corr. 2**).

4.2.2. CHMP discussion on grounds for re-examination

The CHMP considered the detailed grounds as submitted by the MAHs within this re-examination procedure and the scientific data underlying these grounds.

The CHMP reiterated that the findings identified in relation to data generated at Synchron reflect broad problems concerning the suitability of the quality management system and the overall reliability of all data generated at Synchron. The CHMP maintained that it 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. In addition, the CHMP reiterated its opinion that the absence of the identification of any pharmacovigilance signals does not provide sufficient reassurance to conclude on a positive benefit-risk balance in the absence of the demonstration of bioequivalence with the EU reference medicinal product because it is not established that the pharmacovigilance activities may be designed to detect such a signal.

The CHMP considered that the scientific justification provided for the lack of ISR supported the following:

- Metabolic back conversion is not an issue for torasemide as the metabolites of torasemide appear to be stable and back conversion into parent during storage is unlikely. Moreover, due to a difference in molecular weight, in case that metabolites are eluted at the same time as the parent drug, it would not interfere with the detection of torasemide by the tandem mass spectrometry (MS/MS) detector. For the same reason, co-medication with ibuprofen would not have influenced the results, as it has a different molecular weight. In addition, long term stability data did not indicate an issue with possible back-conversion. The CHMP considered the bioanalytical method sufficiently sensitive to be able to detect the analyte and its internal standard without any interference.
- Acceptable data on repeat analysis (based on QC sample analysis) is available.
- Comparison of the pharmacokinetic data obtained in study B034601 with literature data showed these were comparable.
- The 90% CI observed in study B034601 are well within the 80 – 125% limits and therefore the probability of a false positive outcome due to ISR problems is low.

Therefore, whilst no ISR data available using the same bioanalytical method in the same laboratory, the data provided support the validity of the analytical method and a false positive outcome of this bioequivalence study is considered unlikely. The CHMP considered the lack of ISR data sufficiently justified in line with point 1.3 of the EMA Q&A on Clinical pharmacology and pharmacokinetics.

In addition, within-run and between-run accuracy and precision were tested on torasemide quality control (QC) sample concentrations at 25, 250, 2500 and 6000 ng/ml during validation. In principle for the newly added high QC concentration (i.e. 6000 ng/ml), stability should have been shown, however the data obtained at 25, 250 and 2500 ng/ml is considered sufficient to support the conclusion on stability.

Matrix effect was evaluated using matrices from 4 different lots/donors. While, the internal standard normalised matrix factor was not applied, the new ICH guideline M10 on bioanalytical method

validation (EMA/CHMP/ICH/172948/2019) does not include this requirement. Therefore, the CHMP agreed that the matrix effect was sufficiently evaluated.

Selectivity was considered demonstrated in processed blank plasma samples from 6 different sources in line with the requirements of the EMA Guideline on bioanalytical method validation. Haemolysed samples and/or lipemic samples were not evaluated, however this is not a requirement in this case.

Subject samples were obtained in tubes with EDTA as anticoagulant. The same EDTA human plasma was used for both study sample analysis and method validation. Hence, whilst it is noted that the counter-ion was not mentioned (e.g. K2 or K3), CHMP considered that from an analytical perspective it is very unlikely that use of K2 instead of K3-EDTA (or vice versa) would have an impact on the accuracy and precision, or on the stability of torasemide and therefore no additional matrix-anticoagulant testing were considered required.

The CHMP noted that the following stability experiments were performed: room temperature stability, in-process stability and storage stability of extracted samples in refrigerator. The results showed that torasemide was stable for at least forty-eight (48) hours during sample processing at room temperature and therefore it can be extrapolated that the stability remains at colder temperatures. The results also showed that torasemide was stable for at least forty-eight (48) hours during storage in the refrigerator. Based on this experiment, autosampler stability is considered demonstrated (same temperature as in the refrigerator). Working solution stability experiment was not conducted, however, prepared working solution were used for spiking of calibration and quality control samples.

Overall, the CHMP, concluded that the analytical method of study B034601 is sufficiently sensitive, accurate and precise for the analysis of torasemide in plasma.

The CHMP noted that the MAHs of Torasemid AL and Torasemid STADA (Aliud Pharma GmbH and Stadapharm GmbH, respectively) had also referred to study B034601 as alternative evidence of bioequivalence. Taking this into consideration, the above considerations for study B034601 are also applicable to these marketing authorisations.

The CHMP further noted that at time of initial authorisation of those medicinal products, the conduct of a further bioequivalence study for the 5 mg strength had been waived, based on the 10 mg batch used in the Synchron study. The same 10 mg batch was used in the Synchron study, and in study B034601, therefore results of the latter study can be extrapolated to the 5 mg strength.

In conclusion, having assessed the alternative study B034601, the CHMP considered that it supports the bioequivalence of the torasemide-containing products Diuver, Torasemide Teva, Torasemid-ratiopharm, Torasemide, Torasemid AbZ, Torasemide Teva Italia, Torasemid AL and Torasemid STADA to the EU reference medicinal product or, for well-established use products, with the medicinal product referred in the scientific literature.

The CHMP also noted the further grounds for re-examination submitted by the MAHs and summarised under points 1 and 3 in the above section, however, in view of their non-scientific nature and the above conclusion, those are no longer relevant and are therefore not discussed here.

4.2.3. Conclusion on the benefit-risk balance following the re-examination procedure

Based on the totality of the data available, including the information submitted during the initial assessment procedure and the detailed grounds for re-examination put forward by the MAHs, the CHMP recommends the maintenance of the marketing authorisations for Diuver, Torasemide Teva,

Torasemid-ratiopharm, Torasemide, Torasemid AbZ, Torasemide Teva Italia, Torasemid AL and Torasemid STADA.

5. Condition for lifting the suspension of the marketing authorisations

For the suspension of the marketing authorisations referred to in Annex IB 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), or, when applicable for well-established use products, bioequivalence vis-à-vis the medicinal product referred in the scientific literature has been demonstrated.

6. Grounds for Opinion following the re-examination procedure

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 Synchron Research Services, a contract research organisation (CRO) located in Ahmedabad, Gujarat, India, since the set-up of the site under the name Synchron Research Services.
- The CHMP reviewed available data and information provided in writing and in an oral explanation by the MAHs and applicants, as well as information provided by Synchron Research Services. The CHMP considered that Synchron Research Services did not provide any new information that changed the conclusions laid out in the notifications for this procedure.
- The CHMP also considered the grounds for re-examination submitted by the MAHs in writing.
- The CHMP concluded that, for the 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, or to demonstrate that the active substance of the medicinal product has been in well-established medicinal use.
- 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, or, for well-established use products, with the medicinal product referred in the scientific literature, or for which no alternative bioequivalence data or a justification was submitted (annex IB);
    - Marketing authorisation applications for which no alternative bioequivalence data or a justification was submitted (annex IB).

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 the bioequivalence vis-à-vis the EU reference medicinal product has been established, or for which it has been demonstrated that the active substance of the medicinal product has been in well-established medicinal use (annex IA) should be maintained, as the benefit risk balance of these marketing authorisation is considered favourable.

b. Bioequivalence vis-à-vis the EU reference medicinal product has been established for Tianesan and may continue to be assessed by the relevant national competent authorities for Arrox plus and rosuvastatina/ezetimiba Alter listed in annex IA.

c. 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/medicinal product referred in the scientific literature (Annex IB) 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.

   For the suspension of the marketing authorisations to be lifted the MAHs shall provide evidence that 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) or, when applicable for well-established use products, bioequivalence vis-à-vis the medicinal product referred in the scientific literature has been demonstrated.

   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 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(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/medicinal product referred in the scientific literature within 12 months from the Commission Decision.

d. 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.