21 March 2024
EMA/169298/2004
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 Synapse Labs Pvt. Ltd., a contract research organisation (CRO) located in Kharadi, Pune, India

Procedure number: EMEA/H/A-31/1529

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 Spanish Agency of Medicines and Medical Devices (AEMPS) conducted a remote GCP inspection of the bioequivalence (BE) facilities in Synapse Labs Pvt. Ltd. (henceforth referred as Synapse), a contract research organisation (CRO) located at Majestic Plaza, S. No. 21/5, Nr. Nyati Empire, Kharadi-Mundhwa Bypass, Kharadi, Pune – 411014, Maharashtra (India) and Krushna Complex, Kharadi-Mundhwa Bypass, Kharadi, Pune-411014, India).

The findings reported during the inspection cast serious doubts on the validity and reliability of the data of BE studies (clinical and bioanalytical part) conducted at the CRO. The inspection examined studies over the 2009 - 2019 period and Synapse quality management system (QMS) over the 2009-2022 period. Five (5) critical findings (CF) and one (1) major finding were identified:

- The CRO failed to demonstrate the adequacy of the Computerized Systems/Bioanalysis and Data Management to ensure bioanalytical and clinical data integrity. Overall, up to 2023, the CRO lacked robust QMS measures, procedures and control over the data integrity of the data generated (4 CF).
- Significant pharmacokinetics anomalies were observed in over 20 studies conducted from 2013 to 2018 (i.e. multiple pairs of subjects with overlapping plasma time-concentration profiles). This fact, in absence of other acceptable justification would be considered coherent with profile duplication (1 CF).
- Source documentation for clinical and bioanalytical research was not clearly and unequivocally established (1 major finding).
- The CRO acknowledged most of the findings identified. No major disagreement or factual error were reported. The CRO failed to rule out possible intentional misrepresentation of data, which is also considered to potentially compromise the CRO's QMS and the investigations conducted by the CRO as a result of the inspection.

Due to the transversal and systematic nature of the findings observed over several years, in which the QMS has also been compromised, those are considered to have a direct impact on GCP compliance and the data reliability, which would cast serious doubts on the acceptability of both analytical and clinical data generated by Synapse.

On 27 June 2023, Spain 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 Member States on the basis of trials performed at Synapse facilities, as well as for pending procedures, and to issue a recommendation on whether the concerned marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Applications for generic medicinal products, i.e. under Article 10(1) of Directive 2001/83/EC, are required to demonstrate bioequivalence. 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 the bridging of preclinical tests and of clinical trials associated with

the reference medicinal product. Only reference medicinal products authorised under Article 6 of said directive and in accordance with the provisions of Article 8 of the same directive are accepted.

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, i.e. under Article 10(3) of Directive 2001/83/EC, and for well-established use medicinal products, i.e. 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 EU 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 Synapse to demonstrate the bioequivalence could not be considered positive, as the possibility of safety/tolerability or efficacy issues cannot be excluded.

In order to demonstrate a positive benefit-risk balance of their 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 Synapse 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.

2.2. Clinical aspects

Information received from MAHs and applicants for their products and applications are presented below in three categories.

- Category 1: No new biowaiver request or data to establish the bioequivalence vis-à-vis the EU reference medicinal product (apart from BE studies conducted at Synapse facility)
- Category 2: New bioequivalence vis-à-vis the EU reference medicinal product study submitted
- Category 3: New Biopharmaceutics Classification System (BCS)-based biowaiver request submitted

General considerations relative to the assessment of all products reviewed within this procedure are outlined below.

In addition to the submitted studies, some MAHs applicants have highlighted that the CRO Synapse was extensively inspected by competent authorities of several EU MS, MHRA and FDA and found compliant to GCP and principles of GLP. Moreover, they state that all studies were systematically on-

site monitored by the sponsor throughout their execution and the overall process of conduct was satisfactory with respect to in house SOPs and protocol requirements with no observations relating to data integrity. MAHs and applicants have also presented re-analyses of the studies data to support the reliability of the results which they have either preformed themselves, or which were done by the CRO Synapse. Those include controls, pharmacokinetic profiling analysis, risk evaluation of data integrity and the detection of potential manipulation in the study data via dedicated software (e.g. a software developed specially to detect similar or overlapping profiles). No discrepancies or overlapping profiles were identified in those analyses except for two studies. It is further argued that similar PK profiles could be due to the metabolic rate of subjects of the same race and related to each other. The MAHs and applicants argued that, in view of this, the bioequivalence studies conducted at the site can be relied upon as sufficient to support the marketing authorisation of their products or applications. However, in light of the nature, the severity and the extent of the GCP findings identified in the AEMPS's remote inspection in November 2020 and 2022, serious concerns have been raised regarding the overall reliability of all data generated at Synapse. Indeed, given the failure of the quality management system to prevent and detect the occurrence of the findings, failures in other areas of the trials cannot be excluded. It should also be noted that all the BE activities conducted by Synapse are governed under the same QMS, further, 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. Therefore, these arguments do not demonstrate that said studies can be relied upon. Indeed, any mentioned audits and inspections, performed at the site in the past or since the AEMPS's inspection, do not provide sufficient reassurance since they may not have detected serious GCP violations, even if present. Further metabolic rates of subjects of the same race and related to each other cannot be similar to the point of observing the exact same blood levels over time of an active substance. Hence, the CHMP cannot rule out beyond reasonable doubt that critical GCP violations at the site have not affected the validity and reliability of said studies. Therefore, the CHMP is of the opinion that the studies cannot be relied upon to establish bioequivalence vis-à-vis the EU reference medicinal product.

Some MAHs stated that only the clinical or the bioanalytical phase was conducted at Synapse, whereas bioanalytical or clinical, pharmacokinetic and statistical phases of the study were conducted at a different CRO. However, the GCP inspection was conducted by AEMPS on the whole quality management system of Synapse and critical GCP deficiencies were found in the clinical and bioanalytical phases of the studies. Therefore, even if only the clinical or bioanalytical phase of the study was conducted at Synapse, the study cannot be considered reliable.

A number of applicants and MAHs have also argued that pharmacovigilance data collected on their medicinal products have not indicated any problems, which could be attributed to non-bioequivalence, such as reduced efficacy or worsened safety and tolerability. However, the CHMP is of the opinion that the absence of the identification of any pharmacovigilance signals does not provide sufficient reassurance because it is not established that the pharmacovigilance activities may be designed to detect such a signal and, more importantly, pharmacovigilance activities cannot substitute the demonstration of bioequivalence to support a marketing authorisation.

Other MAHs stated that pilot studies carried out at other CROs, supported that their medicinal product was comparable to the EU reference medicinal product and some provided the study synopsis. Some other MAHs/applicants informed that activities to conduct new BE studies have been initiated. However, the complete documentation of the pilot study or alternative BE study has not been submitted and, therefore, in the absence of data supporting bioequivalence it cannot be considered demonstrated.

Some MAHs have provided results from bioequivalence studies conducted at a different CRO but using non-EU medicinal products. Non-EU medicinal products do not meet the definition of "reference medicinal product" provided by Article 10(2)(a) of Directive 2001/83/EC. Accordingly, said studies do not fulfil the criteria of Article 10 of Directive 2001/83/EC and are therefore not acceptable.

2.2.1. Category 1 medicinal products

This category encompasses products for which applicants/MAHs provided miscellaneous statements, as described above, concerning benefit-risk balance of their medicinal products, or who have not responded.

In addition, for authorised products containing nevirapine as a prolonged release dosage form (MAHs: Arrow Génériques, Puren Pharma GmbH & Co. KG, Generis Farmacêutica, S.A., Aurovitas Spain S.A.U., Aurobindo Pharma B.V., Milpharm Limited), the MAHs referred to single dose fed and multiple dose fasting studies conducted at different facilities. The study conducted in Synapse is the single dose fasting. However, for nevirapine prolonged release tablets, three types of studies are requested since each study design intends to address a different aspect of the product bioequivalence. Therefore, the other two studies cannot substitute the demonstration of equivalence required after a single dose in fasted state, which is considered the most sensitive study to detect differences between products.

Therefore the CHMP considered that bioequivalence to the EU reference medicinal product is not established for those products, except for products listed in **Annex IA** containing fesoterodine, metformin, sunitinib and ursodeoxycholic acid whose benefit-risk balance was not affected by the concerns related to the studies performed by Synapse based on the following reasons:

- The study performed with the intermediate strength conducted at Synapse can be waived relying on data from the studies preformed at a different CRO with the highest and lowest strengths, according to the conditions for a bracketing approach described in the Guideline on the investigation of Bioequivalence; CHMP/QWP/EWP/1401/98 Rev. 1. (Metformin - WIN MEDICA, Novatin Limited)
- The fed-state study was conducted at Synapse and a fasted-state study was performed at a different CRO, whereas according to the EMA Product Specific Bioequivalence Guideline a fasted-state study is sufficient to support the demonstration of bioequivalence (Sunitinib – Bluefish Pharmaceuticals AB, Genepharm S.A., Sapiens Pharmaceuticals Ltd and Pharmevid s.r.o.)
- Marketing authorisations relying on alternative bioequivalence studies conducted at different facilities, which are the pivotal studies supporting their marketing authorisation, whereas the studies performed at Synapse were pilot studies (Fesoterodine –Genus Pharmaceuticals Limited and Ursodeoxycholic acid – Teva B.V and Teva UK Limited)

For the remaining products and applications, the CHMP considers that in the absence of demonstration of the bioequivalence vis-à-vis the EU reference medicinal product (including products for which the MAHs or applicants did not provide a response), the efficacy and safety of the concerned category 1 medicinal product cannot be established, and hence the benefit-risk balance cannot be considered positive. This conclusion applies to products listed in **Annex IB** containing:

- Abacavir/lamivudine (MAH: Remedica Ltd, Accord Healthcare S.L.U, Accord Healthcare B.V., Accord Healthcare Polska Sp. z o.o., Biogaran, EG LABO - Laboratoires Eurogenerics, Aliud Pharma GmbH, betapharm, Dr. Reddy's S.r.l., EG SpA, Stada Arzneimittel, Stada Arzneimittel AG, Stada M&D Srl, Reddy Pharma Iberia S.A., Dr Reddy's Laboratories (EU) Limited)
- Acetazolamide (MAH: Zista Pharma Limited)
- Albendazole (Applicants: Remedica Ltd., 2care4 Generics ApS)

- Alimemazine (MAH: Key Pharmaceuticals Limited, Noumed Life Sciences Limited)
- Amantadine (MAHs: Morningside Healthcare (Malta) Ltd., Morningside Healthcare Limited, Manx Healthcare Limited, Zista Pharma Limited. Applicants: Focus Care Pharmaceuticals B.V., Bristol Laboratories Limited)
- Amiloride/hydrochlorothiazide (MAHs: Aurobindo Pharma (Italia) S.r.L., Aurobindo Pharma B.V., Aurovitas Spain S.A.U., Generis Farmacêutica, S.A.)
- Amlodipine (MAHs: Brillpharma (Ireland) Limited, Brillpharma Limited, Bristol Laboratories Limited. Applicant: Brillpharma Limited)
- Amlodipine/irbesartan (MAHs: Win Medica S.A., Elpen Pharmaceutical Co. Inc)
- Amlodipine/irbesartan/hydrochlorothiazide (MAH: Win Medica S.A.)
- Amlodipine/valsartan/hydrochlorothiazide (MAHs: Holsten Pharma GmbH, Zentiva k.s., Pharmacons AD, Alkaloid - INT d.o.o., Jadran Galenski laboratorij d.d., Genepharm S.A., Elpen Pharmaceutical Co. Inc, Mylan SpA, Mylan AB, Mylan Lda, Mylan Pharmaceuticals Limited S.L., Mylan Pharmaceuticals Limited, Enorasis, Laboratorios Cinfa, S.A.)
- Anastrozole (MAHs: Eugia Pharma (Malta) Limited, Generis Farmacêutica, S.A., Milpharm Limited)
- Atazanavir (MAHs: Remedica Ltd, Stada Arzneimittel AG, Sandoz, Arrow Génériques, Biogaran, Hexal AG, Aliud Pharma GmbH, betapharm Arzneimittel GmbH, Rowex Ltd., Sandoz SpA, Sandoz d.d., Generis Farmacêutica, S.A., Stada M&D Srl, LABORATORIO STADA, S.L., Sandoz B.V., Aurobindo Pharma B.V., Dr Reddy's Laboratories (UK) Limited, Sandoz Limited)
- Atorvastatin (MAHs: Umedica Netherlands B.V., Elpen Pharmaceutical Co. Inc (10mg), Aliud Pharma GmbH, Unifarma, SIA, Latvia, Crescent Pharma Limited)
- Baclofen (MAH: Zista Pharma Limited)
- Betahistine (Applicants: Kappler Pharma Consult GmbH, Medreg s.r.o., Biovantic Pharma Limited, Manx Healthcare Limited)
- Bosentan (MAHs: Aurobindo Pharma B.V., Aurobindo Pharma (Malta) Limited, Orion Corporation, Arrow Génériques, Puren Pharma GmbH & Co. KG, Aurobindo Pharma (Italia) S.r.L., Generis Farmacêutica, S.A., Aurovitas Spain S.A.U., Milpharm Limited)
- Carbamazepine (MAHs: Umedica Netherlands B.V., Vegal Farmaceutica S.L., Crescent Pharma Limited)
- Carbimazole (MAHs: Activase Pharmaceuticals Limited, Cygnus Pharma Limited, Morningside Healthcare Limited, Ria Generics Limited, Strides Pharma UK Limited, Tillomed Laboratories Limited. Applicants: Noumed Life Sciences Limited, Strandhaven Limited)
- Carbocisteine (MAHs: Bristol Laboratories Limited, Zista Pharma Limited. Applicant: Bristol Laboratories Limited)
- Cefuroxime (MAH: Baroque Healthcare, Lda)
- Ciprofibrate (MAHs: Amdipharm Limited, Focus Pharmaceuticals Limited)
- Clemastine (MAH: Milstein C.V.)
- Clindamycin (MAH: Morningside Healthcare Limited)
- Colchicine (MAHs: Pharmaselect International Beteiligungs GmbH, RIA Generics Limited, Noumed Life Sciences Limited)
- Dapagliflozin/metformin (MAH: Generis Farmacêutica, S.A. Applicants: Aurobindo Pharma (Malta) Limited, Aurobindo Pharma (Italia) S.r.l., Aurovitas Pharma Polska Sp. z o.o., Aurovitas Spain S.A.U., Milpharm Limited)
- Dapsone (MAHs: Dr Reddy's Laboratories (UK) Limited, Morningside Healthcare Limited, Strandhaven Limited. Applicant: Morningside Healthcare (Malta) Ltd.)
- Darunavir (MAHs: Stada Arzneimittel AG, Stada Arzneimittel, Sandoz GmbH, Sandoz - SA-NV – Belgium, Sandoz d.o.o., Sandoz Pharmaceuticals d.d., Sandoz A/S, Sandoz B.V., Sandoz SpA, Sandoz d.d., Sandoz Farmacêutica, Lda., Sandoz Farmacéutica, S.A., Sandoz S.R.L., Sandoz Limited, Remedica Ltd, Biogaran, EG LABO - Laboratoires Eurogenerics, Hexal AG, Aliud Pharma

GmbH, Elpen Pharmaceutical Co. Inc, Rowex Ltd., Clonmel Healthcare Ltd, EG SpA, LABORATORIO STADA, S.L., Zentiva k.s., Sandoz)

- Deferasirox (MAHs: Stada Arzneimittel, Umedica Netherlands B.V., Teva Sante, Ratiopharm GmbH, Stadapharm GmbH, Aliud Pharma GmbH, Elpen Pharmaceutical Co. Inc, Centrafarm B.V., Teva GmbH, Teva B.V., Stada Arzneimittel AG, Thornton & Ross Limited.)
- Dexamethasone (MAH: Morningside Healthcare Limited)
- Dicycloverine (Applicants: Milpharm Limited, Renata (UK) Limited)
- Digoxin (MAH: Arrow Génériques)
- Dimethyl fumarate (Applicant: Umedica Netherlands B.V.)
- Dipyridamole (MAHs: Syri Pharma Limited t/a Thame Laboratories, Syri Limited)
- Doxepin (MAH: Morningside Healthcare Limited)
- Dutasteride (Applicant: Noumed Life Sciences Limited)
- Efavirenz (MAH: Stada Arzneimittel)
- Efavirenz/emtricitabine/tenofovir (MAHs: Sandoz GmbH, EG (Eurogenerics) NV, Stada d.o.o., Remedica Ltd, Sandoz A/S, Stada Arzneimittel AG, Sandoz Pharmaceuticals d.d., Sandoz, EG LABO - Laboratoires Eurogenerics, Biogaran, Aliud Pharma GmbH, Hexal AG, betapharm Arzneimittel GmbH, Elpen Pharmaceutical Co. Inc, Clonmel Healthcare Ltd, Sandoz S.R.L., Sandoz Farmaceutica, S.A., Reddy Pharma Iberia S.A., Sandoz B.V., Centrafarm B.V., Sandoz Limited, Dr Reddy's Laboratories (UK) Limited. Applicant: PharOS - Pharmaceutical Oriented Services Ltd.)
- Eltrombopag (Applicant: Devatis GmbH)
- Erlotinib (MAHs: EG (Eurogenerics) NV, Sandoz - SA-NV - Belgium , Sandoz d.d., Mylan Pharmaceuticals Limited, PharmaS d.o.o., Remedica Ltd, Mylan AB, Stada Arzneimittel AG, Sandoz A/S, Sandoz Pharmaceuticals d.d., Biogaran, EG LABO - Laboratoires Eurogenerics, Viatris Sante, Sandoz, Hexal AG, Stadapharm GmbH, Mylan Ireland Limited, Sandoz Hungária Kereskedelmi Kft., Zentiva k.s., Viatris Limited, Pharmascience International Limited, Mylan SpA, Sandoz SpA, Mylan, Lda., Sandoz Farmacêutica, Lda., Sandoz Farmaceutica, S.A.. Sandoz S.R.L., Centrafarm B.V., Glenmark Arzneimittel GmbH, Glenmark Pharmaceuticals Europe Limited, Sandoz B.V., Sandoz Limited, Generics (UK) Limited. Applicant: Sandoz Hungaria KFT)
- Ezetimibe (MAH: Key Pharmaceuticals Limited)
- Fludrocortisone (MAHs: Morningside Healthcare Limited, Strandhaven Limited)
- Fluoxetine (MAH: Focus Pharmaceuticals Limited)
- Furosemide (Applicants: Aurobindo Pharma (Italia) S.r.l., Generis Farmacêutica, S.A., Aurobindo Pharma B.V.)
- Gabapentin (MAHs: Brillpharma (Ireland) Limited, Brillpharma Limited. Applicant: Activase Pharmaceuticals Limited)
- Hydrocortisone (MAHs: Bristol Laboratories Limited, Morningside Healthcare Limited. Applicant: Bristol Laboratories Limited)
- Ibuprofen (MAH: Bristol Laboratories Limited. Applicants: Nutra Essential OTC, S.L., Noumed Life Sciences Limited)
- Isosorbide mononitrate (MAH : Bristol Laboratories Limited)
- Lacosamide (MAHs : Stada Arzneimittel, Stada Arzneimittel AG, EG (Eurogenerics) NV, Alkaloid - INT d.o.o., Belupo lijekovi i kozmetika, d.d., Genepharm S.A., Neuraxpharm Bohemia s.r.o., ARDEZ Pharma, spol. s r.o., EG LABO - Laboratoires Eurogenerics, Aliud Pharma GmbH, Stadapharm GmbH, EG SpA, Przedsiębiorstwo Produkcji Farmaceutycznej HASCO-LEK S.A., Laboratorio Stada, S.L., Crescent Pharma Limited, Thornton & Ross Limited)
- Lapatinib (MAHs : Aliud Pharma GmbH, Biogaran, EG SpA, LABORATORIO STADA, S.L., Newbury Pharmaceuticals AB, Pharos Pharmaceutical Oriented Services Ltd., Remedica Ltd, Stada Arzneimittel AG, Stada M&D Srl, Stadapharm GmbH)

- Leflunomide (MAHs : Aurobindo N.V., Aurobindo Pharma (Malta) Limited, Arrow Génériques, Puren Pharma GmbH & Co. KG, Aurovitas Pharma Polska Sp. z o.o., Generis Farmacêutica, S.A., Aurovitas Spain S.A.U., Aurobindo Pharma B.V., Milpharm Limited)
- Levomepromazine (MAH: Morningside Healthcare Limited)
- Linagliptin (Applicant: Genepharm S.A.)
- Loperamide (MAHs: Dr. Max Pharma s.r.o., Dawa Limited, Kent Pharmaceuticals Limited, Special Concept Development (UK) Limited, Strandhaven Limited. Applicant: Bristol Laboratories Limited, Cygnus Pharma Limited, Relonchem Limited)
- Lymecycline (MAHs: Brown & Burk IR Limited, Brown & Burk UK Limited, 2care4 Generics ApS, Laboratórios Atral, S.A., Morningside Healthcare Limited. Applicant: Lyrus Life Sciences Limted)
- Mebeverine (MAH: Morningside Healthcare (Malta) Ltd, Morningside Healthcare Limited. Applicant: Lyrus Life Sciences Limted)
- Mercaptopurine (Applicant: Morningside Healthcare (Malta) Ltd., Morningside Healthcare Limited)
- Metformin (MAHs: Almus France (500 mg), Almus S.R.L. (500 mg), C4 health GmbH, Morningside Healthcare Limited, Special Concept Development (UK) Limited)
- Methocarbamol (MAH: Noumed Life Sciences Limited)
- Methotrexate (Applicant: Focus Care Pharmaceuticals B.V.)
- Metronidazole (MAHs: Dawa Limited, Morningside Healthcare Limited)
- Midodrine (MAHs: Milstein C.V., Strandhaven Limited. Applicant: Crescent Pharma International Limited)
- Montelukast (Applicant: Perennial Pharma Ltd)
- Nefopam (MAH: Brown & Burk IR Limited, Brown & Burk UK Limited)
- Nevirapine (MAHs: Arrow Génériques, Aurobindo Pharma B.V., Aurovitas Spain S.A.U., Generis Farmacêutica, S.A., Milpharm Limited, Puren Pharma GmbH & Co. KG)
- Nilotinib (Applicants: Aenorasis S.A., Egis Pharmaceuticals PLC, Genus Pharmaceuticals Limited, Pharmascience International Limited, PharOS - Pharmaceutical Oriented Services Ltd., Viatris Healthcare Limited, Viatris Limited, Zentiva k.s.)
- Nitrofurantoin (MAHs: Bristol Laboratories Limited, Lyrus Life Sciences Limited. Applicant: Strandhaven Limited)
- Nortriptyline (MAHs: Generics (UK) Limited, Mylan Pharmaceuticals Limited. Applicant: Bristol Laboratories Limited)
- Olanzapine (MAHs: Arrow Génériques, Aurobindo N.V., Aurobindo Pharma (Italia) S.r.L., Aurobindo Pharma (Malta) Limited, Aurobindo Pharma B.V., Aurobindo Pharma Limited, Aurovitas Pharma Polska Sp. z o.o., Aurovitas Spain S.A.U., Bristol Laboratories Limited, Generis Farmacêutica, S.A., Milpharm Limited, Orion Corporation, Pharmacons AD, Pharmconsul s.r.o., PUREN Pharma GmbH & Co. KG. Applicant: PharmConsul s.r.o.)
- Oxcarbazepine (Applicant: Umedica Netherlands B.V.)
- Oxybutynin (MAHs: Brillpharma Limited, Syri Limited, Syri Pharma Limited t/a Thame Laboratories)
- Pazopanib (Applicant: Torrent Pharma (Malta) Ltd, Torrent Pharma (UK) Limited)
- Phenoxymethylpenicillin (MAHs: Alter Pharma NV, Brown & Burk UK Limited, Orifarm Generics A/S)
- Phenytoin sodium (MAH: Accord UK Limited)
- Pilocarpine (MAHs/Applicants: Milstein C.V., Strandhaven Limited. Applicants: Milstein C.V., Morningside Healthcare Limited)
- Pirfenidone (MAH/Applicant: UMEDICA NETHERLANDS B.V.)
- Posaconazole (MAHs: Aliud Pharma GmbH, betapharm Arzneimittel GmbH, Crescent Pharma Limited, Dr Reddy's Laboratories (UK) Limited, EG SpA, Genepharm S.A., Glenmark Arzneimittel GmbH, Glenmark Pharmaceuticals s.r.o., Morningside Healthcare Limited, Mylan Ireland Limited, Mylan, Lda., Mylan SpA, Neon Healthcare Limited, ratiopharm GmbH, Stada Arzneimittel, Stada

Arzneimittel AG, Teva B.V., Thornton & Ross Limited, Viatris Limited, Viatris Sante, Zentiva Pharma GmbH)

- Prednisolone (MAHs: Brillpharma Limited, Bristol Laboratories Limited, Crescent Pharma International Limited, Crescent Pharma Limited)
- Primidone (MAH: Teva UK Limited)
- Propofol (MAHs: Baxter B.V., Baxter Healthcare Limited, Baxter Holding B.V.)
- Racecadotril (MAHs: Arrow Génériques, Generis Farmacêutica, S.A., Klinge Pharma GmbH, Opella Healthcare Austria GmbH, Opella Healthcare Czech s.r.o.., Sanofi Romania SRL, Opella Healthcare Slovakia s.r.o., Zentiva France. Applicant: US Pharmacia Sp. z o.o.)
- Ramipril (Applicant: Brillpharma Limited)
- Ranolazine (MAH: Umedica Netherlands B.V., Rafarm. Applicants: Rafarm, Umedica Netherlands B.V. Applicants: DOC Generici S.r.l., Dr Reddy's Laboratories (UK) Limited, Elpen Pharmaceutical Co. Inc., Hexal AG, Hexal Aktiengesellschaft, Innovis Pharma S.A., Morningside Healthcare Limited, Sandoz Pharmaceuticals d.d., Sandoz SpA, Umedical Limited, Win Medica S.A., Zentiva k.s., Zentiva Pharma UK Limited, Umedica Netherlands B.V.)
- Sertraline (Applicant: Morningside Healthcare Limited)
- Sildenafil (MAHs: Mabo Farma, S.A., Umedica Netherlands B.V., Umedica Limited, Relonchem Limited. Applicants: Remedica Ltd.)
- Sitagliptin/metformin (50/850mg only: +pharma arzneimittel gmbh, Genericon Pharma GmbH, Sandoz GmbH, Belupo lijekovi i kozmetika, d.d., Heaton k.s., Sandoz d.d., Hexal A/S, Biogaran, Evolupharm, Sandoz, 1 A Pharma GmbH, Hexal AG, DOC Generici S.r.l., PharOS - Pharmaceutical Oriented Services Ltd., Sandoz Farmacêutica, Lda., Sandoz Farmaceutica S.A., Sandoz S.R.L., Maddox Pharma Swiss B.V., Sandoz B.V.)
- Solifenacin (MAHs: Brillpharma (Ireland) Limited, Brillpharma Limited)
- Sorafenib (MAHs: EG (Eurogenerics) NV, G.L. Pharma GmbH, Hexal AG, LABORATORIO STADA, S.L., Sandoz Farmaceutica S.A., Remedica Ltd, Sandoz - SA-NV – Belgium, Sandoz B.V., Sandoz d.d., Sandoz d.o.o., Sandoz Farmacêutica, Lda., Sandoz GmbH, Sandoz Pharmaceuticals d.d., Sandoz S.R.L., Stada Arzneimittel AG, Sandoz s.r.o., Stada d.o.o., Stadapharm GmbH, Stada M&D Srl. Applicant: Sandoz A/S)
- Sunitinib (MAH: Farmex d.o.o., LV System Service, Latvia)
- Tadalafil (MAHs: Aflofarm Farmacja Polska Sp. z o.o., Aliud Pharma GmbH, Ardez Pharma, spol. s r.o., Avianta Pharma Limited, Belupo lijekovi i kozmetika, d.d., Ciclum Farma Unipessoal, Lda., Clydesdale Pharma Portugal, Unipessoal Lda., Clydesdale Pharma Ltd, EG (Eurogenerics) NV, Denk Pharma GmbH & Co. KG, Crescent Pharma Limited, G.L. Pharma GmbH, EG LABO - Laboratoires Eurogenerics, EG SpA, Laboratoires Majorelle, Genepharm S.A., GP-Pharm, S.A., Lannacher Heilmittel Ges.m.b.H., LABORATORIO STADA, S.L., Laboratorios Q Pharma S.L., Pharmacons AD, Mabo Farma, S.A., Northumbria Pharma Limited, Sapiens Pharmaceuticals Ltd, Lemesos, Farmak International Sp.z.o.o., Stada Arzneimittel AG, Stadapharm GmbH, Stada M&D Srl, Xantis Pharma Limited, Umedica Netherlands B.V., Umedica Limited. Applicants: Genepharm S.A., LaNova farmaceutici S.r.l., Rontis Hellas Medical and Pharmaceutical Products S.A.)
- Teriflunomide (Applicants: Aurobindo Pharma (Italia) S.r.l., Generis Phar, Unipessoal Lda, Generis Farmacêutica, S.A., Milpharm Limited)
- Timolol (Applicant: Strandhaven Limited)
- Topiramate (Applicants: Arrow Génériques, Milpharm Limited)
- Tramadol (MAHs: Almus France, Almus Farmaceutica S.A.U., Morningside Healthcare Limited, Special Concept Development (UK) Limited. Applicant: Cygnus Pharma Limited)
- Tranylcypromine (Applicant: Morningside Healthcare Limited)
- Trazodone (MAHs: Brillpharma (Ireland) Limited, Bristol Laboratories Limited, Dawa Limited, Neuraxpharm Arzneimittel GmbH, Neuraxpharm Bohemia s.r.o., Strandhaven Limited, Waymade

PLC, Zista Pharma Limited. Applicants: Aurobindo Pharma (Italia) S.r.l., Aurobindo Pharma B.V., Aurovitas Spain S.A.U., Generis Farmacêutica, S.A., Neuraxpharm Bohemia s.r.o., Cygnus Pharma Limited, Phagecon - Servicos e Consultoria Farmaceutica, Lda.)

- Trifluoperazine (MAH: Morningside Healthcare Limited)
- Trospium (MAH: Accord Healthcare Limited)
- Vildagliptin (MAHs: Clydesdale Pharma LTD, Crescent Pharma Limited, Denk Pharma GmbH & Co. KG, Elpen Pharmaceutical Co. Inc, Genepharm S.A., Laboratorios Anova - Produtos Farmacêuticos Lda, LifeWell Pharmaceutical & Healthcare, Lda., Morningside Healthcare Limited, Mylan AB, Mylan Lda, Mylan SpA, Viatris Limited, Viatris Sante, Vipharm S.A., Win Medica S.A. Applicant: Sapiens Pharmaceuticals Ltd)
- Vildagliptin/metformin (MAHs: Elvim, SIA, Latvia, Genepharm S.A., LifeWell Pharmaceutical & Healthcare, Lda., Pharmacons AD, SIA Elvim, Supremex Kft., Vipharm S.A.)
- Zonisamide (Applicant: Rosemont Pharmaceuticals Limited)

2.2.2. Category 2 medicinal products

This category encompasses products for which MAHs have provided data from alternative bioequivalence studies vis-à-vis the EU reference medicinal product conducted at other facilities than Synapse.

Sitagliptin 100 mg. Study code: AS/BE/MAR-20/0005.

Marketing Authorisation Holders: Heaton K.S.; PharOS - Pharmaceutical Oriented Services Ltd; Genericon Pharma GmbH; +pharma arzneimittel gmbh; Maddox Pharma Swiss B.V.; Sandoz GmbH; Sandoz S.R.L.; Sandoz Pharmaceuticals d.d.; Hexal A/S; Hexal AG; Sandoz; 1 A Pharma GmbH; Sandoz d.d.; Sandoz B.V.; Sandoz Farmacêutica, Lda.; Sandoz Farmaceutica S.A., Evolupharm; DOC Generici S.r.l.

Sitagliptin/metformin 50/1000 mg. Study code: AS/BN/MAR-20/0007.

Marketing Authorisation Holders: Heaton K.S.; Sandoz GmbH; Sandoz; Sandoz d.d.; 1 A Pharma GmbH; Hexal A/S; Hexal AG; PharOS - Pharmaceutical Oriented Services Ltd; Sandoz Farmacêutica, Lda.; Sandoz Farmaceutica S.A., Sandoz B.V.; Sandoz S.R.L.; Genericon Pharma GmbH; +pharma arzneimittel gmbh; Maddox Pharma Swiss B.V.; BIOGARAN, Evolupharm; DOC Generici S.r.l., Belupo lijekovi i kozmetika, d.d.

Having assessed both alternative studies, the CHMP considers that they support the bioequivalence of these medicinal products to their respective EU reference medicinal products.

The CHMP further noted that at time of initial marketing authorisation of those sitagliptin-containing medicinal products, the conduct of a further bioequivalence study for the 25 mg and 50 mg strength had been waived, based on the 100 mg batch used in the Synapse study. The same 100 mg batch was used in the Synapse study, and in study AS/BE/MAR-20/0005, therefore results of the latter study can be extrapolated to the 25 mg and 50 mg strengths.

The CHMP noted that the initial marketing authorisation of those sitagliptin/metformin-containing medicinal products relied on separate bioequivalence studies for each strength, both performed at Synapse, whereas no alternative study or data to waive such need has been provided for the 50/850 mg strength.

Therefore, the CHMP is of the opinion that the benefit-risk balance of the medicinal products in category 2 (products listed in **Annex IA** containing sitagliptin and sitagliptin/metformin 50/1000 mg)

remains positive, except for products listed in **Annex IB** containing sitagliptin/metformin 50/850 mg which benefit-risk balance is negative.

2.2.3. Category 3 medicinal products

This category encompasses medicinal products for which applicants/MAHs have requested biowaivers (i.e. claims to fulfil the criteria for a BCS-based biowaiver as described in Appendix III of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98)) to establish bioequivalence to an EU reference medicinal Product.

Nortriptyline 10 mg and 25 mg: Marketing Authorisation Holders: Pharmafile Limited and Alissa Healthcare Research Limited. Nortriptyline can be classified as BCS Class I molecule since its high solubility and complete absorption has been proven. Furthermore, there are no differences in excipients between test and reference product that would be expected to influence the pharmacokinetics of the product. The dissolution test method has been performed according to the guideline and demonstrated similarity of dissolution profiles between the test and reference medicinal product.

Sitagliptin 25 mg, 50 mg and 100 mg: Applicant: Belupo lijekovi i kozmetika d.d. Sitagliptin can be classified as BCS Class I molecule since its high solubility and complete absorption has been proven. In addition, sitagliptin product-specific bioequivalence guidance (EMA/CHMP/158934/2016) classifies sitagliptin as a BCS Class-I molecule. Furthermore, there are no differences in excipients between test and reference product that would be expected to influence the pharmacokinetics of the product. The dissolution test method has been performed according to the guideline and demonstrated similarity of dissolution profiles between the test and reference medicinal product for the three strengths (i.e. 25 mg, 50 mg and 10 mg).

Conclusion:

For products listed in Annex IA containing nortriptyline and sitagliptin, the CHMP considers that the biowaiver request is acceptable. The bioequivalence is therefore established and the benefit-risk balance for these products remains positive.

2.3. Response from the contract research organisation (CRO)

The CRO Synapse 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 made a number of allegations exclusively pertaining to the GCP inspection carried out by the Spanish competent authority (AEMPS), and attempted to explain or resolve the findings. The CRO responses constitute allegations on the validity of the inspections instead of relevant and substantiated information as regards their impact on the benefit-risk balance of authorised medicinal products or pending marketing authorisation applications. The responses submitted by the CRO in reply to the question above are therefore considered to be outside the scope of the CHMP.

Concerns on the validity of the conclusions reached further to the inspections carried out by national inspectorates should be raised to the relevant inspectorate and in accordance with the applicable national rules.

For the purpose of the assessment to be performed by the CHMP in the present referral, EMA consulted with the Spanish Competent Authority with the aim of confirming whether the points raised and the additional information and justifications provided by the CRO brought new elements not taken into account during the GCP inspection process, and whether these new elements could have an impact on the conclusions reached in the inspection report and/or on the scope of the present Article 31 referral.

On 19 October 2023, the Spanish competent authority confirmed that the responses submitted by the CRO do not impact the inspection outcome or the decision of triggering the referral.

In view of the above confirmation, the CHMP continued the assessment of the matter referred to it as per the notification received under Article 31 of Directive 2001/83/EC.

3. Benefit-risk balance

3.1. Initial benefit-risk balance assessment

The severity and the extent of the findings identified further to the inspection carried out by the AEMPS in November 2020 and 2022 in relation to data generated at Synapse indicated that the quality management system was compromised and cast serious doubts on the validity and reliability of the data of BE studies (clinical and bioanalytical part) conducted at the CRO.

The CHMP cannot rule out beyond reasonable doubt that critical GCP violations at the site have affected the validity and reliability of 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. Although it is acknowledged that audits or inspections carried out in the past at Synapse may have had positive outcomes, the absence of findings does not guarantee that the data has not been impacted since GCP violations may have not been detected even if present. The findings identified in relation to data generated at Synapse are considered to reflect broader problems concerning the suitability of the quality management system and the overall reliability of all data generated at Synapse and no review or audit of unreliable data can be used to address the concerns. 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. More importantly, pharmacovigilance activities cannot substitute the demonstration of bioequivalence.

Results of bioequivalence studies with non-EU reference products have been provided. Non-EU medicinal products do not meet the definition of "reference medicinal product" provided by Article 10(2)(a) of Directive 2001/83/EC. As such, results from bioequivalence studies using non-EU reference medicinal products can therefore not be accepted for demonstrating said bioequivalence.

In conclusion, in the absence of reliably proven bioequivalence vis-à-vis the EU reference medicinal product, or, as regards well-established use products, in the absence of demonstration of how the data supporting the medicinal product referred in the scientific literature used for at least ten years is relevant to the well-established product, the requirements of Article 10 or 10a of Directive 2001/83/EC cannot be considered fulfilled. The efficacy and safety of the medicinal products cannot be established and therefore, the benefit-risk balance cannot be considered positive.

Alternative bioequivalence data or appropriate justification for BCS-biowaivers were submitted to demonstrate the bioequivalence of:

- the medicinal products:
    - Nortriptyline: Nortriptyline film-coated tablets Alissa Healthcare Research Limited and Pharmafile Limited;
    - Sitagliptin: Anau, Sitagliptin PharOS, Sitagliptin Genericon, Sitagliptin +pharma, Sitagla, Sitagliptin Sandoz GmbH, Sitagliptin Sandoz, Sitagliptin Hexal, Sitagliptin GNR, Sitagliptin 1 A Pharma, Sitagliptina Sandoz, Sitagliptina Sandoz Farmaceutica, Sitagliptin Evolugen; Sitagliptin DOC Generici;
    - Sitagliptin/metformin (50/1000 mg only): Sipactimet, Sitagliptin/Metformin PharOS, Sitagliptin/Metformin hydrochlorid Genericon, Sitagliptin/Metformin +pharma, sitagliptin/metforminklorid Genericon, Sitagliptine/Metformine hydrochloride Genericon, Sitagliptin/Metforminhydrochlorid +pharma, Sitaglamet, Sitagliptin/Metformin BGR, Sitagliptin/Metformin Sandoz GmbH, Sitagliptin/ Metformin Hydrochloride Sandoz, Sitagliptin/Metformin Hexal, Sitagliptine/Metformine GNR, Sitagliptin/Metformin 1 A PHARMA, Sitagliptine/Metformine Evolugen, Sitagliptine/Metformine hydrochloride DOC Generici, Condias Combi, Metformina+Sitagliptina Sandoz, Sitagliptina/Metformina Sandoz Farmaceutica; and of
- the marketing authorisation applications for Gitas and Condias (sitagliptin).

The CHMP considers that the bioequivalence of those products has been demonstrated and recommends the maintenance of the marketing authorisations mentioned above, and concludes that, with regards to the marketing authorisation application, bioequivalence has been demonstrated vis-à-vis the EU reference medicinal product using alternative data.

Alternative bioequivalence studies carried out at a different CRO and not the studies performed at Synapse were referred to as the pivotal evidence to demonstrate the bioequivalence of Metformin - Win Medica, Novatin Limited, Sunitinib – Bluefish Pharmaceuticals AB, Genepharm S.A., Sapiens Pharmaceuticals Ltd and Pharmevid s.r.o., Fesoterodine - Genus Pharmaceuticals Limited, and Ursodeoxycholic acid – Teva B.V, Teva UK Limited. The CHMP concluded that the benefit-risk balance of Metformin - Win Medica, Novatin Limited, Sunitinib – Bluefish Pharmaceuticals AB, Genepharm S.A., Sapiens Pharmaceuticals Ltd and Pharmevid s.r.o., Fesoterodine - Genus Pharmaceuticals Limited and Ursodeoxycholic acid – Teva B.V, Teva UK Limited, were not affected by the concerns related to the studies performed by Synapse and recommended the maintenance of the marketing authorisations.

All other MAHs/applicants did not submit evidence demonstrating the bioequivalence of their medicinal products. In the absence of the demonstration of bioequivalence vis-à-vis the EU reference medicinal product, or in the absence of demonstration of how the data supporting the medicinal product vis-à-vis the medicinal product referred in the scientific literature demonstrating that the active substance of the medicinal product concerned has been in used for at least ten years is relevant to the well-established medicinal use product, 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).

For marketing authorisation(s) of a medicinal product considered critical by the relevant national competent authorities, 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.

3.2. Re-examination procedure

Following the adoption of the CHMP opinion in December 2023, the below applicants/MAHs, some representing a number of applicants/MAHs as detailed in the next section, requested a re-examination of the CHMP opinion on the Article 31 referral for Synapse Labs Pvt. Ltd. according to Article 32(4) of Directive 2001/83/EC:

- Sandoz B.V. group of companies
- Farmex d.o.o.
- Rontis Hellas Medical and Pharmaceutical Products S.A.
- DOC Generici S.r.l.
- Elpen Pharmaceutical Co. Inc.
- PharOS - Pharmaceutical Oriented Services Ltd group of companies
- Aurobindo Pharma Limited group of companies
- Remedica Ltd

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 legal aspects of administrative procedures laid down in the legislation. As a result, 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.

The re-examination procedure is limited to the points of the opinion identified in grounds for re-examination submitted by the applicants/MAHs having notified the Agency of his intention to request a re-examination of the opinion, within 15 days after receipt of the opinion, and may be based only on the scientific data available to the CHMP for its initial assessment and before its initial opinion. Data submitted in relation to other authorised medicinal products, or not presented before adoption of the initial opinion were not taken into account by the CHMP in the context of the re-examination procedure.

3.2.1. Detailed grounds for re-examination submitted by the applicant/MAH and CHMP conclusions

Detailed grounds for re-examination of the CHMP recommendation were received from the following applicants and MAHs:

1. PharOS - Pharmaceutical Oriented Services Ltd., on behalf of:
    - Accord Healthcare B.V., Accord Healthcare Polska Sp. z o.o., Accord Healthcare S.L.U., STADA Arzneimittel AG, STADA M&D Srl, Stadapharm GmbH, EG LABO - Laboratoires Eurogenerics, Aliud Pharma GmbH, Dr Reddy's Laboratories (UK) Limited, Dr. Reddy's S.r.l., Reddy Pharma Iberia S.A., betapharm Arzneimittel GmbH, Biogaran (for **abacavir/lamivudine**);
    - Aliud Pharma GmbH, betapharm Arzneimittel GmbH, Biogaran, Laboratorio Stada S.L., STADA Arzneimittel AG, STADA M&D Srl, Dr Reddy's Laboratories (UK) Limited (for **atazanavir**);
    - Aliud Pharma GmbH, Biogaran, Clonmel Healthcare Ltd, EG (Eurogenerics) NV, EG LABO - Laboratoires Eurogenerics, EG S.p.A., Elpen Pharmaceutical Co. Inc, Laboratorio Stada S.L., Zentiva, k.s., STADA Arzneimittel GmbH, STADA Arzneimittel AG (for **darunavir**);
    - Aliud Pharma GmbH, Centrafarm B.V., Elpen Pharmaceutical Co. Inc, STADA Arzneimittel GmbH, STADA Arzneimittel AG, Stadapharm GmbH, Thornton & Ross Limited (for **deferasirox**);
    - Aliud Pharma GmbH, Biogaran, Centrafarm B.V., Clonmel Healthcare Ltd, Dr Reddy's Laboratories (UK) Limited, EG (Eurogenerics) NV, EG LABO - Laboratoires Eurogenerics, Elpen Pharmaceutical Co. Inc, Reddy Pharma Iberia S.A., STADA Arzneimittel AG, Stada d.o.o., betapharm Arzneimittel GmbH (for **efavirenz/emtricitabine/tenofovir**);
    - Biogaran, Generics (UK) Limited, Centrafarm B.V., EG (Eurogenerics) NV, EG LABO - Laboratoires Eurogenerics, Glenmark Arzneimittel GmbH, Glenmark Pharmaceuticals Europe Limited, Mylan Pharmaceuticals Limited, Mylan AB, Mylan Ireland Limited, STADA Arzneimittel AG, Stadapharm GmbH, Zentiva, k.s., Viatris Limited, Viatris Sante (for **erlotinib**);
    - Aliud Pharma GmbH, EG S.p.A., Laboratorio Stada, S.L., Newbury Pharmaceuticals AB, PharOS - Pharmaceutical Oriented Services Ltd, STADA Arzneimittel AG, Stadapharm GmbH, Stada M&D Srl, EG S.p.A. (for **lapatinib**);
    - EG (Eurogenerics) NV, G.L. Pharma GmbH, Laboratorio Stada S.L., STADA Arzneimittel AG, STADA M&D Srl, STADA d.o.o., Stadapharm GmbH (for **sorafenib**).
2. Remedica Ltd (for **abacavir/lamivudine, atazanavir, efavirenz/emtricitabine/tenofovir, erlotinib, darunavir, lapatinib** and **sorafenib**).
3. Aurobindo Pharma Limited group of companies, on behalf of:
    - Arrow Génériques, Aurobindo Pharma B.V., Generis Farmacêutica, S.A. (for **atazanavir**)
    - Arrow Génériques, Aurobindo N.V., Aurobindo Pharma S.r.L., Aurobindo Pharma Limited, Aurobindo Pharma B.V., Aurobindo Pharma Limited, Aurovitas Pharma Polska Sp. z o.o., Aurovitas Spain S.A.U., Generis Farmacêutica, S.A., Milpharm Limited, Orion Corporation, PharmConsul s.r.o., PUREN Pharma GmbH & Co. KG. (for **olanzapine**)
4. Sandoz B.V. group of companies on behalf of:
    - Hexal AG, Rowex Ltd., Sandoz Pharmaceuticals d.d, Sandoz, Sandoz B.V., Sandoz Limited, Sandoz S.R.L., Sandoz SpA, (for **atazanavir**);

- Hexal AG, Sandoz GmbH, Sandoz - SA-NV - Belgium, Sandoz d.o.o., Sandoz A/S, Sandoz Pharmaceuticals d.d., Sandoz, Rowex Ltd., Sandoz Farmacêutica, Lda., Sandoz S.R.L., Sandoz Farmaceutica, S.A., Sandoz B.V., Sandoz Limited, Sandoz SpA (for **darunavir**);
- Hexal AG, Sandoz B.V., Sandoz Farmaceutica, S.A., Sandoz Pharmaceuticals d.d., Sandoz GmbH (for **efavirenz/emtricitabine/tenofovir**);
- Sandoz Limited, Sandoz SpA, Sandoz A/S, Sandoz Pharmaceuticals d.d, Sandoz Farmaceutica S.A., Sandoz - SA-NV - Belgium, Sandoz Hungaria KFT., Sandoz B.V., Sandoz GmbH, Hexal AG (for **erlotinib**);
- 1 A Pharma GmbH, Hexal AG, Hexal A/S, Sandoz B.V., Sandoz Pharmaceuticals d.d., Sandoz GmbH, Sandoz Farmaceutica Lda, Sandoz Farmaceutica S.A. (for **sitagliptin/metformin 50/850mg**).
- Sandoz GmbH, Sandoz Pharmaceuticals d.d., Sandoz S.R.L., Sandoz d.o.o., Sandoz - SA-NV - Belgium, Sandoz Hungaria KFT, Sandoz B.V. (for **sorafenib**).

5. Rontis Hellas Medical and Pharmaceutical Products S.A. (for **sitagliptin/metformin 50/850mg**), on behalf of:
    - Genericon Pharma Gesellschaft m.b.H, +pharma arzneimittel gmbh, PharOS - Pharmaceutical Oriented Services Ltd, HEATON K.S., Maddox Pharma Swiss B.V.
6. DOC Generici S.r.l. (for **sitagliptin/metformin 50/850mg**).
7. Farmex d.o.o (for **sunitinib**)

The grounds submitted were taken into consideration and assessed by the CHMP.

The points raised in the applicants and MAHs' detailed grounds for re-examination argue that the benefit risk balance of their products subject to a suspension or not granting of the MA is positive and are summarised below.

3.2.1.1. Abacavir/lamivudine, atazanavir, darunavir, deferasirox, efavirenz/emtricitabine/tenofovir, erlotinib, lapatinib and sorafenib

Based on a number of analyses of study data using dedicated software, the above listed MAHs of abacavir/lamivudine, atazanavir, darunavir, deferasirox, efavirenz/emtricitabine/tenofovir, erlotinib, lapatinib and sorafenib-containing products claimed that no data manipulations could be identified and that the reported study results may well be reliable.

3.2.1.2. Olanzapine

The above listed MAHs of olanzapine-containing products referred to an alternative bioequivalence study conducted at a different facility as the pivotal evidence to demonstrate the bioequivalence of their product and not the studies performed at Synapse. The study conducted at a different facility had been used to establish bioequivalence for a specific polymorphic form of olanzapine active substance (Form-I) to the EU reference medicinal product at the time of the initial marketing authorisation. The study conducted at Synapse having been performed with a different polymorphic form of olanzapine active substance (Form-II). At a later point the use of this form was implemented in the manufacture of olanzapine orodispersible tablets, with no change in the composition of the finished product. According to the MAHs, the change in polymorphic form is unlikely to impact *in vivo* availability. Hence, the BE study conducted with the Form-I would demonstrate the bioequivalence of the current olanzapine orodispersible tablets with the Form-II.

3.2.1.3. Sitagliptin/metformin

Based on analyses of data of the two studies conducted for sitagliptin/metformin using a specially developed software to detect overlapping of data study subjects, the above listed MAHs of sitagliptin/metformin-containing products claims that no such anomalies could be detected. Further, the MAHs claim that their sitagliptin/metformin product fulfils the criteria for a BCS-based biowaiver, and the criteria for a strength biowaiver for the 50/850 mg strength based on the demonstrated bioequivalence of the 50/1000mg strength, and presented data to support this claim.

3.2.1.4. Sunitinib

The MAH Farmex d.o.o claims that the same conclusions reached for "Sunitinib – Bluefish Pharmaceuticals AB, Genepharm S.A., Sapiens Pharmaceuticals Ltd and Pharmevid s.r.o." products, referred above under category I, should also apply to Nibufar as they had submitted the same information and data for the initial assessment and before adoption of the initial opinion.

3.2.2. CHMP discussion on grounds for re-examination

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

Regarding the two claims based on analyses of study data, the CHMP reiterated that in light of the nature, the severity and the extent of the findings identified further to the inspection carried out by the AEMPS in November 2020 and 2022 in relation to data generated at Synapse, the quality management system was considered compromised and serious doubts cast on the validity and reliability of the data of BE studies (clinical and bioanalytical part) conducted at the CRO. Indeed, given the failure of the quality management system to prevent and detect the occurrence of the findings, failures in other areas of the trials cannot be excluded. Hence, the CHMP cannot rule out beyond reasonable doubt that critical GCP violations at the site have not affected the validity and reliability of said studies and the arguments presented do not demonstrate that said studies can be relied upon. Therefore, the CHMP is of the opinion that the studies cannot be relied upon to establish bioequivalence vis-à-vis the EU reference medicinal product.

With regard to the alternative bioequivalence study conducted at a different facility for olanzapine and the data supporting a biowaiver claim for sitagliptin/metformin, the CHMP noted that these scientific data were not available for its initial assessment and before its initial opinion, and as such, in accordance with Article 62(1), fifth subparagraph, of Regulation (EC) No 726/2004, could not take these into account in the re-examination. Further for olanzapine, it is not agreed with the MAH that the study conducted at Synapse was not pivotal to the demonstration of bioequivalence of the current olanzapine orodispersible tablets with the polymorphic Form-II of the active substance as it has not been demonstrated that the change in polymorphic form did not affect the *in vivo* availability of the product.

In the absence of the demonstration of bioequivalence vis-à-vis the EU reference medicinal products, the efficacy and safety of the concerned medicinal products cannot be established and therefore, the benefit-risk balance cannot be considered positive.

The CHMP agrees that, similar to Sunitinib – Bluefish Pharmaceuticals AB, Genepharm S.A., Sapiens Pharmaceuticals Ltd and Pharmevid s.r.o., the benefit-risk balance of Nibufar (sunitinib, Farmex d.o.o) was not affected by the concerns related to the studies performed by Synapse. While the fed-state study was conducted at Synapse, a fasted-state study was performed at a different CRO and according to the EMA Product Specific Bioequivalence Guideline a fasted-state study is sufficient to support the

demonstration of bioequivalence. This was not considered for the initial opinion due to a technical issue. The final opinion is updated accordingly.

3.2.3. 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 identified MAHs/applicants, the CHMP:

1. Concluded that the benefit-risk balance of Nibufar is positive, and recommends the maintenance of the marketing authorisation.
2. Confirmed its previous conclusions that bioequivalence vis-à-vis the EU reference medicinal product had not been demonstrated for the other medicinal products/marketing authorisation applications subject to the re-examination whose benefit-risk balance is considered not favourable. The CHMP therefore confirmed its conclusion that the following marketing authorisation applications do not satisfy the criteria for authorisation, whilst the marketing authorisations of the following medicinal products should be suspended:

    - Abacavir/lamivudine (MAHs: Remedica Ltd, Accord Healthcare S.L.U, Accord Healthcare B.V., Accord Healthcare Polska Sp. Z o.o., Biogaran, EG LABO – Laboratoires Eurogenerics, Aliud Pharma GmbH, betapharm Arzneimittel GmbH, Dr. Reddy's S.r.l., Stadapharm GmbH, Stada Arzneimittel AG, Stada M&D Srl, Reddy Pharma Iberia S.A., Dr Reddy's Laboratories Ltd.)
    - Atazanavir (MAHs: Remedica Ltd, Stada Arzneimittel AG, Sandoz, Sandoz S.R.L., Sandoz B.V., Arrow Génériques, Biogaran, Hexal AG, Aliud Pharma GmbH, betapharm Arzneimittel GmbH, Rowex Ltd., Sandoz SpA, Sandoz Pharmaceuticals d.d., Generis Farmacêutica, S.A., Stada M&D Srl, LABORATORIO STADA, S.L., Aurobindo Pharma B.V., Dr Reddy's Laboratories (UK) Limited, Sandoz Limited)
    - Darunavir (MAHs: Stada Arzneimittel AG, Stada Arzneimittel GmbH, Sandoz GmbH, Sandoz – SA-NV, Sandoz d.o.o., Sandoz Pharmaceuticals d.d., Sandoz A/S, Sandoz B.V., Sandoz, Sandoz SpA, Sandoz Farmacêutica, Lda., Sandoz Farmacéutica, S.A., Sandoz S.R.L., Sandoz Limited, Remedica Ltd, Biogaran, EG LABO – Laboratoires Eurogenerics, Hexal AG, Aliud Pharma GmbH, Elpen Pharmaceutical Co. Inc, Rowex Ltd., Clonmel Healthcare Ltd, EG S.p.A., LABORATORIO STADA, S.L., Zentiva k.s.,)
    - Deferasirox (MAHs: Stada Arzneimittel GmbH, Stadapharm GmbH, Aliud Pharma GmbH, Elpen Pharmaceutical Co. Inc, Centrafarm B.V., Stada Arzneimittel AG, Thornton & Ross Limited)
    - Efavirenz/emtricitabine/tenofovir (MAHs: Sandoz GmbH, EG (Eurogenerics) NV, Stada d.o.o., Remedica Ltd, Stada Arzneimittel AG, Sandoz Pharmaceuticals d.d., Sandoz, EG LABO – Laboratoires Eurogenerics, Biogaran, Aliud Pharma GmbH, Hexal AG, betapharm Arzneimittel GmbH, Elpen Pharmaceutical Co. Inc, Clonmel Healthcare Ltd, Sandoz Farmaceutica, S.A., Reddy Pharma Iberia S.A., Sandoz B.V., Centrafarm B.V., Dr Reddy's Laboratories (UK) Limited)
    - Erlotinib (MAHs: EG (Eurogenerics) NV, Sandoz – SA-NV, Sandoz Pharmaceuticals d.d., Mylan Pharmaceuticals Limited, Remedica Ltd, Mylan AB, Stada Arzneimittel AG, Sandoz A/S, Biogaran, EG – Laboratoires Eurogenerics, Viatris Sante, Sandoz Farmaceutica S.A., Hexal AG, Stadapharm GmbH, Mylan Ireland Limited, Sandoz Hungária Kereskedelmi Kft., Zentiva k.s., Viatris Limited, Mylan SpA, Sandoz SpA, Mylan, Lda., Sandoz, Centrafarm B.V., Glenmark

Arzneimittel GmbH, Glenmark Pharmaceuticals Europe Limited, Sandoz B.V., Sandoz Limited, Generics (UK) Limited. Applicant: Sandoz Hungaria KFT)

- Lapatinib (MAHs: Aliud Pharma GmbH, EG S.p.A., LABORATORIO STADA, S.L., Newbury Pharmaceuticals AB, PharOS – Pharmaceutical Oriented Services Ltd., Remedica Ltd, Stada Arzneimittel AG, Stada M&D Srl, Stadapharm GmbH)
- Olanzapine (MAHs: Arrow Génériques, Aurobindo N.V., Aurobindo Pharma S.r.L., Aurobindo Pharma Limited, Aurobindo Pharma B.V., Aurobindo Pharma Limited, Aurovitas Pharma Polska Sp. Z o.o., Aurovitas Spain S.A.U., Generis Farmacêutica, S.A., Milpharm Limited, Orion Corporation, PharmConsul s.r.o., PUREN Pharma GmbH & Co. KG. Applicant: PharmConsul s.r.o.)
- Sitagliptin/metformin 50/850mg (MAHs: +pharma arzneimittel gmbh, Genericon Pharma GmbH, Sandoz GmbH, Belupo lijekovi i kozmetika, d.d., Heaton k.s., Sandoz Pharmaceuticals d.d., Hexal A/S, Biogaran, Evolupharm, Sandoz, 1 A Pharma GmbH, Hexal AG, DOC Generici S.r.l., PharOS – Pharmaceutical Oriented Services Ltd., Sandoz Farmacêutica, Lda., Sandoz Farmaceutica S.A., Sandoz S.R.L., Maddox Pharma Swiss B.V., Sandoz B.V.)
- Sorafenib (MAHs: EG (Eurogenerics) NV, G.L. Pharma GmbH, Hexal AG, LABORATORIO STADA, S.L., Laboratorios Cinfa, S.A., Remedica Ltd, Sandoz – SA-NV, Sandoz B.V., Sandoz Pharmaceuticals d.d., Sandoz d.o.o., Sandoz Farmacêutica, Lda., Sandoz GmbH, Sandoz S.R.L., Stada Arzneimittel AG, Sandoz s.r.o., Stada d.o.o., Stadapharm GmbH, Stada M&D Srl. Applicant: Sandoz A/S).

4. Conditions 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 as defined in Article 10(2)(a)), or, for well-established use products, bioequivalence vis-à-vis the medicinal product referred in the scientific literature has been demonstrated.

5. 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 Synapse, a contract research organisation (CRO) located in Kharadi, Pune, India, since the set-up of the site under the name Synapse Labs Pvt. Ltd.

- The CHMP reviewed available data and information provided in writing by the applicants and MAHs, as well as information provided by Synapse. Synapse did not provide any new information that changed the conclusions laid out in the notification for this procedure.
- The CHMP also considered the grounds for re-examination submitted by the applicants/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.
- 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 not submitted, or 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 (Annex IB).
    - Marketing authorisation applications for which alternative bioequivalence data or a justification was not submitted, or submitted but considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product (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 (Annex IA) should be maintained, as the benefit risk balance of these marketing authorisation is considered favourable.

b. Marketing authorisations for medicinal products for which bioequivalence data or justification were not submitted or submitted but 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 therefore 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.

c. Marketing authorisation applications for which bioequivalence data or justification were not submitted or submitted but 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.

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