Public Assessment Report
Scientific discussion

Olmesartan /Amlodipino/ Hidroclorotiazida Stadapharm 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, and 40/10/25 mg film-coated tablets
ES/H/0546/01-05/DC

Olmesartan /Amlodipino/ Hidroclorotiazida Cinfa 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, and 40/10/25 mg film-coated tablets
ES/H/0636/01-05/DC

Olmesartan medoxomil/Amlodipine besilate/ Hydrochlorothiazide

Applicant: Intas Third Party Sales 2005, S.L.

This module reflects the scientific discussion for the approval of **Olmesartan/Amlodipino/Hidroclorotiazida Stadapharm/Cinfa film-coated tablets**. The procedure was finalised on **May 2019**. For information on changes after this date please refer to the module 'Update'.

INTRODUCTION

This decentralised procedure application concerns fixed-dose combination (FDC) products of Olmesartan medoxomil (OM) Amlodipine besilate (AB) and hydrochlorothiazide (HCT) film-coated tablets, at different combinations of strengths (i.e., 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, and 40/10/25 mg). The applicant is Intas Third Party Sales 2005, S.L, while the proposed Marketing Authorisation Holders (MAH) are Laboratorio Stada, S.L. (**ES/H/0546/01-05/DC**) and Laboratorios Cinfa, S.A. (**ES/H/0636/01-05/DC)**.

The marketing authorisation application (MAA) for the OM/AML/HCT FDC products is submitted as a mixed MAA according to Article 8(3) of Directive 2001/83/EC as known active substance. During a Scientific Advice on February 17th, 2017, the Spanish Agency of Medicines and Medical Devices (AEMPS) supported the use of this legal basis. According to this Article, the Applicant is not required to provide the results of nonclinical investigations when there is a sufficient well-documented clinical experience to establish all aspects of clinical efficacy and safety. In that event, the test and trial results are replaced by appropriate scientific literature.

The Concerned Member State involved in this procedure is IT.

The approved indication if for the treatment of essential hypertension, as substitution therapy:

- [NAME] is indicated as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a single-component formulation given concomitantly at equivalent therapeutic doses.

The recommended dose of olmesartan medoxomil/amlodipine/hydrochlorothiazide is 1 tablet per day. The maximum recommended dose is 40 mg/10 mg/25 mg per day.

A comprehensive description of the product information is given in the SmPC.

According to the EMA *Guideline on clinical investigation of medicinal products in the treatment of hypertension* (EMA/CHMP/29947/2013/Rev. 4, 2016), "when a substitution indication is sought and all substances of the FDC are well known and the joint application of the three components is already in widespread use in the proposed dosage strengths and has proven to be efficacious and safety, demonstration of bioequivalence of the components in free combination with the FDC is the pivotal aspect in this setting."

The three active substances of the triple FDC have been extensively used as monotherapies in patients with essential hypertension, with a recognized efficacy and acceptable safety profile. In addition, two of the active substances in the FDC are also approved as dual FDCs for combination therapy (OM/AML; OM/HCT) and have substantial clinical use for the same uses than those of the intended MAA indication.

Overall, the Applicant considers that the clinical efficacy and safety profile of the proposed FDC is supported based on: i) the individual effective and safe use of each active component and the dual combinations for the same indication as that proposed in this application; ii) the widespread concomitant use of the three components of this FDC according to clinical guidelines of the European and American medical societies and the World Health Organization; iii) the co-prescription data of the three substances contained in the triple FDC. Therefore,

besides the bioequivalence studies between the Applicant's FDC and the three mono-components taken as free combination, no additional studies to assess the pharmacological properties of the OM/AML/HCT or their potential interactions have been conducted.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Reference Member State has granted a marketing authorisation for Olmesartan/Amlodipino/Hidroclorotiazida Stadapharma/Cinfa 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, and 40/10/25 mg film-coated tablets.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Drug substance
The drug substances are Olmesartan medoxomil, Amlodipine besilate and Hydrochlorothiazide. There are Ph. Eur. monographs for these drug substances.
The applicant has used the CEP procedure.
The Ph. Eur. Certificates of Suitability support the quality of the active ingredients. The CEPs include re-test period for the drug substances.

Drug Product
The drug product is presented as bevel-edged, film-coated tablets, debossed on one side and plain on the other side. Each strength shows different colour and debossing.
The name, address and responsibilities of the finished product manufacturers have been provided. An adequate description of the manufacturing process, indicating critical steps and in-process controls, is included. Industrial batch sizes are stated.
The excipients used in the formulation are compedial, except the Opadry used for the coating.
The specification proposed is acceptable. Analytical methods are adequately described and their validation is performed according to ICH.
Proposed packaging is Aluminium-Aluminium blisters. The material is compliant with the EU Commission Regulation nº 10/2011.
Stability studies have been performed according to ICH. The proposed shelf-life and storage conditions can be accepted.

II-2 Non-clinical aspects

Olmesartan medoxomil, Amlodipine besilate and Hydrochlorothiazide are well known active substances. For the present Application, and taking into account that it is a fixed combination of three well-known active substances, the non-clinical information has been obtained from the published literature. The dossier describes, mainly using data and results of published literature, the pharmacodynamics, pharmacokinetics and general toxicity profile of Olmesartan medoxomil, Amlodipine besilate and Hydrochlorothiazide. The Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005) has been taken into account for this Assessment Report.

Pharmacology

The three components of the medical product (olmesartan medoxomil, amlodipine besilate and hydrochlorothiazide) are well known active substances with extensive use in clinical practice either in monotherapy or combined.

The results presented in this section exhibit that each one of the components are effective for the long-term treatment of hypertension. Additionaly, no pharmacodynamic interactions are expected as all three active substances work through different but complementary pathways and have been already used in combination in patients.

According to the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005), when the fixed combination under development includes compounds for which there is sufficiently documented human experience of their individual and combined use, safety studies in animals are in general not required (CPMP/EWP/240/95). The three drug substances are routinely used in the clinical practice. Therefore, no new non-clinical pharmacological investigations have been conducted in support of this Application.

Pharmacokinetics

No new non-clinical pharmacokinetics studies were performed with the triple combination (OM/AML/HCT). Nevertheless, there is extensive clinical experience with the combination and available non-clinical data about each substance were summarized by the Applicant.
Olmesartan is able to distribute to milk in rats. Olmesartan does not interact with CYP metabolism and, consequently, no relevant pharmacokinetic drug interactions between Olmesartan and drugs metabolized by CYP are expected. On the other hand, it is published that amlodipine is also an inhibitor of CYP3A2; so, CYP3A4 inhibitors and inducers play a critical role in amlodipine metabolism. Moreover, in vitro studies suggest that HCT is a P-gp inhibitor. However, non-clinical data suggesting pharmacokinetic drug interactions between HCT and other P-gp regulators were not found in the literatureInformation regarding pharmacokinetic drug-drug interactions for the dual and triple combinations of OM, AML and HCT were not found in the literature.

Toxicology

The toxicological information has been obtained from studies available in the literature. The three components have been extensively studied in a variety of preclinical species and additionally through the therapeutic use in humans over many years.
Chronic toxicity studies indicate all three active substances are well tolerated, and based on the non-clinical toxicity profile of each substance, no novel safety issues of clinical concern are expected for the fixed dose combination product at therapeutic doses. In accordance with Guideline on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (ICH M3), the three compounds are considered as late stage entities (Phase III or post marketing medicinal products). Consequently, no combination studies are recommended unless there is a significant concern.

Environmental Risk Assessment (ERA)

Since this pharmaceutical product contains three well-known chemical entities that are already marketed in the EEA, it will not lead to an increased use of the products and exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

II.3 Clinical aspects

Introduction

The three active substances of the triple FDC have been extensively used as monotherapies in patients with essential hypertension, with a recognized efficacy and acceptable safety profile. In addition, two of the active substances in the FDC are also approved as dual FDCs for combination therapy (OM/AML; OM/HCT) and have substantial clinical use for the same uses than those of the intended MAA indication. Overall, the Applicant considers that the clinical efficacy and safety profile of the proposed FDC is supported based on: i) the individual effective and safe use of each active component and the dual combinations for the same indication as that proposed in this application; ii) the widespread concomitant use of the three components of this FDC according to clinical guidelines of the European and American medical societies and the World Health Organization; III) the co-prescription data of the three substances contained in the triple FDC. Therefore, besides the bioequivalence studies between the Applicant's FDC and the three mono-components taken as free combination, no additional studies to assess the pharmacological properties of the OM/AML/HCT or their potential interactions have been conducted.

Biowaiver

The Applicant applies for the 20/5/12.5, 40/5/12.5, 40/5/25, 40/10/12.5, and 40/10/25 strengths. The Applicant performed bioequivalence studies on 40/5/25 mg, 40/5/12.5 mg, 40/10/12.5 and 40/10/25 mg.
A biowaiver for the remaining 20/5/12.5 mg is claimed based on the following general requirements described in section 4.1.6 of the Guideline on Investigation of BE: same manufacturing process, drugs input is linear over the therapeutic range, same qualitative composition, same ratio between active substance and excipients and similar dissolution profile under identical conditions between all strengths.
The compositions of the strengths are proportional (i.e., 20/5/12.5 and 40/10/25 strengths).
With regard to the dissolution profile, the Applicant has submitted the dissolution profiles in the three pHs 1.2, 4.5 and 6.8 (QC media).
At pH 1.2, the average values dissolved in all batches of both strengths for all the three analytes are higher than 85% at 15 minutes. Therefore, they are considered similar.
At pH 4.5, the average values dissolved in all batches of both strengths for HCT and Amlodipine are higher than 85% at 15 minutes. Therefore, they are considered similar. For olmesartan, the dissolution profiles for both strengths (test and reference product) are poor and incomplete (not exceed 24% of the dose), but the same incomplete profiles are observed in all strengths. Therefore, they are considered similar.
The Applicant submitted dissolution profiles at pH 6.8 to compare 2 tablets of 20/5/12.5 mg strength versus 1 tablet of 40/10/25 mg strength as recommended in the guideline. Since not more than 85% is dissolved in 15 minutes for olmesartan, the f_2 similarity factors were calculated. For the batches PT1729, PT02680 and PT2683 the f_2 similarity factors conclude similarity ($f_2 > 50$).
The bioequivalence between test and reference products has been demonstrated consistently for the 40/10/25 mg strength. Those data data can be extrapolated to the additional strength (i.e. 20/5/12.5 mg), since all general biowaiver criteria described in section 4.1.6 of the Guideline on investigation of bioequivalence are fulfilled.

Bioequivalence

To support the application, the Applicant has submitted the following studies:

a) Bioequivalence study no. 0334-17: an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of fixed dose combination of Olmesartan Medoxomil, Amlodipine, Hydrochlorothiazide Tablets 40/5/25 mg of Intas Pharmaceuticals Limited India with co-administration of Olmetec® 40 mg film-coated tablets of, Istin™ 5 mg tablets and Esidrex® 25 mg tablets in normal healthy, adult, human subjects under fasting condition.

b) Bioequivalence study 0337-17: an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of fixed dose combination of Olmesartan Medoxomil, Amlodipine Besilate, Hydrochlorothiazide Tablets 40/5/12.5 mg of Intas Pharmaceuticals Limited, India with co-administration of Olmetec® (olmesartan medoxomil 40 mg film coated tablets), Istin™ (amlodipine besilate 5 mg tablets) and Esidrex® (hydrochlorothiazide 25 mg tablets) (one half tablet of 25 mg equivalent to 12.5 mg dose) in normal healthy, adult, human subjects under fasting condition,

c) Bioequivalence study 0335-17: an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of fixed dose combination of Olmesartan Medoxomil, Amlodipine Besilate, Hydrochlorothiazide Tablets 40/10/12.5 mg of Intas Pharmaceuticals Limited, India with co-administration of Olmetec® (olmesartan medoxomil 40 mg film coated tablets), Istin™ (amlodipine besilate 10 mg tablets) and Esidrex® (hydrochlorothiazide 25 mg tablets) (one half tablet of 25 mg equivalent to 12.5 mg dose) in normal healthy, adult, human subjects under fasting condition,

d) Bioequivalence study 0096-18: an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of fixed dose combination of Olmesartan Medoxomil, Amlodipine, Hydrochlorothiazide Tablets 40/10/12.5 mg of Intas Pharmaceuticals Limited, India with co-administration of Olmetec® 40 mg film-coated tablets, Istin™ 10 mg tablets and Esidrex® 25 mg tablets (one half tablet of 25 mg equivalent to 12.5 mg dose) in normal healthy, adult, human subjects under fasting condition,

e) Bioequivalence study 0336-17; an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of fixed dose combination of Olmesartan Medoxomil, Amlodipine, Hydrochlorothiazide Tablets 40/10/25 mg of Intas Pharmaceuticals Limited India with co-administration of Olmetec® 40 mg film-coated tablets, Istin™ 10 mg tablets and Esidrex® 25 mg tablets in normal healthy, adult, human subjects under fasting condition,

f) Bioequivalence study 0097-18: an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of fixed dose combination of Olmesartan Medoxomil, Amlodipine, Hydrochlorothiazide Tablets 40/10/25 mg of Intas Pharmaceuticals Limited, India with co-administration of Olmetec® 40 mg film-coated tablets, Istin™ 10 mg tablets and Esidrex® 25 mg tablets in normal healthy, adult, human subjects under fasting condition.

No additional clinical pharmacology studies were conducted taking into consideration that the pharmacokinetic characteristics of the components are already well established.

The above approach is considered acceptable, since the Applicant seeks an indication of substitution therapy in adult patients whose BP is adequately controlled on the combination of OM, AML and HCT for the FDC under development. The bioequivalence studies have been conducted between the co-administered products as free combination and the triple FDC.

All bioequivalence studies were performed in the fasting conditions since all the three reference monocomponents can be taken without regard to food.

Analytical methods

The pre-study validation of the analytical methods is satisfactory and demonstrated adequate precision and accuracy (both intra- and inter-run) within the calibration ranged and adequate selectivity, sensitivity, no matrix effect and no-carry-over effect.

The long-term freezer stability for HCT and olmesartan has been established for three hundred and forty-eight (348) days and ninety-eight (98) days in presence of combination drug (Amlodipine) at -65 ± 10°C and -22 ± 5°C in the method validation and covers the maximum study sample storage period from first blood draw to last sample preparation in all studies.

The long-term freezer stability for R-and S-amlodipine has been established for two hundred and twenty-four (224) days and two-hundred and twenty-five (225) days in presence of combination drug (HCT and olmesartan) at -65 ± 10°C and -22 ± 5°C in the method validation and covers the maximum study sample storage period from first blood draw to last sample preparation in all studies.

The QC samples were shown to be stable under the conditions of the bioanalytical method.

The calibration standards and QCs of the in-study validation were acceptable in all studies.

The QCs are representative of the study samples concentration.

The study samples were analysed, with a calibration curve, and four sets of four non-zero QCs (16 QCs) for HCT and olmesartan and two sets of four non-zero QCs (8 QCs) for R- and S-amlodipine. Since study samples of the 2 periods of two subjects (100 samples for olmesartan and HCT and 92 samples for R- and S-amlodipine) were analysed in each run, the number of QCs samples relative to the number of study samples is adequate (>5%).

The same instrument that was used for validation was used for samples analysis.

The reasons for reanalysis of the samples are acceptable (sample concentration above the ULOQ, Internal Standard Variation, No ISTD response was obtained and significant analyte concentration in pre-dose samples.

Dilution of some samples was necessary (factor x5 was validated).

No sample re-injection was performed.

The ISRs were performed in all studies in a total of 190 samples for HCT and olmesartan and 179 samples for R- and S-amlodipine which is in accordance with section 6 “Incurred Samples reanalysis” of the Guideline on bioanalytical method validation (10% of the samples should be reanalysed in case the number of samples is less than 1000 samples and 5% of the number of samples exceeding 1000 samples). For the samples reanalysed, the ISRs were acceptable for all bioequivalence studies for all analytes as the ISRs was greater than 95.0% of the samples reanalysed were within the acceptance range (± 20%).

Approximately twenty percent of the subject’s chromatograms have been submitted for all studies.

To support the application, the Applicant has submitted the following studies:

- Bioequivalence study no. 0334-17 for the 40/5/25 mg strength.
- Bioequivalence study 0337-17 for the 40/5/12.5 mg strength

- Two bioequivalence studies 0335-17 and 0096-18 for the 40/10/12.5 mg strength.
- Two bioequivalence studies 0336-17 and 0097-18 for the 40/10/25 strength.

40/5/25 mg strength (Study 0334-17)
Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product administered concomitantly with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ln-transformed C_{max} and AUC_{0-t}, or AUC_{0-72} (for R- and S-amlodipine) are within the acceptance range of 80-125%.
40/5/12.5 mg strength (Study 0337-17)
Based on the statistical analysis submitted by the Applicant the test the test product is equivalent to the reference product administered concomitantly with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ln-transformed C_{max} and AUC_{0-t}, or AUC_{0-72} (for R- and S-amlodipine) are within the acceptance range of 80-125%.
40/10/12.5 mg strength
For this strength, two bioequivalence studies were performed (i.e., 0335-17 and 0096-18). For the first one, the test product is not equivalent to the reference as the 90% confidence intervals for the ln-transformed C_{max} for olmesartan is outside the acceptance range of 80-125%, although for the second one, the bioequivalence was demonstrated since the 90% confidence intervals for the ln-transformed C_{max} is within the acceptance range of 80-125%.
40/10/25 mg strength
For this strength, two bioequivalence studies were performed (i.e., 0336-17 and 0097-18). For the first one, the test product is not equivalent to the reference as the 90% confidence intervals for the ln-transformed AUC_{0-t} for olmesartan is outside the acceptance range of 80-125%, although for the second one, the bioequivalence was demonstrated since the 90% confidence intervals for the ln-transformed C_{max}, AUC_{0-t} or AUC_{0-72} are within the acceptance range of 80-125%.
20/5/12.5 mg strength
The biowaiver for the 20/5/12.5 mg strength is claimed based on the data of the studies carried out with the 40/10/25 strength. These data can be extrapolated to the lower strength since all general biowaiver criteria described in section 4.1.6 of the Guideline on investigation of bioequivalence are fulfilled.

Pharmacokinetics and Pharmacodynamics

No clinical studies evaluating the PK and PD of the Applicant's FDC are available. OM/AML/HCT combines three antihypertensive compounds with complementary mechanisms to control BP in patients with essential hypertension. Bibliographic search data analysis has been provided for clinical pharmacology, which is acceptable for this kind of application.

Clinical efficacy and safety

The Applicant has not conducted specific clinical efficacy or safety studies with the triple FDC, since the monocomponents are well-known substances with well-defined efficacy, safety and tolerability profiles, administered alone and concomitantly in clinical practice in Europe.

A summary of published data on the efficacy and safety of each active substance as well as of the concomitant use of the three monocomponents as a free combination and in the authorised dual FDC formulations for the treatment of essential hypertension has been provided. In addition to those studies demonstrating efficacy of the monocomponents, four studies were identified that support the efficacy of the Applicant's triple FDC at all to-be-marketed formulations. The four studies included a total of 3.063 patients, with essential hypertension (of

which 1,022 patients received the triple combination) with all being open-label studies (Neutel et al., 2004; Chrysant et al., 2009; Volpe et al., 2009b; Ruilope et al., 2013), and three of these were study extension periods of controlled designs. The higher strength of the triple combination (40/10/25), which is expected to have the higher risk of side effects, was used in the four studies and was well-tolerated.

Of the triple combination trials, active treatment lasted between 24 and 44 weeks, and 2 trials had a 2–4-week run-in phase with placebo (Neutel et al., 2004) or with monotherapy (Ruilope et al., 2013). The primary efficacy endpoint for the majority of studies was mean change in BP from baseline for each treatment until the end of study and between treatments (Chrysant et al., 2009; Volpe et al., 2009b,; Ruilope et al., 2013), or the percentage of patients who achieved BP goal for each treatment and/or by the end of the study (Neutel et al., 2004).

Justification of proposed doses: The primary aim of FDC therapy is to reduce the number of tablets the patient has to take, which may potentially enhance adherence to therapy, and therefore the efficacy of treatment. Thus, the target population for the proposed FDC are those patients who are already stabilized on an optimal dose of the three active substances, that is OM + AML + HCT, where the single-component formulations will be substituted by the triple FDC. The current FDC is not for initial use or add-on therapy.

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From a clinical standpoint, the fixed-dose combination is justified for the treatment of hypertension as a substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a single-component formulation given concomitantly at equivalent therapeutic doses.

Bioequivalence of the applied product has been shown in compliance with the requirements of European Union guidance documents to the mono-component reference products. A biowaiver for the 20/5/12.5 mg strength was accepted.

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the mono-components. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in May 2019.