

Public Assessment Report Scientific discussion

TRINOMIA 100 mg/20 mg/2.5 mg hard capsules
TRINOMIA 100 mg/20 mg/5 mg hard capsules
TRINOMIA 100 mg/20 mg/10 mg hard capsules
(Acetylsalicylic Acid, Atorvastatin calcium
tryhydrate and Ramipril)
Registration number in Spain: 74980

EU-procedure number:
ES/H/0241/001-003/DC
ES/H/0241/001/E/001-003

Applicant: Ferrer International, S.A

This module reflects the scientific discussion for the approval of TRINOMIA 100 mg/20 mg/2.5 mg hard capsules, TRINOMIA 100 mg/20 mg/5 mg hard capsules and TRINOMIA 100 mg/20 mg/10 mg hard capsules.

The initial decentralized procedure ES/H/0241/001-003/DC was finalized on December 17th, 2013 and the repeat use ES/H/0241/001-003/E/001 was finalised on October 1st, 2014. For information on changes after this date please refer to the module 'Update'.



I. INTRODUCTION

This application concerns a fixed dose combination of Acetylsalicylic Acid, Atorvastatin calcium trihydrate and Ramipril under TRINOMIA 100 mg/20 mg/2.5 mg, TRINOMIA 100 mg/20 mg/5 mg and TRINOMIA 100 mg/20 mg/10 mg hard capsules trade names.

The legal basis of the application is Article 10b of Directive 2001/83/EC, as amended, i.e. fixed combination application.

With Spain as the Reference Member State in the initial Decentralized Procedure started in April 2013, Ferrer Internacional, S.A. applied for the Marketing Authorisations in the following Concerned Member States: EL, RO and SE.

The intended indication is the secondary prevention of cardiovascular accidents as substitution therapy, in patients adequately controlled with the monocomponents given concomitantly at equivalent therapeutic doses.

In a repeat use procedure with Spain as the Reference Member State, which was started in July 2014, Ferrer Internacional, S.A., applied for the Marketing Authorisations for TRINOMIA 100 mg/20 mg/2.5 mg hard capsules, TRINOMIA 100 mg/20 mg/5 mg hard capsules and TRINOMIA 100 mg/20 mg/10 mg hard capsules in AT, BE, BG, CZ, FI, FR, DE, IT, PL, PT and IE for the same indication as described above.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted the authorisation of TRINOMIA 100 mg/20 mg/2.5 mg, TRINOMIA 100 mg/20 mg/5 mg and TRINOMIA 100 mg/20 mg/10 mg hard capsules for Ferrer International S.A.

II. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

DRUG SUBSTANCE

Acetylsalicylic acid

General Information

The drug substance is described in Ph.Eur.

The quality of Acetylsalicylic acid is supported by CEP Procedure.

Manufacturing, Control and Stability

For the drug substance Acetylsalicylic acid batch analytical data have been provided for three production batches demonstrating compliance with the drug substance specification.



The proposed re-test period/ storage condition is included in the CEP.

Ramipril

General Information

The drug substance is described in Ph.Eur.

The quality of Ramipril is supported by CEP Procedure.

Manufacturing, Control and Stability

For the drug substance Ramipril batch analytical data have been provided for three production batches demonstrating compliance with the drug substance specification.

The proposed re-test period/ storage condition is included in the CEP or supported by stability data.

Atorvastatin Calcium Trihydrate

General Information

Atorvastatin calcium trihydrate is described in Ph.Eur.

The quality of Atorvastatin Calcium Trihydrate is supported by the ASMF procedure.

Manufacturing, Control and Stability

For the drug substance Atorvastatin Calcium Trihydrate, sufficient information about specifications and analytical methods has been provided.

Batch analytical data have been provided for three production batches demonstrating compliance with the drug substance specification.

Stability studies have been performed with the drug substance. The proposed re-test period/ storage condition is justified.

DRUG PRODUCT

Description of the Drug Product

The finished product corresponds to a fixed-dose combination medicinal product containing acetylsalicylic acid, atorvastatin and ramipril as drug substances. The pharmaceutical dosage form is a hard capsule which contains 5 film-coated immediate release tablets: Two film-coated tablet of 50 mg acetylsalicylic acid, Two film-coated tablet of 10 mg atorvastatin, One film-coated tablet of 2.5, 5 or 10 mg ramipril.

Composition of the Drug Product

Trinomia 100 mg/20 mg/ 10 mg hard capsules

Size 0 hard shell gelatin capsules (approx. length: 21.7 mm) with opaque pale pink-coloured body and cap, imprinted with öAAR 100/20/10ö containing two white or nearly white film-coated tablet engraved öASö of 50 mg Acetylsalicylic acid, two greenish-brownish film-coated



tablets engraved öATö of 10 mg atorvastatin and one pale yellow film-coated tablet engraved öR1ö of 10 mg ramipril.

Trinomia 100 mg/20 mg/ 5 mg hard capsules

Size 0 hard shell gelatin capsules (approx. length: 21.7 mm) with opaque pale pink-coloured cap and opaque light grey-coloured body, imprinted with öAAR 100/20/5ö containing two white or nearly white film-coated tablet engraved öASö of 50 mg Acetylsalicylic acid two greenish-brownish filmcoated tablets engraved öATö of 10 mg atorvastatin and one pale yellow film-coated tablet engraved öR5ö of 5 mg ramipril

Trinomia 100 mg/20 mg/ 2.5 mg hard capsules

Size 0 hard shell gelatin capsules (approx. length: 21.7 mm) with opaque light grey-coloured body and cap, imprinted with öAAR 100/20/2.5ö containing two white or nearly white film-coated tablet engraved öASö of 50 mg acetylsalicylic, two greenish-brownish film-coated tablets engraved öATö of 10 mg atorvastatin and one pale yellow film-coated tablet engraved öR2ö of 2.5 mg ramipril.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained. The discriminatory power of the proposed dissolution methods has been demonstrated.

Manufacture

The steps of the manufacturing process are described in detail. IPCs are defined. Satisfactory validation data have been provided.

Control of Drug Product

The product specifications cover appropriate parameters for this dosage form.

Validations of the analytical methods have been presented. Batch analysis has been performed on three batches of each dose. The batch analysis results show that the finished products meet the proposed specifications.

Container Closure System

The information about the reference standards and container closure system is acceptable. The hard capsules of Acetylsalicylic acid 100 mg / Atorvastatin 20 mg / Ramipril 2.5/5/10 mg are packed in aluminium oriented polyamide film (OPA)/Aluminium/polyvinylchloride (PVC) blister.

Stability

The conditions used in the stability studies are according to the ICH stability guideline.

The proposed shelf-life of 24 months without special storage conditions is acceptable.

II-2 Non-clinical aspects

Trinomia contains three active substances, ramipril, atorvastatin and acetylsalicylic acid. Ramipril is an angiotensin-converting enzyme (ACE) inhibitor, used to treat hypertension and congestive heart failure, atorvastatin is a statin, used for lowering blood cholesterol and



acetylsalicylic acid belongs to the group of acid-forming non-steroidal anti-inflammatory drugs with analgesic, antipyretic anti-inflammatory and platelet aggregation inhibiting properties.

For the present application of Trinomia, no new nonclinical data have been submitted. Since is a fixed combination of three well-known active substances, the non-clinical information has been mainly obtained from the published literature. Furthermore, taking into account the wide post-marketing experience and the different clinical trials that have been performed with these active substances, shown a high effectiveness and an optimal safety profile in the prevention of cardiovascular events, no new non-clinical studies are considered necessary.

The dossier describes, using data and results of published literature, the pharmacodynamics, pharmacokinetics and general toxicity profile of ramipril, atorvastatin and acetylsalicylic acid. *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.

The Applicant has performed an Environmental Risk Assessment Report (ERA). This report includes a Phase I Estimation of Exposure and a bibliographic Phase II Tier A Environmental Fate and Effects analysis. There is no concern related to environmental risk.

Regarding the excipients, all are used at accepted concentrations and none are anticipated to have any effect on the pharmacology or safety-in-use of the product.

Aniline, benzaldehyde and p-fluorobenzaldehyde compounds as impurities have been identified as having structural alert for genotoxicity. Although aniline possesses a structural alert for genotoxicity (in the form of an aromatic amino group), numerous negative bacterial reverse mutation assays (Ames test) overrule a structural alert and no further studies would be required providing the level of aniline remains below ICH Q3A (R2) qualification threshold. In view of the absence of a structural alert and the extensive negative Ames-test data, benzaldehyde and 4-fluorobenzaldehyde are of no concern with respect to genotoxicity and these non-genotoxic impurities can be present in a drug substance up to the relevant ICH Q3A (R2) qualification threshold according to *the Q&A on the CHMP Guideline on the Limits of Genotoxic Impurities*.

Pharmacology

The three components of the Trinomia, ramipril, atorvastatin and acetylsalicylic acid have pharmacological actions that have been examined in experimental animals and in humans over many years. As a consequence, a vast amount of data has been accumulated on their actions and the mechanisms by which they achieve their beneficial cardiovascular effects. Each possesses particular individual properties that offer protection against aspects of cardiovascular disease and also properties that may offer positive benefits to existing cardiovascular conditions. Since the majority of these properties overlap, there is good evidence available that a combination of the three offers positive therapeutic benefits, and they have been offered in combination for a long period. Trinomia offers a convenient form of this treatment, and there is no reason to suspect that this form of treatment will have any deleterious effects on the pharmacology of each of the components.

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). Trinomia contains drug substances that have already been used in

combination in clinical practice. Both the proposed doses for the drug substances and the dosing schedule for the Trinomia correspond to those of the drug substances when administered individually. The concomitant use of statins, ACE inhibitors and acetylsalicylic acid is a common practice for the prevention of cardiovascular complications. The updated Guideline from the American Heart Association and American College of Cardiology Foundation (AHA/ACCF) for the secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease reported the recommendations for the treatment of these patients largely based on results from recent clinical trials. Therefore, no new pharmacological investigations have been conducted in support of this Application.

Pharmacokinetics

No pharmacokinetics studies were carried out with Trinomia. A considerable amount of data has been published that relates to the pharmacokinetics (absorption, distribution, metabolism and excretion) of the active ingredients of Trinomia. Published information from the usual nonclinical species is limited but, where there are gaps in the database, the nonclinical data have been augmented with clinical data. In addition, all the active ingredients of Trinomia have been used clinically for a long period of time and these data are really intended to assist in demonstrating safety in clinical use rather than to validate the nonclinical safety studies (which have previously been validated in their separate Marketing Authorisation Applications).

Similarly, there is a very limited amount of preclinical data relating to pharmacokinetic drug interactions whereas clinical data are far more extensive. Again, because of the extended clinical experience with the individual active ingredients of Trinomia, clinical data are far more relevant to this Application and help to underscore the likelihood for safety in use of Trinomia. The anticipated clinical findings are well known and adverse interactions are considered to be predictable and monitorable. Clinically, there are no significant interactions between the three components when they are taken concurrently, and there are no serious adverse effects due to pharmacological interactions between the drugs at standard doses routinely taken in separate treatment schedules where the dosages employed are comparable to those doses that will be used with the Trinomia. In conclusion, no further nonclinical pharmacokinetic is considered necessary.

Toxicology

The Applicant submits data from some studies available in the literature. The three components of Trinomia have been extensively studied in experimental animals and in human therapeutic use over many years. Therefore, the combination product consists of three well-described compounds and the potential toxicities associated with each are well understood, limited, and in the target population are unlikely to pose significant risk at the dosages proposed. No new toxicological studies have been conducted to support this Application and it is deemed acceptable considering the pre-clinical knowledge of the individual compounds in the combination product. The lack of new nonclinical pharmacological and pharmacokinetic investigations is considered wholly acceptable because the information available is extensive and covers a history of considerable clinical use. According to 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 RMS considers that the toxicity profiles of ramipril, atorvastatin and acetylsalicylic acid have been well-defined, that all areas of potential concern have been adequately documented and there is no information

contained in the literature that would suggest that any of these compounds would be hazardous in combination at the doses proposed in the Applicant's Trinomia.
Therefore, new studies are not deemed necessary.

Environmental Risk Assessment (ERA)

An Environmental Risk Assessment report has been submitted. In the ERA phase I, calculation of the Predicted Environmental Concentration (PEC) and action limits has been determined. As the PEC_{surfacewater} values for ramipril (0.05 g/L), atorvastatin (0.2 g/L), and acetylsalicylic acid (0.5 g/L), are all above the action limit of 0.01 g/L further risk assessment in Phase II of the procedure is required. A bibliographic ERA Phase II has been conducted for the three drug substances of the fixed combination.

Furthermore, the Applicant submits a review from the Swedish environmental classification of pharmaceuticals, in which ramipril and atorvastatin are recognised to have an insignificant environmental risk. As regards acetylsalicylic acid, it is degraded in the environment and does not accumulate in aquatic organisms, hence the environmental impact due to acetylsalicylic acid usage can be considered very low.

II.3 Clinical aspects

Introduction

No specific efficacy clinical studies have been carried out with the fixed-dose combination developed by Ferrer Internacional, S.A. since the proposed indication is the substitution therapy in patients adequately controlled with the monocomponents given concomitantly at equivalent therapeutic doses according to the Guideline on Clinical Development of Fixed Combination Medicinal products (CHMP/EWP/240/95 Rev. 1) and the Questions and Answers Document on the Clinical Development of Fixed Combinations of Drugs belonging to different Therapeutic Classes in the field of Cardiovascular Treatment and Prevention (CHMP/EWP/191583/2005).

The monocomponents are already being given concomitantly to the patients, it is not expected any different interaction to that existing in treated patients. However, the Applicant has submitted a bibliographic revision of the individual components.

All three active substances of the fixed-dose combination have Marketing Authorisations in European Countries and have been used as free combination in the clinical practice for long time with an adequately established benefit/risk ratio for the secondary prevention of cardiovascular events. The use of this fixed-dose combination is expected to simplify therapy and improve patient compliance.

Ramipril (ATC Code: C09AA05) is a blood-pressure-lowering drug that belongs to the pharmacotherapeutic class of the angiotensin converting enzyme (ACE) inhibitors (ACEI). It is used in the treatment of hypertension, heart failure, and after myocardial infarction to improve survival in patients with clinical evidence of heart failure. It is also used to reduce the risk of cardiovascular events in patients with several risk factors. ACE inhibitors lower the production of angiotensin II, therefore causing smooth muscle cell relaxation, vasodilatation and the reduction of peripheral vascular resistance (PVR). On the other hand, it reduces the cardiac output (CO) through the reduction of aldosterone activity. Both the reduction of PVR and CO leads to pressure reduction. Ramipril was initially launched by Aventis in 1991 under the name Altace. Proprietary medicinal products containing this compound are available worldwide.

Atorvastatin (ATC Code: C10AA05) is a lipid-lowering drug which belongs to the pharmacotherapeutic class of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins). Atorvastatin was first synthesised in 1985 at Parke-Davis Warner-Lambert Company (now Pfizer) as Lipitor. In many countries, it is now available as a generic preparation. Likewise, proprietary medicinal products containing this compound are available worldwide.

Acetylsalicylic acid (ATC Code: B01AC06), commonly known as aspirin, belongs to the class of antiplatelet drugs. It inhibits platelet aggregation by acetylation of the platelet cyclooxygenase (COX) at the functionally important amino acid serine529. This prevents the access of the substrate, arachidonic acid, to the catalytic site of the enzyme at tyrosine385 and results in an irreversible inhibition of platelet-dependent thromboxane formation in blood platelets. Furthermore, in blood vessel walls the enzyme inhibition prevents the synthesis of prostacyclin, which is a potent vasodilator. This compound was launched in 1899 by Bayer under the tradename Aspirin and it has been marketed worldwide for more than a century under different tradenames.

Pharmacokinetics

To support the application, the Applicant has submitted a bioequivalence study öAn open label, two periods, two sequences, crossover, controlled, randomised, single dose pivotal bioequivalence study of atorvastatin 20mg, ramipril 10mg and acetylsalicylic acid 100mg fixed-dose combination capsule vs. equal doses of coadministered Cardyl® 20mg film coated tablets + Acovil® 10mg tablets + Aspirin N® 100mg, tablets (reference formulations) in healthy volunteers under fasting conditionsö.

Since all components of the fixed combination will be administered at the same dose interval and timing than in monotherapy, scenario A of Question 1 of the Questions and answers document on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention (CHMP/EWP/191583/2005) applies for the clinical development of the proposed fixed-dose combination. According to this, single bioequivalence studies testing the rate and extent of absorption of each component of the combination as compared to each substance administered in monotherapy it is acceptable to support a claim for a substitution indication in cardiovascular prevention for a fixed-dose combination which components are administered at the same dose interval and timing. Since ramipril kinetics is linear over the entire therapeutic dosage range (Manhem et al., 1985; Meisel et al., 1994), the highest strength of ramipril was selected to conduct the bioequivalence study and it is considered acceptable.

In addition, as the overall bioavailability of three drugs was unaffected by food, (the reason to administer acetylsalicylic acid preferably after meal is in order to reduce the risk of gastrointestinal effects) the study under fasting condition is acceptable.

Biowaiver

The fixed-dose combination is formulated as a hard gelatine capsule containing 5 film-coated tablets (two 50 mg acetylsalicylic acid tablet (100 mg), two 10 mg atorvastatin-tablets (20 mg) and one 2.5, 5 or 10 mg ramipril tablet (for more information please refer to biowaiver in the Clinical AR)

The bioequivalence of test and reference products has been demonstrated for 100/20/10 mg strength (please refer to section of results). These data can be extrapolated to 100/20/5 mg and 100/20/2.5 mg strengths because the criteria regarding manufacture process, qualitative composition of excipients, dissolution profiles and the ratio between amounts of active substances is fulfilled

Bioequivalence

Study Protocol number: ARA-BESD-02-ITQ/12

The clinical part of the study was performed at Institutia Medico-Sanitaria Publica, Clinical Hospital of the Ministry of Health of Moldavian Republic-Chisinau, Puskin Str. 51-The Republic of Moldavia.

The analytical portion was conducted at the analytical laboratory of Pharma Serv International Srl, 52 Sabinelor St., 050853-Bucharest, Romania within the validated stability period.

An open label, two period, two sequence, crossover, controlled, randomised, single dose pivotal bioequivalence study of atorvastatin 20mg, ramipril 10mg and acetylsalicylic acid 100mg fixed-dose combination capsule vs. equal doses of co-administered Cardil® 20mg film coated tablets + Acovil® 10mg tablets + Aspirin N® 100mg, tablets (reference formulations) in healthy volunteers under fasting conditions with a wash-out period of 28 days.

Blood samples were collected pre-dose and up to 12h for the quantification of acetylsalicylic acid and pre-dose and up to 72h for the quantification of ramipril and atorvastatin.

As described in the innovators SmPC, the bioavailability of the three drugs is unaffected by concomitant administration with food, therefore a 2x2 single-dose, cross-over in fasting condition is adequate.

The wash-out period of 28 days is considered adequate since the initial plasma elimination is approx. 14 hours for atorvastatin.

Considering the expected time to peak concentration (approx. between 0.25 to 2 hours) and the initial plasma elimination for the three drugs, the sampling schedule and the sampling time period of 72 hours seems long enough to estimate PK parameters.

Sampling is reasonably frequent over the first 2 hours and should be sufficient to allow an accurate measurement of T_{max} .

As the dosage of ASA and atorvastatin remain constant and the only active substance to be used at several doses is ramipril and since ramipril kinetics is linear over the entire therapeutic dosage range (Manhem et al., 1985; Meisel et al., 1994), the highest strength of ramipril was selected to conduct the bioequivalence study and it is considered acceptable.

The reference products are adequate and are from Spanish market (Cardil® and Acovil®) and from German market (Aspirin N®)

All batches were tested before expiry date and the CoA shows a similar content of acetylsalicylic acid, atorvastatin and ramipril. Therefore, content correction is not necessary.

In the present study, 127 adult healthy male and female (65) were screened. Out of 127, a number of 104 were enrolled (39 males and 65 females) and 101 completed the study and 102 subjects underwent the follow-up examination.

The number of subjects is adequate to show equivalence based on the intra-subject variability of the drugs and the study population is considered acceptable with regards to demographic characteristics.

The inclusion and exclusion criteria are considered to be acceptable.

The subject's withdrawals and drop-outs are considered to be acceptable.

The time deviations were minor and they had no impact on the study outcome. The other deviations were minor and have no impact on results of the study.

Pharmacokinetic data analysis

The following pharmacokinetic parameters were calculated using SAS® ver. 9.1 for atorvastatin, ramipril and acetylsalicylic acid after a single oral study using a non-compartmental method:

Primary parameters

- Maximum plasma concentration (C_{max}) was taken directly from the plasma concentration-time curve.



- AUC_{0-t}: area under the curve integrated, by the trapezoidal rule, from plasma concentration between time 0 to the last quantifiable sample.

Secondary parameters

- Time point of maximum plasma concentration (t_{max}) was taken directly from the plasma concentration-time curve.

Additional parameters

- AUC_{0- ∞} : area under the curve integrated from plasma concentration extrapolating to terminal elimination period
- AUC%extra: extrapolated area ($AUC_{0-\infty} - AUC_{0-t}$)/ $AUC_{0-\infty} * 100$
- $t_{1/2}$: calculated as $0.693/K_{el}$
- MRT: mean residence time

Statistical analysis

All statistical calculation was performed using PROC GLM SAS® ver. 9.1. Descriptive calculation was done for all pharmacokinetic parameters (arithmetic mean, geometric mean, SEM, standard deviation, median, range).

The effect of sequence, subject-within-sequence, period and treatment for C_{max} , AUC_{0-t} and AUC_{0- ∞} have been evaluated on log-transformed data, using ANOVA model implemented by GLM procedure of SAS®.

Values for the T_{max} parameter will be analyzed by a non-parametric approach (Wilcoxon Signed-Rank Test)

Based on the log-transformed parameters, the following criteria will be used to evaluate the bioequivalence between the test and reference products:

- The 90% confidence intervals of the relative mean plasma for atorvastatin, ramipril and acetylsalicylic acid AUC_{0-t} and C_{max} of the test to reference products should be between 80-125%.

The non-compartmental linear-trapezoidal rule calculation is adequate.

The pharmacokinetic software and method for AUC and C_{max} estimation are considered acceptable.

These pharmacokinetic variables are appropriate for a single dose bioequivalence study.

The statistical software is considered acceptable.

Using ANOVA model implemented by GLM procedure of SAS® is acceptable.

ANOVA analysis has been performed correctly. The terms used in the ANOVA model were sequence, subject within sequence, period and formulation and it is considered acceptable.

Analytical methods

Determinations of acetylsalicylic acid were performed by HPLC-MS/MS. Statement on GLP compliance and bio-analytical audits is given.

The pre-study validation of the analytical method is satisfactory. The in-study validation shows acceptable calibration standards and QC's.

Results

Linear and log-linear plots have been submitted and they show a correct characterisation of the exposure.

The 90% confidence intervals mean treatment T/R ratios were:

Drug	Parameter	Ratio T/R (%)	Lower CL	90%	Upper CL	90%
Atorvastatin	C_{max}	104.81	94.58		116.14	
	AUC_{0-t}	100.58	95.50		105.93	
Ramipril	C_{max}	101.52	91.51		112.62	
	AUC_{0-t}	113.96	108.13		120.11	
ASA	C_{max}	89.51	84.51		95.79	
	AUC_{0-t}	96.92	96.92		104.47	

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ln-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} for atorvastatin, ramipril and acetylsalicylic acid are within the acceptance range of 80-125%.

Pharmacodynamics

As the three components are well established in clinical use for a number of years the pharmacodynamics of each has been detailed in the individual development programmes. No specific clinical pharmacological study is needed for this dossier, in agreement with the requirements stated in the document CHMP/EWP/191583/2005 entitled "Questions and answers on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention."

Clinical efficacy

No efficacy clinical studies have been conducted with the fixed-dose combination taking into account:

- Ramipril, atorvastatin and acetylsalicylic acid have been widely used for decades and showed an adequate benefit risk/ratio which has been clearly established.
- The efficacy of all three active components of the fixed-dose combination for the secondary CV prevention is fully documented and evidence-based.
- The therapeutic indication of the fixed-dose combination as a substitution therapy.

The applicant has presented the co-prescription data for Ramipril/ASA, Atorvastatin/ASA and Atorvastatin/Ramipril in patients with a myocardial infarction or angina pectoris diagnosis (according to the secondary prevention indication) for Spain and four countries of UE (France, UK, Germany and UK). Co-prescription data, mainly from its use in secondary prevention after ischemic heart disease, support the use of the FDC.

The selected doses for ramipril and ASA are consistent with the innovators SmPC and supported by the recommendations from the available guidelines for secondary CV prevention.

Evidence suggests that reducing dosage demands is an effective single approach to enhancing medication adherence (*European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)*), so the fixed combination is expected at least from a theoretical point of view to improve therapeutic compliance over the three drugs administered separately.

In order to support a clinical benefit in medication adherence with the FDC, the applicant provided a meta-analysis in which the use of a FDC resulted in a 26% decrease in the risk of non-compliance compared with free-drug component regimen ($p < 0.0001$) (Bangalore, et al.

Am J Med. 2007; 120: 713-9). In addition, the UMPIRE trial results have been recently published (Thom, et al. JAMA. 2013;310:918-29). This study was designed to assess whether FDC delivery of aspirin, statin, and 2 blood pressure-lowering agents vs. usual care improves long-term adherence to indicated therapy and 2 major CVD risk factors, systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C). Results concluded that among patients with or at high risk of CVD, use of an FDC strategy for blood pressure, cholesterol, and platelet control vs. usual care resulted in significantly improved medication adherence at 15 months, supporting the enhancing medication adherence of the FDC vs. free-drug components. Improved medication adherence, however, was not translated into better cardiovascular outcomes. Despite UMPIRE was unable to show a reduction in CV events with the FDC strategy, it did not show major concerns precluding from the authorisation of the FDC. In fact, a positive improved medication adherence was found.

Clinical safety

A literature search and further bibliographic data analysis showing an extensive use of the three components as free combination in secondary cardiovascular prevention, with a recognised safety profile is provided by the applicant. Taking into account that the intended indication of the fixed-dose combination is a pure substitution indication that contains the three active substances with a wide therapeutic experience in the claimed indication at the proposed dosing schedule, a safety database based on the available experience on the free combination is deemed sufficient and therefore the need of additional safety data is precluded, according to the Guideline on Clinical Development of Fixed Combination Medicinal products (CHMP/EWP/240/95 Rev. 1).

The feasibility of the pharmaceutical form was questioned from a clinical perspective (capsules containing 5 individual tablets which are easily accessible by patients and may suppose a risk in terms of medication errors/compliance/mix-up). However, it is agreed that the closure of the gelatine capsules protects against accidental opening. Additional information regarding the protection of the closure system of capsules was included in SmPC.

The risk of prescription errors when dose-adjustment of individual components was questioned, too. However, since Trinomia is a substitution therapy no dose adjustment should be made. The patients adequately controlled with the monocomponents are directly switched to Trinomia and the prescriptor should substitute the prescription of the three monocomponents as free combination by the FDC.

During the procedure, the applicant clarified that the Trinoma capsule is size 0, which is worldwide accepted for medicinal use. Therefore, no particular difficulties in swallowing of the capsule are expected.

Discussion on the clinical aspects

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 AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} for atorvastatin, ramipril and acetylsalicylic acid are within the acceptance range of 80-125%. The bioequivalence of test and reference products has been demonstrated for 100/20/10 mg strength. These data can be extrapolated to 100/20/5 mg and 100/20/2.5 mg strengths because the criteria regarding manufacture process, qualitative composition of excipients, dissolution profiles and the ratio between amounts of active substances is fulfilled.



From a clinical standpoint, the fixed-dose combination is justified as a substitution therapy. On the one hand, co-prescription data indicates that there is a significant combined use of the monocomponents, mainly in secondary prevention after ischemic heart disease. Furthermore, literature data available from meta-analyses and several studies, conducted with a FDC of aspirin, statin, and antihypertensives, have shown an improved adherence to treatment with the FDC vs. free-drug components in the cardiovascular setting.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From a clinical standpoint, the fixed-dose combination is justified as a substitution therapy.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the monocomponents. 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 procedures. Both the initial decentralised procedure and the repeat use procedure were finalised with a positive outcome in December 2013 and October 2014, respectively.