CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Triveram
FI/H/840/01-05/DC

Stapressial
FI/H/842/01-05/DC

10 mg / 5 mg / 5 mg film-coated tablet
20 mg / 5 mg / 5 mg film-coated tablet
20 mg / 10 mg / 5 mg film-coated tablet
20 mg / 10 mg / 10 mg film-coated tablet
40 mg / 10 mg / 10 mg film-coated tablet

Atorvastatin, Perindopril arginine, Amlodipine

Date: 8.1.2016

This module reflects the scientific discussion for the approval of Triveram and Stapressial. The procedures was finalised at 2015-07-23 (Day 210). For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Triveram/Stapressial 10 mg/5 mg/5 mg, 20 mg/5 mg/5 mg, 20 mg/10 mg/5 mg, 20 mg/10 mg/10 mg and 40 mg/10 mg/10 mg film-coated tablets from Les Laboratoires Servier, France.

The product is indicated for the treatment of essential hypertension and/or stable coronary artery disease, in association with primary hypercholesterolaemia or mixed hyperlipidaemia, as substitution therapy in adult patients adequately controlled with perindopril, amlodipine and atorvastatin given concurrently at the same dose level as in the combination. A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article of Directive 2001/83/EC.

Cardiovascular disease is the leading cause of death in both developed and developing countries, accounting for approximately one third of all deaths worldwide. In Europe, it is the foremost cause of premature mortality and of disability-adjusted life years among both men and women, causing almost 4.1 million deaths per year, or 46% of all deaths. Almost 1.8 million of these deaths (20% of all deaths) were due to coronary heart disease.

Apart from age and sex, three modifiable risk factors – smoking, hypertension and hypercholesterolemia – make a major contribution to cardiovascular risk, particularly in combination. These account for 80% of all cases of premature coronary artery disease.

Hypertension has a wide prevalence of up 50% in middle-aged populations the western world and the prevalence is currently rising steeply also in the developing world. Hypertension is a major risk factor for an array of cardiovascular and related diseases: coronary events, stroke, heart failure, peripheral artery disease and renal disease. According to the bulk of evidence, lowering elevated blood pressure decreases significantly the risk of major cardiovascular events, regardless of age, race, sex, or other factors.

Regarding antihypertensive therapy, blood pressure elevation being usually multifactorial, it is very difficult to normalise pressure by interfering with only a single pressor mechanism. Moreover, monotherapy can provide blood pressure control in only 30 – 40% of treated patients.

According to many studies, the use of combination therapy with 2 agents having complementary mechanisms of action aim to target multiple regulatory mechanisms and results in a greater BP reduction than doubling the dose of one agent.

A further advantage is that physiological and pharmacological synergies between different classes of antihypertensive agents may not only justify a greater BP reduction but also cause fewer side effects thus providing larger benefits than those offered by a single monotherapy.

Evidence supported by clinical studies in primary prevention and secondary prevention shows that reducing total cholesterol and low-density lipoprotein cholesterol with statins prevents the incidence of cardiovascular diseases. According to the pooled data of the randomised studies, every 1.0 mmol/L (~40 mg/dL) reduction in low-density lipoprotein cholesterol is associated with a corresponding 22% reduction in cardiovascular mortality and morbidity.

A high prevalence of patients with combined hypertension and dyslipidaemia has been reported. In addition, the co-existence of the two risk factors has more than an additive adverse impact on the vascular endothelium, which results in enhanced atherosclerosis, leading to an increase in coronary heart disease-related events. Cardiovascular disease risk management should focus on multifactorial therapeutic interventions to manage a patient's overall risk of, rather than treating single cardiovascular risk factors as recommended by the European Society of Cardiology / European Society of Hypertension therapeutic guidelines for management of hypertension, of stable coronary artery disease, of cardiovascular disease prevention and of secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease.

Factors that may play a role in the poor control rates of hypertension and/ or dyslipidaemia include patients' poor adherence to medication. Adherence with concomitant anti-hypertensive and lipid lowering therapy is poor, with only 1 in 3 patient adherents with both medications at 6 months. In addition, meta-analyses and observational studies in patients with hypertension and hyperlipidaemia have shown that 'poor' adherence leads to higher incidence of cardiovascular events, and hence more physician visits/hospital admissions and longer hospital stays. Therefore, there is a potential need to develop a fixed-dose combination product that treats an individuals' overall cardiovascular risk with good adherence on prescribed drug treatment.

II. QUALITY ASPECTS

II.1 Introduction

The drug products are formulated as immediate release film-coated tablets containing fixed-dose combination of atorvastatin, perindopril arginine and amlodipine.

10mg/5mg/5mg:
The drug product is a yellow, round, film-coated tablet of 7 mm diameter, with a curvature radius of 25 mm, engraved with '1' on one face and ' ' on the other face, containing 10 mg of atorvastatin, 5 mg of perindopril arginine and 5 mg of amlodipine.

20mg/5mg/5mg:
The drug product is a yellow, round, film-coated tablet of 8.8 mm diameter, with a curvature radius of 32 mm, engraved with '2' on one face and ' ' on the other face, containing 20 mg of atorvastatin, 5 mg of perindopril arginine and 5 mg of amlodipine.

20mg/10mg/5mg:
The drug product is a yellow, square-shaped, film-coated tablet of 9 mm side length, with a curvature radius of 16 mm, engraved with '3' on one face and ' ' on the other face, containing 20 mg of atorvastatin, 10 mg of perindopril arginine and 5 mg of amlodipine.

20mg/10mg/10mg:
The drug product is a yellow, oblong-shaped, film-coated tablet of 12.7 mm length and 6.35 mm width, engraved with '4' on one face and ' ' on the other face, containing 20 mg of atorvastatin, 10 mg of perindopril arginine and 10 mg of amlodipine.

40mg/10mg/10mg:
The drug product is a yellow, oblong-shaped, film-coated tablet of 16 mm length and 8 mm width, engraved with '5' on one face and ' ' on the other face, containing 40 mg of atorvastatin, 10 mg of perindopril arginine and 10 mg of amlodipine.

The excipients are lactose monohydrate, calcium carbonate (E170), hydroxypropylcellulose (E463), sodium starch glycolate, microcrystalline cellulose (E460), maltodextrin and magnesium stearate

(E572) in core, and glycerol (E422), hypromellose, macrogol 6000, magnesium stearate (E572), titanium dioxide (E171) and yellow iron oxide (E172) in film-coating.

The tablets are packed in polypropylene (PP) tablet containers closed with low density polyethylene stopper containing desiccant, and in high density polyethylene (HDPE) tablet containers with polypropylene screw cap containing desiccant. HDPE tablet containers contain additional desiccant capsules. Pack sizes are 30, 90 and 100 tablets.

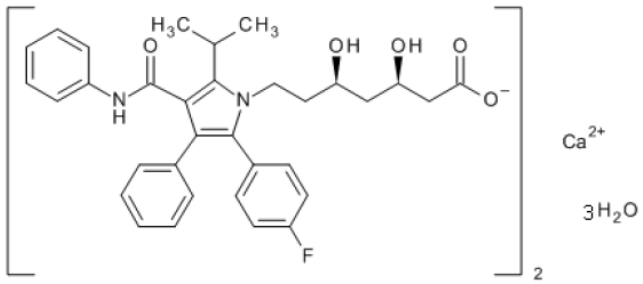
II.2 Drug Substance

Atorvastatin

INN: Atorvastatin

Chemical name: Calcium (3*R*,5*R*)-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate trihydrate

Structure:



Molecular formula: $C_{66}H_{68}CaF_2N_4O_{10}\cdot 3H_2O$

Molecular weight: 1209.4

Description: White or almost white powder

Solubility: Very slightly soluble to practically insoluble in purified water, slightly soluble to practically insoluble in ethanol (96 per cent), practically insoluble in methylene chloride.

The active substance atorvastatin calcium trihydrate is described in European Pharmacopoeia. The Applicant included full information of the active substance atorvastatin calcium trihydrate in the dossier.

Synthesis of the active substance atorvastatin calcium trihydrate from designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

In general, the drug substance specification is in line with the Ph. Eur. monograph. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided that comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards.

Suitable specification has been provided for the packaging used.

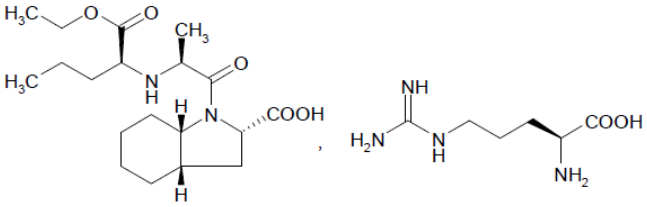
Appropriate stability data according to ICH guidance have been generated supporting a suitable re-test period when stored in the proposed packaging.

Perindopril arginine

INN: Perindopril

Chemical name: L-arginine (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)butyl]amino] propanoyl]octahydro-1*H*-indole-2-carboxylate

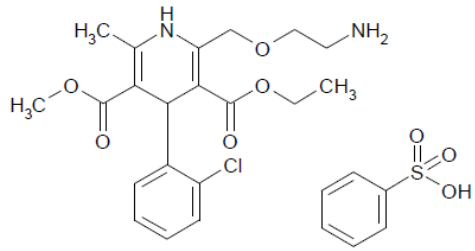
Structure:



Molecular formula: $C_{19}H_{32}N_2O_5$, $C_6H_{14}N_4O_2$
Molecular weight: 542.7
Description: White to almost white powder
Solubility: Freely soluble in water, slightly soluble in ethanol 96%, practically insoluble in methylene chloride

The active substance perindopril arginine is not described in Ph. Eur. The Applicant included full information of the active substance perindopril arginine in the dossier.
Synthesis of the active substance perindopril arginine from designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents.
Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.
The control tests and specifications for perindopril arginine are adequately drawn up. The specification has been set partly as per Ph. Eur. monograph for perindopril *tert*-butylamine. Additionally, specific limits have been adopted for perindopril arginine. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analytical data demonstrating compliance with the drug substance specification have been provided.
Satisfactory certificates of analysis have been provided for reference standards.
Suitable specification has been provided for the packaging used.
Appropriate stability data according to ICH guidance have been generated supporting a suitable re-test period when stored in the proposed packaging.

Amlodipine
INN: Amlodipine
Chemical name: 3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(*o*-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, benzenesulfonate
Structure:



Molecular formula: $C_{20}H_{25}ClN_2O_2$, $C_6H_6O_3S$
Molecular weight: 567.1
Description: White or almost white powder
Solubility: Slightly soluble in purified water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol

The active substance amlodipine besilate is purchased from a manufacturer who has a Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) for their substance. Thus the quality of amlodipine besilate is suitably controlled by the monograph in Ph. Eur. A re-test period of the active substance when stored in container closure system defined is included in the CEP.
The finished product manufacturer controls the quality of amlodipine besilate following the Ph. Eur. requirements and analytical methods. Additional limits have been set and analytical methods have been appropriately validated for their intended purposes. Batch analytical data demonstrating compliance with the drug substance specification have been provided.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been adequately described, the choice of excipients has been justified and their functions explained. The compatibility of the active substances with the excipients has been confirmed. A number of experiments were carried out in order to optimize the formulation and the productions process. The choice of the package and manufacturing process is justified. The particle size distribution of drug substances used in biobatches has been presented and the discriminatory power of the chosen dissolution method has been demonstrated.

Two bioequivalence studies have been conducted to support the marketing authorization; one study with the test product 20/10/10 mg film-coated tablets compared to one tablet of atorvastatin 20 mg (Lipitor®) plus one tablet of amlodipine 10 mg (Norvasc®) plus one tablet of perindopril arginine 10 mg (Coversyl®) and one study with the test product 40/10/10 mg film-coated tablets compared to one tablet of atorvastatin 40 mg (Lipitor®) plus one tablet of amlodipine 10 mg (Norvasc®) plus one tablet of perindopril arginine 10 mg (Coversyl®). Comparative dissolution studies were performed using biobatches at pH 1.2, 4.5 and 6.8. Slight differences in dissolution profiles of test and reference products were seen. However, the test and reference products are found to be bioequivalent.

Biowaiver has been applied for the other three dosage strengths. In vitro dissolution tests to support the biowaiver have been performed. Dissolution profiles are similar with the exception of amlodipine from 20/5/5 mg strength and 40/10/10 mg strength the similarity factors are lower than 50. However, adequate justification for similarity of dissolution profiles has been presented.

Manufacturing process

The manufacturing process consists of preparation of two granulates by wet granulation, mixing of granulates and compression to tablets, and film-coating. The manufacturing process is considered as a standard process, except the manufacturing of 20/5/5mg and 40/10/10mg film-coated tablets is considered as specialised pharmaceutical dose form due to the low content of perindopril arginine, and thus as non-standard manufacturing process. Full-scale validation data have been provided for the manufacture of 20/5/5mg and 40/10/10mg film-coated tablets. The Applicant commits to perform the validation of the manufacturing process for full-scale batches of 10/5/5 mg, 20/10/5 mg and 20/10/10 mg strengths according to the validation scheme prior to product commercialization. Holding times and storage conditions for granulates and uncoated tablets have been justified.

Control of excipients

The excipients are commonly used in this type of products and they are of Ph. Eur. quality except the colouring agent yellow iron oxide which conforms to the relevant EC Directive.

Magnesium stearate is of vegetable origin. Lactose is the only excipient of animal origin. It is prepared in accordance with the requirements of the Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents in medicinal products.

Quality control of drug product

The product specification covers appropriate parameters for this type of dosage form. The acceptance limits for the identified impurities of drug substances have been set at or below the qualification threshold of 0.5% for the drug substances according the ICH Q3B and the acceptance limits exceeding the qualification threshold have been qualified by toxicological studies. The proposed specifications are acceptable.

Validations of the analytical methods have been presented and they are acceptable.

Batch analytical data on three or six batches of each tablet strength have been presented. The results show that the finished products meet the specifications proposed.

Stability of drug product

Stability studies according to ICH guidelines were performed for two batches of each strength packed into PP container with desiccant in stopper and HDPE container with desiccant in stopper and as capsules in container. The presented data support the proposed shelf-life of 2 years with no special temperature storage conditions. However, 40/10/10mg tablets stored in HDPE container should be stored below 30 °C. The containers should be tightly closed in order to protect from moisture. The proposed stability after first opening of the tablet container (30 days for the 30 tablet container and

100 days for the 100 tablet container) is acceptable. Suitable post-approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of Triveram and Stapressial film-coated tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No new data.

III.2 Pharmacology

No new data.

III.3 Pharmacokinetics

No new data.

III.4 Toxicology

No new data.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Triveram/Stapressial is intended to substitute the concomitant use of the components of the product as single products. The approval of the product will not change the total quantity of atorvastatin, amlodipine or perindopril released in the environment. All substances of the applied product are widely used and they do not include any new component that would result in any hazard to the environment during the course of the product's life. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of atorvastatin, amlodipine and perindopril are well known. All substances are clinically widely used for years as separate products and also in concomitant use and therefore further studies are not generally required. The non-clinical overview provided by the Applicant is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

Pharmacodynamics, pharmacokinetics (PK), efficacy and safety of atorvastatin, amlodipine and perindopril, given separately, are well established.

The proposed indication for the Product is the treatment of essential hypertension and/or stable coronary artery disease, in association with primary hypercholesterolaemia or mixed hyperlipidaemia, as substitution therapy in adult patients adequately controlled with perindopril, amlodipine and atorvastatin given concurrently at the same dose level as in the combination. The indication is in accordance with the authorised indications of the single components of the Product.

The proposed posology of the Product is one tablet once daily in the morning before a meal. The Product is not suitable for patients with glomerular filtration less than 60 ml/min due to the dose of perindopril component (5-10 mg). It is stated in the Section 4.2 and 4.4 of the proposed SmPC that due to the effects of atorvastatin, amlodipine and perindopril, the Product is contra-indicated in patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal. In addition, the Product should be used with caution in patients with hepatic impairment and in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Since there is no data of the use of perindopril or of the concomitant use of the single components of the Product in paediatric population, the use of the Product in children and adolescents is not recommended. There are no specific dosing recommendations for the elderly patients.

IV.2 Pharmacokinetics

Atorvastatin

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins.

Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Due to hepatic metabolism by CYP3A4, the potential interactions between atorvastatin and known CYP3A4 inhibitors (e.g. ciclosporin, ketoconazole) and inducers (e.g. rifampicin) are relevant to take into account for safety and efficacy reasons in clinical practice.

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for C_{max} and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.

Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in Cmax and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown. The potential interaction between atorvastatin and hepatic uptake inhibitors (e.g. ciclosporin) should be taken into account in clinical practice.

Amlodipine

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The bioavailability of amlodipine is not affected by food intake.

The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine. As with atorvastatin, the potential interactions between amlodipine and known CYP3A4 inhibitors and inducers are to be taken into account in clinical practice to avoid over- or underexposure of amlodipine.

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Perindopril

After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, perindopril arginine should be administered orally in a single daily dose in the morning before a meal. Therefore also the proposed FDC is to be ingested once a day in the morning, before breakfast. This recommendation is in line with current approved dosing schedule of all single components of the proposed FDC.

It has been demonstrated that there is a linear relationship between the dose of perindopril and its plasma exposure.

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days. Elimination of perindoprilat is decreased in older people, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance). Dialysis clearance of perindoprilat is equal to 70 ml/min. Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required.

Potential interactions between the single components of the Product

As stated in the Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95, Rev.1, Feb 2009), the possibility of clinically meaningful interactions between the substances of the fixed-dose combination (FDC) should always be considered. The applicants are encouraged to submit appropriate data to establish that such interactions do not occur. In the current marketing authorisation process, the applicant has provided the report of the interaction study assessing the possible interactions between atorvastatin 40 mg, amlodipine 10 mg and perindopril 10 mg.

Bioequivalence studies and biowaiver

To support the application, the applicant has submitted two separate bioequivalence (BE) study reports comparing 20/10/10 mg and 40/10/10 mg tablet strengths of the Product with the corresponding strengths of the single reference products (Lipitor, Norvasc and Coversyl).

Before initiation of the BE studies, an exploratory PK study was performed in order to select the best formulation and the best manufacturing process for the development of the Product, testing 3 different formulations as regards atorvastatin component.

In addition, a separate PK study to evaluate the interaction between atorvastatin 40 mg, amlodipine 10 mg and perindopril arginine given concomitantly in free combination compared to administration of each single component alone was conducted.

All BE studies were conducted outside European Union (Canada). The application is attached with statement where the applicant confirms that all studies met the ethical requirements of Directive 2001/20/EC.

The PK interaction study was a single centre, randomised, single dose, open-label, 4-period, 4-sequence, crossover, study to assess drug interaction between perindopril arginine, amlodipine and atorvastatin following the free combined versus the individual administrations of perindopril arginine 10 mg, amlodipine 10 mg and atorvastatin 40 mg in healthy, adult, male human subjects under fasting conditions. Based on the results of the study, there was a significant interaction for C_{max} of perindopril showing a 19% increase in concomitant administration. There was no interaction found for AUC of perindopril. In addition, there were no interactions shown for C_{max} or AUC for the active metabolite perindoprilat. Therefore, the identified interaction on C_{max} of perindopril can be considered as clinically not relevant. There were no significant interactions found for amlodipine in the study.

The results of the study showed that there was a statistically significant increase of 23% in AUC of atorvastatin in concomitant administration. In addition, the C_{max} of the 2-Hydroxyatorvastatin was decreased by 28%, while there were no interaction with the AUC. Correspondingly, there were no

significant interactions found with the other active metabolite 4-Hydroxyatorvastatin. The identified interactions for atorvastatin and 2-Hydroxyatorvastatin have previously been discussed in marketing authorisation data of Caduet (FDC of atorvastatin and amlodipine). The assessor was of the opinion, that the found interactions are clinically not relevant since the AUCs of the main active metabolites of atorvastatin are not significantly affected.

The first BE study was a single centre, randomised, single dose, laboratory-blinded, 3-period, 3-sequence, semi-replicate, crossover, bioequivalence study of the 20/10/10 mg tablet strength of the Product manufactured by Les Laboratoires Servier Industrie, France, with Lipitor 20 mg tablet and Norvasc 10 mg tablet, both manufactured by Pfizer Manufacturing Deutschland, GmbH, Germany, and with Coversyl 10 mg tablet, manufactured by Les Laboratoires Servier Industrie, France, in healthy, adult, male human subjects under fasting conditions. Based on the results of the study, the fixed dose combination of Atorvastatin/ Amlodipine/ Perindopril Arginine 20/10/10 mg by Servier Industrie, France was considered bioequivalent with the concomitant administration of innovator products Lipitor 20 mg tablet and Norvasc 10 mg tablet, both manufactured by Pfizer Manufacturing Deutschland, GmbH, Germany, and with Coversyl 10 mg tablet, manufactured by Servier Industrie, France. In vitro dissolution tests showed that the dissolution profiles of the reference products and the test product were similar at clinically relevant pHs of 4.5-6.8 (at least 85% of active substances were dissolved within 15 minutes). The results of study can be extrapolated to other strengths 20/10/5 mg and 10/5/5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr. 1/2010, section 4.1.6.

The second BE study was a single centre, randomised, single dose, laboratory-blinded, 3-period, 3-sequence, semi-replicate, crossover, bioequivalence study of the Product 40/10/10 mg tablet strength manufactured by Les Laboratoires Servier Industrie, France, with Lipitor 40 mg tablet and Norvasc 10 mg tablet, both manufactured by Pfizer Manufacturing Deutschland, GmbH, Germany, and with Coversyl 10 mg tablet, manufactured by Les laboratoires Servier Industrie, France, in healthy, adult, male human subjects under fasting conditions. Based on the results of the study, a fixed dose combination of Atorvastatin/ Amlodipine/ Perindopril Arginine 40/10/10 mg by Servier Industrie, France) was considered bioequivalent with the concomitant administration of innovator products Lipitor 40 mg tablet and Norvasc 10 mg tablet, both manufactured by Pfizer Manufacturing Deutschland, GmbH, Germany, and with Coversyl 10 mg tablet, manufactured by Servier Industrie, France. In vitro dissolution tests showed that the dissolution profiles of the reference products Lipitor and Norvasc and the test product did not demonstrate an exact similarity between the products at clinically relevant pHs. About 98% and 87% of amlodipine in the reference product were dissolved in 15 min at pHs 4.5 and 6.8, respectively, whereas the corresponding proportions of amlodipine in the Product were 84% and 65%. Respectively, 96% and 98% of atorvastatin in the reference product were dissolved in 15 min at pHs 4.5 and 6.8, whereas the corresponding proportions of atorvastatin in the Product were 84% and 89%. Taking into account the absorption profiles of the both substances the most relevant of the studied pHs is the pH 4.5. Therefore, the Assessor was of the opinion that despite only 84% (instead of 85%) of atorvastatin and amlodipine in the Product were dissolved in 15 minutes, this finding is not clinically significant due to the shown similarity in the actual BE study.
The results of study can be extrapolated to the strength 20/5/5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

There were no significant safety concerns in any of the above-referenced studies.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies, the fixed-dose combination product TRIVERAM/STAPRESSIAL (strengths 20/10/10 mg and 40/10/10 mg) is considered bioequivalent with the single Reference medicinal products (Lipitor, Norvasc and Coversyl).

The results of the BE studies can be extrapolated to other strengths 20/10/5 mg, 20/5/5 mg and 10/5/5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

IV.3 Pharmacodynamics

Atorvastatin is a selective, competitive inhibitor of 3 –hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase. It lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic low-density lipoprotein receptors on the cell surface for enhanced uptake and catabolism of LDL.

Amlodipine is a dihydropyridine calcium channel blocker, which prolongs inhibition of calcium entry via the slow calcium channels in the smooth muscular and myocardial cells. It's direct vasodilating effect on vasculature is the main cause for the blood pressure lowering effect. Amlodipine reduces myocardial ischemia probably through the dilation of the main coronary arteries, improving oxygen delivery to the heart, and through the reduction of peripheral resistance and myocardial oxygen consumption.

Perindopril is angiotensin converting enzyme (ACE) inhibitor which acts by its active metabolite, perindroprilat. The inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone.by lowering peripheral resistance and systemic blood pressure.

IV.4 Clinical efficacy and safety

The effects of the single components of the applied Product in separate and concomitant use on cardiovascular efficacy and safety are relatively well-known.

The efficacy and safety of the proposed FDC has been assessed in the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study. ASCOT was an international randomised trial with a 2x2 factorial design. The study aimed to compare the effects of two antihypertensive treatment regimens in 19,257 patients (Blood Pressure Lowering Arm – ASCOT-BPLA) and the effects of the addition of atorvastatin 10 mg, compared with placebo, in 10,305 patients (Lipid Lowering Arm – ASCOT-LLA) on non-fatal and fatal coronary events.

The study population comprised patients aged 40-79 years with no history of myocardial infarction or treatment for angina. All patients had at least 3 of the predefined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first degree relative, TC:HDL C > 6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria.

Patients received antihypertensive treatment with either amlodipine or atenolol. To achieve the goal of blood pressure control (< 140/90 mmHg in non-diabetic patients, < 130/80 mmHg in patients with diabetes), perindopril could be added in the amlodipine group and bendroflumethiazide in the atenolol group. The third-line antihypertensive used in the both

randomised groups was doxazosin. In addition to the antihypertensive therapy, the patients with total cholesterol < 6.5 mmol/l (<250 mg/dl) and with no lipid-lowering drug therapy were randomised to either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

In the analyses of ASCOT-BPLA, after 5.5 years of follow-up, the amlodipine arm was found to be superior compared to atenolol arm in prevention of strokes (0.77, 95% CI 0.66-0.89), total cardiovascular events and procedures (0.84, 95% CI 0.78-0.90 and all-cause mortality (0.89, 95% CI 0.81-0.99). The incidence of developing diabetes was less on the amlodipine-based regimen (0.70, 95% CI 0.63-0.78).

Adding atorvastatin to antihypertensive therapy (ASCOT-LLA) was associated with 36% (95% CI 0.50-0.83) reduction in the combined primary end-point of non-fatal myocardial infarctions and fatal coronary heart disease. The combination of atorvastatin and amlodipine showed a significant reduction in the primary endpoint of 53% (95% CI 0.31-0.69) compared to placebo + amlodipine arm and of 39% (95% CI 0.08-0.59) compared to atorvastatin + atenolol arm.

The most frequently reported adverse events in the patients with concomitant use of atorvastatin, perindopril and amlodipine were hypotension (1.5%), angioedema (0.7%) and liver injury (0.6%). Myopathy occurred in 0.3% of the patients. The frequency of serious adverse events was higher in the patients using atorvastatin, atenolol plus bendroflumethiazide based regimen (0.8% vs. 0.2%, p=0.0057).

The results above were also substantiated with by the Applicant with the post-hoc analysis of ASCOT-LLA, in the patients treated concurrently with atorvastatin, amlodipine and perindopril.

The clinical study data of the concomitant use of atorvastatin dose of 20 mg or higher with amlodipine and perindopril are scarce. There should however not be in that respect any significant safety concerns, since the below-reviewed interaction study do not indicate any clinically significant changes in concentrations of atorvastatin during concomitant use. In addition, the safety of the higher doses of atorvastatin has been established in many previous trials and also the safety of higher doses than 10 mg of atorvastatin should be first established in concomitant use of single substances (substitution therapy indication).

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to TRIVERAM/STAPRESSIAL.

- Summary table of safety concerns as approved in RMP

Important identified risks	– Hypotension – Drug-induced hepatitis – Hyperkalaemia – Neutropenia / agranulocytosis / thrombocytopenia – Angioedema / hypersensitivity – Myopathy / rhabdomyolysis – Foetotoxicity / embryotoxicity / use during pregnancy New onset of diabetes in patients with increased risk

	of diabetes
Important potential risks	Interstitial lung disease
Missing information	– Use in children and adolescents (< 18 years of age) – Use in lactating women – Use in patients with severe hepatic impairment Use in patients with severe renal impairment

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Hypotension	Information included in sections 4.3, 4.4, 4.5 and 4.8 of the SmPC	None proposed
Hyperkalaemia	Information included in sections 4.3, 4.4, 4.5 and 4.8 of the SmPC	None proposed
Angioedema / hypersensitivity	Information included in sections 4.3, 4.4, 4.5 and 4.8 of the SmPC	None proposed
Neutropenia/Agranulocytosis/ Thrombocytopenia	Information included in sections 4.4, and 4.8 of the SmPC	None proposed
Foetotoxicity/ Embryotoxicity/ Use during pregnancy	Information included in sections 4.3, and 4.6 of the SmPC	None proposed
Myopathy/Rhabdomyolysis	Information included in sections 4.4, 4.5, 4.8 and 5.2 of the SmPC	None proposed
Drug-induced hepatitis	Information included in sections 4.2, 4.3 and 4.4 of the SmPC	None proposed
New onset of diabetes in patients with increased risk of diabetes	Information included in sections 4.4, and 4.8 of the SmPC	None proposed
Important Potential Risks		
Interstitial lung disease	Information included in sections 4.4, and 4.8 of the SmPC	None proposed
Missing Information		
Children and adolescents (<18 years old)	Information included in sections 4.2 and 5.1 of the SmPC	None proposed
Lactating women	Information included in sections 4.3, and 4.6 of the SmPC	None proposed
Patients with severe renal impairment	Information included in sections 4.2, 4.4, 4.5 and 5.2 of the SmPC	None proposed
Patients with severe hepatic impairment	Information included in sections 4.2, 4.3, 4.4 and 5.2 of the SmPC	None proposed

IV.6 Discussion on the clinical aspects

The combination treatment of ACE inhibitor and calcium-channel is recommended as one of the preferred antihypertensive combinations according to the 2013 ESC/ESH hypertension guideline. In addition, this same guideline recommends the use of statin to hypertensive patients with moderate or high cardiovascular risk. Moreover, the 2013 ESC Guidelines on the management of coronary artery disease recommend the use of statins and ACE inhibitors for reduction of cardiovascular events and the use of amlodipine for prevention of angina.

The Product is intended for substitution therapy and could therefore possibly increase the patient compliance due to lesser pill burden.

The efficacy and safety of the concomitant use of the single substances of the Product in hypertensive patients is demonstrated in the ASCOT study. The data of the clinical study data to support the use of Triveram/Stapressial in stable coronary heart disease is scarce. However, since the single reference products are authorized in stable coronary heart disease and Triveram/Stapressial is indicated to substitution therapy only, the applied indication including also this patient-population is approvable.

The clinical study data of the concomitant use of atorvastatin dose of 20 mg or higher with amlodipine and perindopril are scarce. There should however not be in that respect any significant safety concerns, provided that the below-reviewed interaction study do not indicate any significant changes in concentrations of atorvastatin during concomitant use. In addition, the safety of the higher doses of atorvastatin has been established in many previous trials and also the safety of higher doses than 10 mg of atorvastatin should be first established in concomitant use of single substances (substitution therapy indication).

The clinical sections of the proposed SmPC are in accordance with the latest SmPC of the single reference products of proposed FDC.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This decentralised procedure application concerns a fixed dose combination tablet of atorvastatin calcium trihydrate, perindopril arginine and amlodipine besylate, under trade names of Triveram and Stapressial. Both applied products have five different strengths (10/5/5 mg, 20/5/5 mg, 20/10/5 mg, 20/10/10 mg and 40/10/10 mg). The Products are intended for treatment of essential hypertension and/or stable coronary artery disease, in association with primary hypercholesterolaemia or mixed hyperlipidaemia, as substitution therapy in adult patients adequately controlled with perindopril, amlodipine and atorvastatin given concurrently at the same dose level as in the combination.

The application contained an adequate review of published clinical data of the concomitant use of

single components of the proposed fixed-dose combination. The efficacy and safety of the concomitant use of the substances in hypertensive patients is demonstrated in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).

The data of the clinical study data to support the use of Triveram/Stapressial in stable coronary heart disease is scarce. However, since the single reference products are authorized in stable coronary heart disease and Triveram/Stapressial is indicated to substitution therapy only, the applied indication including also this patient-population is approvable.

The clinical study data of the concomitant use of atorvastatin dose of 20 mg or higher with amlodipine and perindopril are scarce. There should however not be in that respect any significant safety concerns, since a separate interaction study did not indicate any significant changes in concentrations of atorvastatin during concomitant use of the mono-components. In addition, the safety of the higher doses of atorvastatin has been established in many previous trials and also the safety of higher doses than 10 mg of atorvastatin should be first established in concomitant use of single substances (substitution therapy indication).

Based on the submitted bioequivalence studies, Triveram/Stapressial 40/10/10 mg and 20/10/10 mg strenghts by Servier Industrie, France are considered bioequivalent with the concomitant administration of the single innovator products of the combination. The applicant's proposal for biowaiver for Triveram/Stapressial strengths 10/5/5 mg, 20/10/5 mg and 20/5/5 mg is justified. There were no significant safety concerns in any of the BE studies.

Benefit/risk is positive and approval of the application was recommended.