CBG MEB

Public Assessment Report

Scientific discussion

Euvascor 10 mg/5 mg, 20 mg/5 mg, 40 mg/5 mg, 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg, hard capsules

(atorvastatin calcium trihydrate/ perindopril arginine)

NL/H/3871/001-006/DC

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This module reflects the scientific discussion for the approval of Euvascor 10 mg/5 mg, 20 mg/5 mg, 40 mg/5 mg, 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg, hard capsules. The procedure was finalised on 3 December 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Events
ASMF	Active Substance Master File
ASA	Acetylsalicylic acid
AUC0-t	Area Under the plasma concentration-time Curve from time zero to t hours
AUClast	Area Under the Curve from zero to the last measurable point
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum Plasma Concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
FDC	Fixed dose combination
ICH	International Conference of Harmonisation
LLT	Lipid Lowering Therapy
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SSADR	Serious Suspected Adverse Drug Reaction
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Euvascor 10 mg/5 mg, 20 mg/5 mg, 40 mg/5 mg, 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg, hard capsules from Les Laboratoires Servier.

The product is indicated as substitution therapy as part of cardiovascular risk management, in adult patients adequately controlled with atorvastatin and perindopril given concurrently at the same dose level but as separate products.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a fixed dose combination (FDC) application. Fixed dose combinations (pursuant to article 10b of Directive 2001/83/EC) contain active substances from medicinal products already authorised in the EEA but not hitherto used in combination for therapeutic purposed. In these kind of applications pre-clinical and clinical data relating to that combination are provided. However, it is not necessary to provide pre-clinical and clinical data relating to each individual active substance.

The concerned member states (CMS) involved in this procedure were Belgium, Bulgaria, Croatia (only 20 mg/5 mg, 40 mg/5 mg, 20 mg/10 mg and 40 mg/10 mg strengths), Cyprus, Czech Republic, Estonia, Greece, Finland, France, Ireland, Italy, Lithuania, Luxembourg, Latvia, Malta, Poland, Portugal, Romania, Slovenia and the Slovak Republic.

The innovator product containing atorvastatin calcium trihydrate, is Lipitor 10 mg, 20 mg, 40 mg, and 80 mg film-coated tablets (NL License RVG 21081-21083 and 27148) indicated in hypercholesterolaemia and prevention of cardiovascular diseases. The 10 mg, 20 mg, and 40 mg strengths have been registered in the Netherlands by Pfizer B.V. since 21 April 1997 through MRP DE/H/0109/001-003.
Perindopril arginine is registered in the Netherlands by Les Laboratoires Servier, for the indication hypertension under the name Coversyl arg 2.5 mg, 5 mg and 10 mg tablets (NL License RVG 31957-31959). The product was approved through a Mutual Recognition Procedure in September 2005 (FR/H/0265/001-003) and is now registered in more than 100 countries and marketed in more than 50 countries worldwide.

The atorvastatin/perindopril arginine fixed dose combination would allow a simplification of therapy by decreasing the number of individual dose units to be taken by patients from 2 to 1 daily capsule, which may improve patients' compliance to treatment.

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC.

Scientific advice
Written scientific advice was given by RMS in the second half of 2015. This was related to the legal basis, and the results of the bioequivalence studies.

Paediatric development
The MAH has submitted an application for a product specific paediatric investigation plan (PIP) waiver for atorvastatin/perindopril (EMA-001876-PIP01-15) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council. The applied product specific waiver has been granted by the European Medicines Agency (decision P/0112/2016 of 15 april 2016) to the MAH. No paediatric studies have to be performed.

II. QUALITY ASPECTS

II.1 Introduction

- Euvascor 10 mg/5 mg is a size 2 hard gelatin capsule, with black imprint “10 5” on light blue body and black imprint “ ” on light blue cap, containing white to slightly white spherical pellets, with a content of 10.82 mg atorvastatin calcium trihydrate equivalent to 10 mg atorvastatin, 5 mg perindopril arginine equivalent to 3.395 mg perindopril.
- Euvascor 20 mg/5 mg is a size 2 hard gelatin capsule, with black imprint “20 5” on light blue body and black imprint “ ” on blue cap, containing white to slightly white spherical pellets, with a content of 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin, 5 mg perindopril arginine equivalent to 3.395 mg perindopril.
- Euvascor 40 mg/5 mg is a size 2 hard gelatin capsule, with black imprint “40 5” on blue body and black imprint “ ” on blue cap, containing white to slightly white spherical pellets, with a content of 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin, 5 mg perindopril arginine equivalent to 3.395 mg perindopril.
- Euvascor 10 mg/10 mg is a size 2 hard gelatin capsule, with black imprint “10 10” on light green body and black imprint “ ” on light green cap, containing white to slightly white spherical pellets, with a content of 10.82 mg atorvastatin calcium trihydrate equivalent to 10 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril.
- Euvascor 20 mg/10 mg is a size 2 hard gelatin capsule, with black imprint “20 10” on light green body and black imprint “ ” on green cap, containing white to slightly white spherical pellets, with a content of 21.64 mg atorvastatin calcium trihydrate equivalent to 20 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril.
- Euvascor 40 mg/10 mg is a size 2 hard gelatin capsule, with black imprint “40 10” on green body and black imprint “ ” on green cap, containing white to slightly white spherical pellets, with a content of 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin, 10 mg perindopril arginine equivalent to 6.79 mg perindopril.

The hard capsules are packed in PP containers closed with a LDPE stopper and HDPE bottles closed with a PP stopper.

The excipients are:
***Capsule content*:**
- Talc (E553b)
- Atorvastatin pellets:
  - Calcium carbonate (E170)
  - Hydroxypropyl cellulose (E463)
  - Polysorbate 80 (E433)
  - Croscarmellose sodium (E468)
  - Sugar spheres (sucrose and maize starch)
- Perindopril arginine pellets:
  - Hydroxypropyl cellulose (E463)
  - Sugar spheres (sucrose and maize starch)

Capsule shell:
Euvascor 10 mg/5 mg, 20 mg/5 mg and 40 mg/5 mg:
- Titanium dioxide (E171)
- Brilliant blue FCF – FD&C Blue 1 (E133)
- Gelatin

Euvascor 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg:
- Titanium dioxide (E171)
- Brilliant blue FCF – FD&C Blue 1 (E133)
- Yellow iron oxide (E172)
- Gelatin

Ink content:

- shellac (E904)
- propylene glycol (E1520)
- strong ammonia solution (E527)
- black iron oxide (E172)
- potassium hydroxide (E525)

II.2 Drug Substances

The active substances are atorvastatin, as hydrochloride salt, trihydrate and perindopril (as arginine salt). Both are established active substances.

Atorvastatin hydrochloride trihydrate

Atorvastatin hydrochloride trihydrate is described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white crystalline powder, and is very slightly soluble to practically insoluble in water and ethanol (96%) and practically insoluble in methylene chloride. The substance is manufactured as the polymorphic form P1 and possesses two asymmetric carbons, both with the R-configuration. The MAH included full information of the active substance atorvastatin hydrochloride trihydrate in the dossier.

Manufacturing process

The manufacturing process of atorvastatin hydrochloride trihydrate consists in total of six synthesis steps, one synthetic step and two salt-formation steps. The starting materials are acceptable. No class 1 solvents are used in the synthesis. A heavy metal catalyst is used in the first step. The synthesis has been described in sufficient detail, the drug substance has been adequately characterised, and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional tests for tetrahydrofuran content, nickel content and particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. Additional methods have been adequately described and validated. Batch analytical data demonstrating compliance with this specification have been provided for 8 batches.

Stability of drug substance

Stability data on the active substance have been provided for 3 pilot scale batches, stored at 25°C/60% RH (36 months), 30°/65% RH (36 months), 30°/75% RH (36 months), and 40°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines. No noticeable change was observed on any parameter, therefore, the proposed re-test period of 36 months, with the storage condition ‘Store away from moisture’ and no special temperature storage conditions is justified.

Perindopril arginine

Perindopril arginine is not described in the Ph. Eur. However, the intermediate perindopril tert-butylamine has a monograph in the Ph. Eur. The active substance is a white or almost white crystalline powder and is freely soluble in water, slightly soluble in ethanol (96%) and practically insoluble in methylene chloride. The substance has the α-crystal form as polymorphic form. Perindopril has five asymmetric carbons, all with the S-configuration. The MAH included full information of the active substance perindopril arginine in the dossier.

The CEP procedure is used for the intermediate perindopril tert-butylamine. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
The manufacturing process of perindopril arginine is carried out in one step from the key intermediate. The starting materials are defined according to the CEO, what is acceptable. No class 1 solvents or heavy metal catalysts have been used in the synthesis. The drug substance has been adequately characterised, and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is based on the Ph. Eur. Monograph for perindopril tert-butylamine with additionally, specific methods for perindopril arginine and particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. The additional methods have adequately been described and validated. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 8 batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches stored at 25°C/60% RH (36 months), 30°/65% RH (36 months), 30°/75% RH (36 months), and 40°C/75% RH (6 months). The batches have been stored in accordance with applicable European guidelines. Although an increase in degradation products is seen, all results remain within specification, therefore, the proposed re-test period of 36 months, with no special storage condition is justified.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The compatibility of the two drug substances was investigated and no incompatibility was observed. The drug substance pellets were developed in a previous procedure, for a FDC product (capsule) containing in addition to the Atorvastatin and Perindopril pellets an Acetylsalicylic acid (ASA) gastro-resistant tablet, and no further development of the pellets was performed for the current drug product.

Two bioequivalence studies were performed on the related product containing besides the same atorvastatin and perindopril pellets an acetylsalicylic acid gastroresistant tablet in similar capsules (40 mg/10 mg/100 mg capsules), under fasting and fed conditions, with the three individual reference products Lipitor (Atorvastatin), Coversyl (perindopril), and Aspirin protect (acetylsalicylic acid). Certificates of analysis for the test batch and reference batches used in the bioavailability studies confirm that the difference between their assayed content is less than 5%. The bioequivalence study in fasting condition could be used to support the current product provided that the quality of the pellets is exactly the same, there is no chemical - pharmaceutical interaction between the components of the capsules and the absence of a pharmacokinetic interaction between acetylsalicylic acid, perindopril, and atorvastatin is adequately shown. The MAH has sufficiently demonstrated that the quality of the pellets is exactly the same, and that there is no chemical - pharmaceutical interaction between the components of the capsules. From a quality point of view this is sufficient, the absence of a pharmacokinetic interaction between acetylsalicylic acid, and perindopril/atorvastatin is discussed in the clinical overview.
Comparative dissolution studies were performed between all the strengths of the current product and the 40 mg/10 mg/100 mg capsules, at pH 1.2, 4.5 and 6.8, at a stirrer speed of 75 rpm. A lower paddle speed than 75 rpm was not possible due to the occurrence of coning in the dissolution vessel.

Manufacturing process
The manufacturing process consists of three main steps: manufacture of two intermediate products and final capsule filling. Process validation data on the product have been presented for 3 full-scale batches for both active substance pellets. Capsule filling was validated on three batches of the extreme dosage strengths (10 mg/5 mg and 40 mg/10 mg), each, and on one batch of 40 mg/5 mg and one batch of 10 mg/10 mg strengths, all at the lowest industrial scale and on one batch of each other intermediate dosage strengths 20 mg/5 mg and 20 mg/10 mg at small scale. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches

will be performed post authorisation. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
The excipients used for the drug substance pellets all comply with Ph. Eur. requirements. The gelatin used for the capsules can be from different sources, all sources holding a certificate of suitability to the European Pharmacopoeia. All other excipients used for the capsules and printing ink comply with the Ph. Eur. or EU regulation 231/2012 for food additives. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass of content, microbiological quality, identity, drug substance content, degradation products content, uniformity of dosage units, and dissolution. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Except for drug substance and related substance content, the release and shelf-life requirements/limits are identical. The wider shelf-life specifications for specified- and total impurities are acceptable in view of the statistical analysis performed on the provided stability results, obtained at the acceptable storage conditions. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three batches of the extreme dosage strengths (10 mg/5 mg and 40 mg/10 mg), each, and on one batch of 40 mg/5 mg and one batch of 10 mg/10 mg strengths, all at the lowest industrial scale, and on one batch of each other intermediate dosage strengths 20 mg/5 mg and 20 mg/10 mg at small scale, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three batches, each, of the 10 mg/5 mg and 40 mg/10 mg strengths, and one batch, each, of the 10 mg/10 mg and 40 mg/5 mg strengths, stored at 25°C/60% RH (12 months), 30°/65% RH (12 months), 30°/75% RH (12 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline and stored in the proposed packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The proposed shelf-life of 24 months is acceptable based on the provided long term and accelerated stability results.
In-use stability data has been provided demonstrating that the product remains stable for at least 100 days following first opening of the container, when stored at 25°C/60%RH or at 30°C/75%RH. As the stability after opening is comparable to the stability in the unopened container, no separate in-use stability is declared in the SmPC.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
Certificates of suitability issued by the EDQM have been provided, for the used gelatin of the capsules, and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Euvascor has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since the Euvascor fixed dose combination is intended for substitution of separately used atorvastatin and perindopril containing products, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

Euvascor is a combination of two approved medicinal products, marketed worldwide for many years, and with an established safety and efficacy profile.
Pharmacodynamic, pharmacokinetic and toxicological properties of atorvastatin and perindopril are well known. The MAH provided only a few new studies related to impurity qualification and further studies are not required. A non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology has been provided. The MAH reviewed the relevant literature for atorvastatin and the data supporting the approval of perindopril and summarises this in the non-clinical overview, which is of acceptable quality and appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Atorvastatin calcium trihydrate and perindopril arginine are well-known active substances with established efficacy and tolerability.

To support the application, the MAH submitted several interaction studies and bioequivalence studies at the highest strength of atorvastatin (40 mg) and perindopril (10 mg). For the other strengths (10 mg/5 mg, 20 mg/5 mg, 40 mg/5 mg, 10 mg/10 mg, 20 mg/10 mg) a biowaiver was claimed. The studies are sufficient for this type of application. The clinical pharmacokinetic studies are shortly summarised below and the biowaiver is also discussed.

IV.2 Pharmacokinetics

In the pharmacokinetic studies, the test formulation used is similar to the proposed formulation, except for the addition of the acetylsalicylic acid (ASA). ASA is formulated in a gastro-resistant tablet and added to the capsule. ASA can be considered as an individual component of the capsule. As there is no interaction between ASA and atorvastatin/perindopril, the study submitted for the ASA + atorvastatin/perindopril capsule can also be applied for the atorvastatin/perindopril capsule.

Pharmacokinetic interaction studies
The MAH performed study *PKH-05151-002* to investigate PK interactions between atorvastatin 40 mg, perindopril arginine 10 mg and ASA 100 mg free combination. The PK interaction study *PKH-05151-002* evaluated the interaction between the three substances mentioned above compared to administration of each mono-components alone. This interaction study indicates that there is no clinically relevant interaction between the individual components of the FDC. Moreover, the MAH demonstrated that ASA does not affect the PK of atorvastatin and perindopril (see paragraph supportive studies).

Bioequivalence studies
Pivotal study PKH-05151-003
In the pivotal fasting study, the relative bioavailability of the capsule of the triple combination FDC and co-administration of the corresponding mono-components under fasting conditions was evaluated. This study is considered pivotal as bioequivalence for the IR atorvastatin and IR perindopril was evaluated under fasting conditions. Lipitor 40 mg (atorvastatin) 40 mg tablet by Pfizer, Coversyl (perindopril arginine) 10 mg tablet by Les Laboratoires Servier Industrie, France and Aspirin Protect (acetylsalicylic acid) 100 mg gastro-resistant were used as reference formulations. The results of this comparative bioavailability study indicate that these formulations are bioequivalent. The test to reference ratios and corresponding 90% confidence interval for C_{max} (maximum plasma concentration) and AUC_{0-t} (area under the plasma concentration-time curve from time zero to t hours) were within the range of 80.00 to 125.00% for perindopril and atorvastatin.

Supportive studies
In addition the MAH provided a supportive study PKH-S5988-008 with another formulation of atorvastatin/perindopril arginine FDC in a tablet. This study was carried out to investigate interactions between atorvastatin 40 mg and perindopril arginine 10 mg FDC compared to administration of each

mono-component alone. In the supportive fasting study *PKH-005988-007*, one tablet of the fixed combination of atorvastatin 40 mg/perindopril arginine 10 mg versus one tablet of atorvastatin 40 mg plus one tablet of perindopril arginine 10 mg was evaluated. The 90% confidence intervals of the geometric mean ratios test/reference of AUC_{last} (area under the curve from zero to the last measurable point) and C_{max} for atorvastatin and AUC_{last} of perindopril were within the acceptance range of 80.00–125.00%, to conclude the bioequivalence between the two treatments, except of C_{max} of perindopril of the test product for which the upper bound is slightly outside the accepted limit (127.97% instead of 125.00%). The MAH justified that the slight increase of perindopril C_{max} observed in these studies is not due to an interaction with the other active substances of the atorvastatin/perindopril arginine FDC, acetylsalicylic acid or atorvastatin.

Biowaiver
A biowaiver was requested for the lower 10 mg/5 mg, 20 mg/5 mg, 40 mg/5 mg, 10 mg/10 mg, 20 mg/10 mg strengths using the biobatch triple combination formulation (atorvastatin/perindopril/ASA) as reference, which is considered acceptable. Moreover, the highest 40/10mg strength without the ASA EC tablet was also evaluated. Comparative dissolution studies were performed between the biobatch and the other strengths, in three media, i.e. pH 1.2 (NaCl, HCl medium), 4.5 (phosphate buffer) and 6.8 (phosphate buffer), at a stirrer speed of 75 rpm and a volume of 900 ml. The MAH provided a justification to justify deviation of the used stirrer speed (75 rpm) which is higher than the usual stirrer speed of 50 rpm, according to the guideline on bioequivalence.

IV.3 Pharmacodynamics

Atorvastatin and perindopril are well known active substances with established pharmacodynamics. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which lowers plasma cholesterol, whereas perindopril is an inhibitor of the angiotensin converting enzyme that reduces blood pressure. Atorvastatin and perindopril have different mechanism of action but are both considered cardio-protective drugs.

IV.4 Clinical efficacy

The effect of each mono component in reducing cardiovascular events has extensively been described in the literature.

The MAH submitted the following three post-hoc analysis:
- Post-hoc analysis of the EUROPA study - perindopril + Lipid Lowering Therapy versus placebo + Lipid Lowering Therapy
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- Post-hoc analysis of the ASCOT-LLA trial in the amlodipine arm – perindopril + atorvastatin versus perindopril +placebo
- Post-hoc analysis of the GREACE study - statin+ACEi vs statin vs ACEi vs neither

EUROPA study
A multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years. 12218 patients with evidence of coronary artery disease with no evidence of clinical signs of heart failure aged over 18 were randomised to 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) (n=6110) or placebo (n=6108). The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint (composite of cardiovascular mortality, non-fatal myocardial infarction and/or cardiac arrest with successful resuscitation) of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).
In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

Post hoc analysis of EUROPA evaluated the effect of perindopril in the subgroup of 7703 patients on lipid lowering therapy (LLT) (58% of the randomised patients of the EUROPA main study, of which 89.41% of patients with LLT received statins including atorvastatin). In this subgroup, composite efficacy endpoint of cardiovascular mortality, non-fatal acute myocardial infarction and cardiac arrest with successful resuscitation occurred in 4.9% of patients treated with perindopril + LLT compared with

6.6% of patients treated with placebo + LLT corresponding to 22% relative risk reduction (absolute risk reduction of 1.7%) (p=0.021). Based on prescription data, most likely ~ 31% of all the 7703 patients who were taking a LLT were taking atorvastatin.

GREACE Study

A total of 1600 patients with established coronary heart disease were randomised either to atorvastatin or to 'usual' medical care. The dose of atorvastatin was titrated from 10 to 80 mg/day, in order to reach the goal of LDL-C < 100 mg/dl (2.6 mmol/l). All patients were followed up for a mean period of 3 years.

In this study, atorvastatin (10-80 mg/d) improved the primary endpoints mortality (total and coronary) and morbidity (non-fatal MI, unstable angina pectoris, revascularisation, congestive heart failure, and stroke) rates significantly more than usual care over a mean of 3 years, in patients with established coronary heart disease.

In a post hoc subgroup analysis of the GREACE results, the long-term effect of combined treatment with a statin plus an angiotensin converting enzyme inhibitor (ACEI) in comparison to each drug alone or neither drug, regardless of the initial assignment of patients in the structured or usual care groups was assessed. From those on ACEI, 25% were administered with perindopril. From those on statins, 807 (92%) were on atorvastatin. During the 3-year follow-up there were 292 cardiovascular events (primary end point). There were 45 (10%) in the group with a statin and ACEI (group A), 61 (14.5%) in the group of patients on a statin but not an ACEI (group B), 91 in the group with an ACEI but not a statin (24.5%) (group C), and 95 events in the group neither on a statin or an ACEI (27%) (group D). Relative risk reductions and 95% confidence interval in the primary end point between Group A and all the rest was statistically significant (table 1).

Table 1: Comparisons of the percent RRR and 95% CI for the primary endpoint and its individual components in the four treatment groups

	Cardiovascular death + nonfatal MI	Cardiovascular death + nonfatal MI + revascularization
	RRR (95% CI) P-value	RRR (95% CI) P-value
Group A *vs* B	-34% (-62–14%) 0.08	-38% (-61--3%) 0.02
Group A *vs* C	-63% (-78—38%) <0.0001	-63% (-76--44%) p<0.0001
Group A *vs* D	-71% (-82--54%) <0.0001	-70% (-82--57%) p<0.0001
Group B *vs* C	-44% (-65--10%) 0.01	-40% (-59--13%) 0.004
Group B *vs* D	-57% (-73--32%) <0.0001	-55% (-68--35%) <0.0001
Group C *vs* D	-23% (-48-12%) 0.1	-22% (-38-6%) 0.06

MI=myocardial infarction, ACEI=angiotensin-converting enzyme inhibitor,
Group A=Statin + ACEI, Group B= Statin no ACEI, Group C=ACEI no statins, Group D= no ACEI no statins.

ASCOT–LLA Study

Of 19342 hypertensive patients (aged 40-79 years with at least three other cardiovascular factors) randomised to one of two antihypertensive regimens, 10305 with non-fasting total cholesterol concentrations 6.5 mmol/L or less were randomly assigned additional atorvastatin 10 mg or placebo. Treatment was stopped after a median follow-up of 3.3 years. By that time, 100 primary events of coronary heart disease had occurred in the atorvastatin group compared with 154 events in the placebo group (hazard ratio 0.64 [95% CI 0.50-0.83], p=0.0005). Fatal and non-fatal stroke (89 atorvastatin vs 121 placebo, 0.73 [0.56-0.96], p=0.024), total cardiovascular events (389 vs 486, 0.79 [0.69-0.90], p=0.0005), and total coronary events (178 vs 247, 0.71 [0.59-0.86], p=0.0005) were also significantly lowered. There were 185 deaths in the atorvastatin group and 212 in the placebo group (0.87 [0.71-1.06], p=0.16).

The post hoc analysis in the amlodipine arm showed that the combinations placebo + perindopril and atorvastatin + perindopril both reduced mean total cholesterol and LDL-Cholesterol. However, the reduction was more pronounced with atorvastatin + perindopril. Compared with placebo + perindopril, the decrease of total cholesterol and of LDL-Cholesterol in the atorvastatin + perindopril group was statistically and clinically significant: total cholesterol was reduced by -0.71 (95% CI, -0.783, -0.651); p<0.001 and LDL-Cholesterol by -0.708 (95% CI, -0.773, -0.643); p<0.001.
Compared with placebo + perindopril combination, atorvastatin + perindopril combination reduced the risk of all cardiovascular events and of all-cause mortality. Among them, main clinically relevant CV outcomes were reduced:

- By 46% for the risk of cardiovascular mortality, P=0.008
- By 44% for the risk of non-fatal MI (excl silent) + fatal CHD, P=0.005
- By 42% for the risk of non-fatal MI (incl silent) + fatal CHD; P=0.004
- By 41% for the risk of total CHD + coronary revascularisation procedures, P=0.001
- By 40% for the risk of CV mortality + MI + stroke, P=<0.001
- By 36% for the risk of total CHD + fatal and non-fatal stroke, P=0.002
- By 32% for the risk of total coronary events, P=0.004
- By 29% for the risk of all-cause mortality, P=0.008

Open label studies
In addition, the combined use of atorvastatin and perindopril was further supported by several open label studies.

Moreover, the proposed fixed dose combination of atorvastatin and perindopril is intended as a substitution therapy in patients already treated with atorvastatin and perindopril given concurrently at the same dose level. Overall, these data support the submission of a fixed dose combination for atorvastatin and perindopril.

IV.5 Clinical safety

The safety of atorvastatin and perindopril has already been established during the clinical development of each substance. The dosages proposed for atorvastatin/perindopril FDC correspond to the combination of doses approved for the single medicinal products.

Monocomponents
Atorvastatin
Common adverse events (AEs) are: nasopharyngitis, allergic reactions, hyperglycaemia, headache, pharyngolaryngeal pain, epistaxis, constipation, flatulence, dyspepsia, nausea, diarrhoea, myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain, liver function test abnormal, blood creatine kinase increased (Lipitor SmPC).

Perindopril
The most common AEs reported with perindopril are: dizziness, headache, vertigo, paraesthesia, visual disturbances, tinnitus, hypotension, cough, dyspnoea, nausea, vomiting, abdominal pain, dysgueusia, dyspepsia, diarrhoea, constipation, rash, pruritus, muscle cramps and asthenia (Coversyl SmPC).

Combination
EUROPA post-hoc analysis
14 patients experienced serious suspected adverse drug reactions (SSADRs): 7 patients receiving perindopril + lipid lowering therapy (LLT) (0.1%) and 7 patients receiving placebo + LLT (0.1%). Hypotension (4 cases) was the most frequent serious suspected adverse drug reaction (SSADR) in the perindopril + LLT group. Other SSADRs included one case of angioneurotic oedema, one case of unstable angina, one case of bradycardia and one patient experienced dizziness, blindness and chest pain. There were one case of bronchitis and one case of persistent dry cough.
In total 2.0% of patients died during the study: 1.9% of patients died in the perindopril + LLT group and 2.2% in the placebo + LLT group. Cardiovascular death was reported for 1.3% and 1.6% of the patients respectively. Biochemistry parameters remained stable in both groups throughout the study.

ASCOT-LLA post hoc analysis
The most frequently reported adverse events in the placebo + perindopril group were cough (74.8 per 1000 PY), arthralgia (31.6), peripheral oedema (29.2) and dizziness (24.3) while in the atorvastatin + Perindopril group, cough (68.0 per 1000 PY), arthralgia (36.3), peripheral oedema (29.8) and back pain (25.7) were the most frequent.
A total of 383 patients experienced at least one serious non-fatal adverse event during the therapy period, 198 patients in the placebo + perindopril group (10.3%) and 185 patients in the atorvastatin + perindopril group (9.5%) The difference was statistically significant, p=0.006.
Most frequent non-fatal serious AE reported in the placebo + perindopril group were chest pain (0.4% vs 0.3%), fall 0.4% vs 0.1%) and prostate cancer (0.4% vs 0.2%) and most frequent non-fatal serious AE reported in the atorvastatin + perindopril group were chest pain (0.4% vs 0.3%) and colon cancer (0.2% vs 0.3%).

Safety data from bioequivalence and PK interaction studies
The incidence of AEs reported during the PK and bioequivalence studies was very low and the AEs were either mild or moderate in severity.
No severe AEs were observed during these studies. Furthermore, no serious AEs or deaths were reported during these studies.

Pharmacovigilance
An analysis was performed to compare the safety profile of the association perindopril-atorvastatin with known safety profiles of perindopril and atorvastatin. To perform this analysis, the MAH safety database has been queried in order to extract patient-cases where atorvastatin was reported as a co-suspected or a concomitant medicinal product in patients receiving perindopril.

From 22 June 1988 to 31 August 2016, 11629 case-reports (22066 events) were received for perindopril. Out of these case-reports, 785 patient-cases were found for perindopril and atorvastatin free association. In the analysis all patient-cases reporting the association of perindopril with atorvastatin whatever the salt or dosage of perindopril and atorvastatin were included.

The most involved SOCs were:
- Skin and subcutaneous tissue disorders (204 cases - 260 events representing 13.0 % of all reported events): the most frequently reported events were angioedema (95/260, 36.5%), urticaria (24/260, 9.2%), pruritus (24/260, 9.2%), rash (20/260, 7.7%) and rash pruritic (10/260, 3.8%).
- Respiratory, thoracic and mediastinal disorders (208 cases - 251 events representing 12.6% of all reported events): the most frequently reported events were cough (140/251, 55.8%) and dyspnea (33/251, 13.1%).
- Gastrointestinal disorders (158 cases - 221 events representing 11.1% of all reported events): the most frequently reported events were swollen tongue/tongue oedema (32/221, 14.5%), diarrhoea (30/221, 13.6%), nausea (26/221, 11.8%), vomiting (17/221, 7.7%), lip swelling/lip oedema (16/221, 7.2%), abdominal pain (15/221, 6.8%) and dysphagia (11/221, 5.0%).
- General disorders and administration site conditions (155 cases - 203 events representing 10.2% of all reported events): the most frequently reported events are fatigue and malaise (both 21/203, 10.3%), drug interaction (18/203, 8.9%), oedema peripheral (17/203, 8.4%), face oedema (16/203, 7.9%) and asthenia (15/203, 7.4%).
- Nervous System disorders (137 cases - 169 events representing 8.5% of all reported events): the most frequently reported events were dizziness/dizziness postural (35/169, 20.7%) and headache (25/169, 14.8%).

The analysis of all adverse events reported when perindopril and atorvastatin were associated as free combination did not reveal any new safety information compared with those already known for each product. The majority of the reported events are expected for perindopril, atorvastatin or for both. No safety signal has been detected regarding the unlisted events.

IV.6 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 Euvascor.

- Summary table of safety concerns as approved in RMP

Important identified risks	– Drug-induced hepatitis – Rhabdomyolysis / myopathy – New onset of diabetes in patients with increased risk of diabetes – Stevens-Johnson syndrome and toxic epidermal necrolysis – Interstitial lung disease – Hyperkalaemia – Increased risk of hypotension, hyperkalaemia and acute renal failure when combining RAS-agents – Neutropenia /agranulocytosis/ thrombocytopenia – Foetotoxicity / embryotoxicity / use during pregnancy – Angioedema
Important potential risks	– Haemorrhagic stroke – Autoimmune events
Missing information	– Children and adolescents – Lactating women – Patients with severe hepatic impairment – Patients with severe renal impairment

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

The pharmacokinetic studies were designed to demonstrate bioequivalence between the recognised reference formulations of the individual mono-components with the proposed fixed-dose combination as well as to investigate a possible pharmacokinetic interaction of the components. Results were satisfactory: the fixed dose combination can be used instead of the separate mono-components. Overall, the provided clinical overview is considered sufficient to justify the rationale of this particular combination when used to substitute patients already on stable doses of the separate agents. Data from clinical practice do not suggest any substantial different safety profile from that which is known for the mono-components.

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 test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. A satisfactory outcome was achieved when 90% of the participants were able to find information and when 90% was able to show that they could understand the information. 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

Euvascor 10 mg/5 mg, 20 mg/5 mg, 40 mg/5 mg, 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg, hard capsules have a proven chemical-pharmaceutical quality and are considered an approvable fixed dose combination. Atorvastatin calcium trihydrate and perindopril arginine are well known, established active substance, which are used as a combination in clinical practice.

The proposed combination product was demonstrated to be bioequivalent with co-administration of the

separate reference products Lipitor and Coversyl. The results of an interaction study demonstrate that there is no significant pharmacokinetic interaction between the co-administered components of the applied combination product. The efficacy and safety profile is considered the same as for the monocomponents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that fixed dose combination is approvable, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 December 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/xxxx/WS/286	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data. The proposed additions are in line with the outcome and changes to product information for Coversyl (perindopril) following procedure FR/H/xxxx/WS/078.	Yes	25-06-2018	Approved	-
NL/H/3871/1-6/IA/002/G	– Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance: o Addition of a new specification parameter to the specification with its corresponding test method o Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) – Change to in-process tests or limits applied during the manufacture of the finished product; other variation – Change in test procedure for the finished product; minor changes to an approved test procedure	No	07-08-2018	Approved	-