Public Assessment Report
Scientific discussion

Rosuvastatin/Amlodipine 10 mg/5 mg, 10 mg/10 mg, 20 mg/5 mg and 20 mg/10 mg film-coated tablets

(Rosuvastatin calcium and Amlodipine besilate)

ES/H/0320/001-004/DC

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Registration number in Spain: xxx

This module reflects the scientific discussion for the approval of **Rosuvastatin/Amlodipine 10 mg/5 mg, 10 mg/10 mg, 20 mg/5 mg and 20 mg/10 mg film-coated tablets**. The procedure was finalised on December 2015. For information on changes after this date please refer to the module 'Update'.

INTRODUCTION

This decentralised procedure application concerns a fixed dose combination of rosuvastatin calcium/amlodipine besilate under Rosuvastatin/Amlodipine 10 mg/5 mg, 10 mg/10 mg, 20 mg/5 mg and 20 mg/10 mg film-coated tablets trade names.

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

The Concerned Member States involved in this procedure are IS and MT.

Fixed combination rosuvastatin + amlodipine is proposed as substitution therapy for those patients who are adequately controlled with rosuvastatin and amlodipine given concurrently, at the same dose level as in the combination for the treatment of hypertension in adult patients who are estimated to have a high risk for a first cardiovascular event (for prevention of major cardiovascular events) or with one of the following coincident conditions: primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (type IIb) or homozygous familial hypercholesterolaemia. According to scenario A of Q&A document on the clinical development of fixed combination of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention [CHMP/EWP/191583/2005]), the proposed clinical packaged is acceptable since the bioequivalence has been demonstrated between the free combination of the recognised reference formulations of the individual monocomponents and the marketing formulation (please refer to results section)

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

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for Rosuvastatin/Amlodipine 10 mg/5 mg, 10 mg/10 mg, 20 mg/5 mg and 20 mg/10 mg film-coated tablets.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

ACTIVE SUBSTANCE

- Rosuvastatin calcium

Rosuvastatin calcium is a known active substance described in Ph.Eur. An ASMF procedure has been submitted to support the quality of the active ingredient.

- Amlodipine besilate

Amlodipine besilate is a known substance described in Ph.Eur. A Ph.Eur. Certificate of Suitability has been submitted to support the quality of the active ingredient. The CEP includes re-test period.

FINISHED PRODUCT

Description of the product

10 mg/5 mg: yellowish brown, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark 10-5 on one side of the tablet with a diameter of approx. 8.6mm.
10 mg/10 mg: light pink, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark 10-10 on one side of the tablet with a diameter of approx. 11mm.
20 mg/5 mg: light yellow, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark 20-5 on one side of the tablet with a diameter of approx. 11mm.
20 mg/10 mg: white, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark 20-10 on one side of the tablet with a diameter of approx. 11mm.

The qualitative composition is as follows:
Rosuvastatin calcium
Amlodipine besilate
Cellulose, microcrystalline
Lactose, anhydrous
Crospovidone
Silica, colloidal anhydrous
Magnesium stearate

Film coating for 10 mg/5 mg:
Poly(vinyl) alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Ferric oxide yellow colour (E172)

Film coating for 10 mg/10 mg:
Poly(vinyl) alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Ferric oxide yellow colour (E172)
Ferric oxide red colour (E172)

Film coating for 20 mg/5 mg:
Poly(vinyl) alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Ferric oxide yellow colour (E172)

Film coating for 20 mg/10 mg:
Poly(vinyl) alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc

The film coated-tablets are packed in Blister (OPA/Alu/PVC//Alu).

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The pharmaceutical development has been adequately described.

Manufacture of the product and process controls

The manufacturing process is sufficiently described and the process controls are appropriate, considering the nature of the product and the manufacturing method.
The commercial batch size is defined.
The dossier includes sufficient validation data to guarantee that the manufacturing process is controlled and to ensure batch to batch reproducibility and compliance with product specifications.

Excipients

The information provided is adequate. The specifications for the different excipients are justified by their official adoption in the relevant Ph. Eur. monograph or by an in-house monograph (for the non-compendial excipient).

Product specification

The product specifications proposed are adequate. The limits proposed for the different parameters have been adequately justified.
The analytical methods have been properly described and validated.

Container closure system

The film-coated tablets are packed in Blister (OPA/Alu/PVC//Alu).
The components of the container closure system comply with the specifications established in the applicable Ph. Eur. monographs.

Stability of the product

The stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life and storage conditions.

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and the Member States agreed that no further non-clinical studies are required.

Environmental Risk Assessment (ERA)

No ERA was submitted. This was justified by the Applicant since the Rosuvastatin/Amlodipine 10 mg/5 mg, 10 mg/10 mg, 20 mg/5 mg and 20 mg/10 mg film-coated tablets are presented as fixed dose combination and are proposed for the substitution therapy of the mono components of rosuvastatin and amlodipine and as such will replace use of the co-administered single products. The exposure of the environment to rosuvastatin and to amlodipine will not increase by use of this product and would thus not be expected to have an adverse effect upon the

environment.
In addition, Rosuvastatin/Amlodipine 10 mg/5 mg, 10 mg/10 mg, 20 mg/5 mg and 20 mg/10 mg film-coated tablets are unlikely to result in any significant increase in the combined sales volumes for all rosuvastatin or amlodipine products. With this regard and on the basis of CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), a formal environmental risk assessment is not considered necessary.
The justification for the absence of ERA is considered acceptable.

II.3 Clinical aspects

Introduction

As rosuvastatin/amlodipine is a fixed combination tablet containing the well established active ingredients rosuvastatin (as calcium) and amlodipine (as besilate) as substitution therapy for those patients who are adequately controlled with rosuvastatin and amlodipine given concurrently (according to scenario A of Q&A document on the clinical development of fixed combination of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention [CHMP/EWP/191583/2005]), the proposed clinical packaged is acceptable since the bioequivalence has been demonstrated between the free combination of the recognised reference formulations of the individual monocomponents and the marketing formulation.

To support the application, the Applicant has submitted two bioequivalence studies which are discussed below.

Biowaiver

The bioequivalence of test and reference products has been demonstrated for 20mg /10 mg and 15 mg/10 mg strengths (please refer to section of results). These data can be extrapolated to the rest of the strength as all the requirements described in section 4.1.6 of the BE guideline are fulfilled.

Bioequivalence

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

- Comparative, single-dose, 2-way cross-over bioavailability study of rosuvastatin/amlodipine 20 mg/10 mg fixed dose combination tablet formulation and co-administration of rosuvastatin 20 mg and amlodipine 10 mg as separate tablets in healthy male volunteers under fasting conditions.
- Comparative, single-dose, 2-way cross-over bioavailability study of rosuvastatin/amlodipine 15 mg/10 mg fixed dose combination tablet formulation and co-administration of rosuvastatin 5 mg, rosuvastatin 10 mg and amlodipine 10 mg as separate tablets in healthy male volunteers under fasting conditions

<u>Bioequivalence study 14-409 (CRO Study Code: SMA-620-14)</u>
This was a comparative, single-dose, 2-way cross-over bioavailability study of Rosuvastatin/Amlodipine 20 mg/10 mg fixed dose combination tablet formulation and co-administration of rosuvastatin 20 mg and amlodipine 10 mg as separate tablets in healthy male volunteers under fasting conditions with a washout of 28 days.

The study was carried out from April 11th, 2014 to May 14th, 2014 at the Clinical part of the study was performed at Medical Faculty of Ss. Cyril and Methodius University, Department of Preclinical and Clinical Pharmacology & Toxicology, 50 Divizija b.b., 1000 Skopje, R. Macedonia.

The analytical portion was conducted:
Rosuvastatin: May 20th, 2014 to June 01st, 2014 at inVentiv Health Clinical, Inc. (formerly PharmaNet Inc.) 2500, rue Einstein Québec (Québec), Canada, G1P 0A2
Amlodipine: June 27th, 2014 to July 14th, 2014 at KRKA, d. d., Novo mesto R&D, R&D, Pharmacokinetics and Preclinical Research Pharmacokinetics Novo mesto, Slovenia

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP were issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

Design
A single-dose, 2-way cross-over bioavailability study in healthy male volunteers under fasting conditions with a washout of 28 days.

The application concerns an oral immediate release formulation (film-coated tablets) with a linear PK over the therapeutic dose for both drugs. In addition, as described in the references SmPC, amlodipine or rosuvastatin tablets can be administered with or without food. Therefore, a single dose bioequivalence study under fasting conditions with the 20 mg/10mg strengths is considered adequate for the application.

The wash-out period and the sampling schedule are considered acceptable for an adequate characterisation of the systemic exposure of a drug with such a half-life and Tmax.

Test product: Rosuvastatin/Amlodipine 20 mg/10 mg tablets Batch number: 3089 04 P013 0314. Batch size: 100,000 tablets. Expiry date (Retest day): September 2014. Assay (content): 99% for rosuvastatin and 98% for amlodipine of label claim.
Reference products:
Crestor® 20 mg tablets manufactured by AstraZeneca UK Limited, UK, EUExpiry date: April 2016. Rosuvastatin assay (content): 99 % of label claim.
Norvasc® 10 mg tablets manufactured by Pfizer Manufacturing Deutschland GmbH, Germany. Expiry date: August 2015. Amlodipine assay (content): 98 % of label claim.

The reference product is adequate with regards to expiry date, content and it was obtained from Slovenian market.
All batches were tested before expiry date and a similar content of active substance is shown. Therefore, content correction is not necessary.

In the present study, forty six (46) subjects were enrolled and randomised to a treatment sequence in the study, in accordance with the protocol. Forty-five (45) healthy male subjects completed clinical part of this study. The subject No 08 didn't come at check in of Period II from the study for personal reason.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples..

Pharmacokinetic data analysis
Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable

Statistical analysis
The methods used in this study for the statistical evaluation are considered acceptable. ANOVA was performed on log-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} were considered as the primary pharmacokinetic parameters. The analysis of variance model included the following factors: sequence, subjects nested within sequence, period and treatment.
Values for the T_{max} parameter were analysed by a non-parametric approach (Wilcoxon Signed-Rank Test).

Based on the log-transformed parameters, the 90% confidence intervals of the relative mean plasma for AUC_{0-t} and C_{max} of the test to reference products should be between 80-125% to conclude bioequivalence.

Results
The 90% confidence intervals mean treatment T/R ratios are shown in the following table:

Bioequivalence evaluation of rosuvastatin

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	96.34	90.92-102.09
Ln (C_{max})	96.39	89.27-104.07

Bioequivalence evaluation of amlodipine

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	99.28	96.59-102.04
Ln (C_{max})	99.10	96.05-102.25

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 ï 1.25 and therefore bioequivalence has been proven. No clinically significant differences were observed between the median Tmax of test and reference products.

Bioequivalence study 14-431 (CRO Study Code: SMA-1770-14)

This was a comparative, single-dose, 2-way cross-over bioavailability study of rosuvastatin/amlodipine 15 mg/10 mg fixed dose combination tablet formulation and co-administration of rosuvastatin 5 mg, rosuvastatin 10 mg and amlodipine 10 mg as separate tablets in healthy male volunteers under fasting conditions with a washout of 21 days.

The study was carried out from June 27th, 2014 to July 23rd, 2014 at the Clinical part of the study was performed at Medical Faculty of Ss. Cyril and Methodius University, Department of Preclinical and Clinical Pharmacology & Toxicology, 50 Divizija b.b., 1000 Skopje, R. Macedonia.
The analytical portion was conducted at inVentiv Health Clinical, Inc. (formerly PharmaNet Inc.) 2500, rue Einstein Québec (Québec), Canada, G1P 0A2 for both analytes between the following days:
Rosuvastatin: July 28th, 2014-August 09th, 2014.
Amlodipine: July 28th, 2014-August 08th, 2014.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

Design
A single-dose, 2-way cross-over bioavailability study in healthy male volunteers under fasting conditions with a washout of 21 days.

The application concerns an oral immediate release formulation (film-coated tablets) with a linear PK over the therapeutic dose for both drugs. In addition, as described in the references SmPC, amlodipine or rosuvastatin tablets can be administered with or without food. Therefore, a single dose bioequivalence study under fasting conditions with the 15mg/10mg strength is considered adequate as supportive for the application.

The wash-out period and the sampling schedule are considered acceptable for an adequate characterisation of the systemic exposure of a drug with such a half-life and Tmax.

Test product: Rosuvastatin/Amlodipine 15 mg/10 mg tablets. Batch size: 100,000 tablets. Expiry date (Retest day): November 2014. Assay (content): 100% for rosuvastatin and 99% for amlodipine of label claim.
Reference products:
Crestor® 5 mg tablets manufactured by AstraZeneca UK Limited, UK, EU. Batch number: KH508. Expiry date: June 2016. Assay (content): 97 % of label claim.
Crestor® 10 mg tablets manufactured by AstraZeneca UK Limited, UK, EU. Batch number: KP474. Expiry date: June 2016. Assay (content): 99 % of label claim.
Norvasc® 10 mg tablets manufactured by Pfizer Manufacturing Deutschland GmbH, Germany. Batch number: B10462831 SV. Expiry date: August 2015. Assay (content): 98 % of label claim.
The reference product is adequate with regards to expiry date, content and it was obtained from Slovenian market.

All batches were tested before expiry date and a similar content of active substance is shown. Therefore, content correction is not necessary.

In the present study, forty eight (48) subjects were enrolled and randomised to a treatment sequence in the study, in accordance with the protocol. Forty-eight (48) healthy male subjects completed clinical part of this study.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples..

Pharmacokinetic data analysis
Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable

Statistical analysis
The methods used in this study for the statistical evaluation are considered acceptable. ANOVA was performed on log-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} were considered as the primary pharmacokinetic parameters. The analysis of variance model included the following factors: sequence, subjects nested within sequence, period and treatment.
Values for the T_{max} parameter were analysed by a non-parametric approach (Wilcoxon Signed-Rank Test).

Based on the log-transformed parameters, the 90% confidence intervals of the relative mean plasma for AUC_{0-t} and C_{max} of the test to reference products should be between 80-125% to conclude bioequivalence.

Results
The 90% confidence intervals mean treatment T/R ratios are shown in the following table:

Bioequivalence evaluation of rosuvastatin

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	95.72	89.46-102.42
Ln (C_{max})	95.64	87.41-104.65

Bioequivalence evaluation of amlodipine

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	101.39	98.68-104.17
Ln (C_{max})	101.72	98.82-104.70

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 ï 1.25 and therefore bioequivalence has been proven. No clinically significant differences were observed between the median Tmax of test and reference products.

Risk Management Plan

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

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

Discussion on the clinical aspects

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product.
Efficacy and safety of the active substances rosuvastatin calcium and amlodipine besilate are well documented for the reference medicinal product. The design of the submitted bioequivalence studies is adequate and the results allow us to conclude bioequivalence with the reference.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

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

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

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in December 2015.