CBG MEB

Public Assessment Report

Scientific discussion

Rosuvastatine Accord 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets

(rosuvastatin calcium)

NL/H/3255/001-004/DC

Date: 15 August 2016

This module reflects the scientific discussion for the approval of Rosuvastatine Accord 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets. The procedure was finalised on 16 July 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rosuvastatine Accord 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets, from Accord Healthcare Ltd.

The product is indicated for:

Treatment of hypercholesterolaemia
Adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Prevention of cardiovascular events
Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Crestor 10 mg, 20 mg and 40 mg film-coated tablets (NL License RVG 26872-4), which have been registered in the Netherlands by AstraZeneca BV since 6 November 2002 through mutual recognition procedure NL/H/0343/001-003. The innovator product of the lower strength, Crestor 5 mg film-coated tablets, was approved in the Netherlands on 20 July 2004 (NL License RVG 30823; NL/H/0343/004).

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Cyprus, Denmark, Estonia, Finland, France (only 5 mg, 10 mg and 20 mg strengths), Ireland, Italy, Lithuania, Latvia, Malta, Norway, Sweden and the UK.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Rosuvastatine Accord is a film-coated tablet in 4 different strengths:

- 5 mg - Yellow, round, approximately 7.0 mm in diameter, biconvex, film-coated tablet, debossed “5” on one side and “R” on other side
- 10 mg - Pink, round, approximately 7.0 mm in diameter, biconvex, film-coated tablet, debossed “10” on one side and “R” on other side
- 20 mg - Pink, round, approximately 9.0 mm in diameter, biconvex, film-coated tablet, debossed “20” on one side and “R” on other side
- 40 mg - Pink, oval, approximately 11.5 mm in length and 6.9 mm in width, biconvex, film-coated tablet, debossed “40” on one side and “R” on other side

Each tablet contains 5 mg, 10 mg, 20 mg or 40 mg of the active substance rosuvastatin (as rosuvastatin calcium).

Tablets are packed in Alu-Alu blisters and HDPE bottle pack (white opaque HDPE bottle with white opaque PP closure and white opaque desiccant canister with blue printing).

The excipients are:

Core tablet
- Lactose, anhydrous
- Cellulose, microcrystalline (E460)
- Magnesium oxide
- Magnesium stearate (E470b)
- Crospovidone (E1202)

Film coating
For 5 mg:
- Hypromellose (E464)
- Triacetin (E1518)
- Titanium dioxide (E171)
- Lactose monohydrate
- Iron oxide yellow (E172).

For 10 mg and 20 mg:
- Opadry II 39K540032 pink
    - Hypromellose (E464)
    - Triacetin (E1518)
    - Titanium dioxide (E171)
    - Lactose monohydrate
    - Iron oxide red (E172)
    - Quinoline yellow aluminum lake (E104)
    - Brilliant blue FCF aluminum lake (E133)

For 40 mg:
- Opadry II 39K540012 pink
    - Hypromellose (E464)
    - Triacetin (E1518)
    - Titanium dioxide (E171)
    - Lactose monohydrate
    - Sunset yellow FCF aluminum lake (E110)
    - Allura red AC aluminum lake (E129)
    - Brilliant blue FCF aluminum lake (E133)

The 5 mg and the 10 mg tablets have the same composition of the core tablet with the exception of the amount of active substance and corresponding amount of lactose monohydrate and microcrystalline cellulose. The same is the case for the 20 mg and the 40 mg tablets.

II.2 Drug Substance

The active substance is rosuvastatin calcium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Rosuvastatin calcium is a white to almost white powder, freely soluble in glacial acetic acid, sparingly soluble in chloroform and acetonitrile, very slightly soluble in water and insoluble in ethyl ether and ethyl acetate. Rosuvastatin calcium has two chiral centres, corresponding to theoretically four diastereoisomers. The manufactured rosuvastatin calcium has a 3R,5S geometry. The amorphous form is produced.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The synthesis of rosuvastatin calcium covers several steps. The choice of starting materials has been adequately justified. The manufacturers and specifications have been provided. Specifications of the intermediates, critical process parameters and in-process control tests from the starting materials are presented. The carry over of potential impurities and residual solvents have been adequately discussed.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
Three commercial scale batches have been stored for 18 months at 5°C, 18 months at 25°C/60% RH and 6 months at 40°C/75% RH. During the stability studies the following parameters have been tested: description, identification, water content, specific optical rotation, determination of related substances and assay. All stability results were in accordance with the set drug substance specification. Based on the stability results, a retest period could be granted of 18 months when stored protected from light and moisture, below 25°C.

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 main development studies were formulation trials, manufacturing process optimisation studies and comparative dissolution studies. The choice of excipients is justified and their functions explained. For the 40 mg product, azo-colouring agents are used. Considering the lower dosing schedule in the paediatric population, 5-20 mg orally once a day, this is considered acceptable.

Bioequivalence studies were performed with the 5 mg and the 40 mg drug product. The batches used in the bioequivalence study have the same composition and are manufactured in the same way as the future commercial batches. The bioequivalence batches are of sufficient size in relation to the intended commercial batch size.
As the composition of the 5 mg and 10 mg formulations are dose proportional and also the 20 and 40 mg tablets are dose proportional, the use of the bracketing approach is acceptable. The MAH submitted dissolution test according the current guideline. With all formulations dissolution was more than 85% within 15 minutes. A biowaiver for the 10 mg and 20 mg tablets was therefore granted (see also section IV.2 ‘Pharmacokinetics).

Manufacturing process
The manufacturing process consists of mixing, compression, coating and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches of each strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
All excipients used comply with the requirements of their respective Ph.Eur. or USP/NF monographs, except for the ready to use coating materials. In-house specification have been provided for the coating materials. The 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, identification, average weight, water content, hardness, uniformity of dosage units, dissolution, related substances, assay and microbial quality. The release and shelf life specification are identical except for related substances and water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data on three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches of each strength in accordance with applicable European guidelines demonstrating the stability of the product for 6 months (40°C/75% RH) 18 months (25°C/60% RH). The batches were stored in Alu-Alu blister and two sizes of HDPE bottles. On basis of the data submitted, a shelf life was granted to both the Alu-Alu blister and the HDPE bottles of 24 months.

Based on the photostability data provided the following storage condition should be applied to both the Alu-Alu blister and the HDPE bottles: This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture and light.

In-use stability studies have been performed with two batches of 5 mg and two batches of 40 mg tablets packed in 90 and 500 count HDPE bottles. It is demonstrated that the product remains stable for 90 days following first opening of the container, when stored at long term conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
None of the materials used is of animal or human origin except for lactose. The milk is sourced from healthy animals in the same conditions as milk collected for human consumption and the lactose is prepared without the use of other ruminant materials than calf rennet. The calf rennet is in accordance with Public Statement EMEA/CPMP/571/02.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rosuvastatine Accord has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rosuvastatine Accord is intended for generic substitution, 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

These products are generic formulations of Crestor which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rosuvastatin calcium is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies with the 5 mg and 40 mg formulation and requested a biowaiver for the 10 mg and 20 mg formulation. The bioequivalence studies and biowaivers are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Rosuvastatine Accord 5 mg film-coated tablets (Accord Healthcare Ltd, UK) is compared with the pharmacokinetic profile of the reference product Crestor 5 mg film-coated tablets (AstraZeneca, UK). In addition a second bioequivalence study was conducted in which the pharmacokinetic profile of the test product Rosuvastatine Accord 40 mg film-coated tablets (Accord Healthcare Ltd, UK) is compared with the pharmacokinetic profile of the reference product Crestor 40 mg film-coated tablets (AstraZeneca, UK).

The choice of the reference products in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

As these products can be taken regardless of food intake, studies under fasting conditions are justified.

Biowaiver

With respect to the 10 and 20 mg tablet strengths, the MAH provided a justification for a biowaiver. The 5 mg and the 10 mg tablets have the same composition of the core tablet with the exception of the amount of active substance and corresponding amount of lactose monohydrate and microcrystalline cellulose. The same is the case for the 20 mg and the 40 mg tablets. However criterion c) the *Guideline on the Investigation of Bioequivalence* is not met as the amount of active substance in 10 mg, 20 mg and 40 mg tablets is more than 5% of the tablet core weight. However in this case it is considered acceptable based on the following considerations:

- the drug substance is highly soluble within the pH range of 1.2 – 6.8
- lactose monohydrate and microcrystalline cellulose are not expected to affect the bioavailability
- the drug load of the 10 mg and 20 mg tablets are bracketed by the drug load of the 5 mg and 40 mg tablets which were found to be bioequivalent *in vivo*

Therefore, the requested biowaiver of strength for the 10 mg and 20 mg tablets was granted.

Analytical/statistical methods

In both studies the analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – 5 mg tablet

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover, open label, balanced bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 18-45 years. Each subject received a single dose (5 mg) of one of the 2 rosuvastatin calcium formulations. The tablet was orally administered with 240 ml water after. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected at 0.0 (pre-dose) and at 0.33, 0.66, 1.0, 1.3, 1.66, 2.0, 2.3, 2.67, 3.0, 3.3, 3.67, 4.0, 4.3, 4.67, 5.0, 5.5, 6.0, 8.0, 10, 12, 16, 20, 24, 36 and 48 hours post-dose administration.

The overall study design is acceptable considering the absorption rate and half-lives. Also the washout period is acceptable.

Results

In this study, 39 subjects were included for pharmacokinetic analysis. One subject was withdrawn for personal reasons in period I, two subjects withdrew on their own accord in period II and six subjects were withdrawn on medical grounds in period II.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 5 mg rosuvastatin calcium under fasted conditions.

Treatment N=39	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	42.330 ± 19.4059	44.333 ± 20.0296	4.848 ± 2.1144	4.33 (0.67 – 5.00)
Reference	42.050 ± 20.2395	43.979 ± 20.7510	4.603 ± 2.4700	4.33 (1.33 – 4.68)
***Ratio (90% CI)**	1.00 (0.94 - 1.07)	1.00 (0.94 - 1.07)	1.06 (0.98 - 1.14)	--
CV (%)	16.7	16.7	20.0	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Bioequivalence study II – 40 mg tablet

Design

An open label, balanced, randomised, two-treatment, two period, two-sequence, two-way crossover, single oral dose, bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 18-45 years. Each subject received a single dose (40 mg) of one of the 2 rosuvastatin calcium formulations. The tablet was orally administered with 240 ml water after a fasting period. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected at 0.0 (pre-dose) and at 0.33, 0.66, 1.0, 1.3, 1.66, 2.0, 2.3, 2.67, 3.0, 3.3, 3.67, 4.0, 4.3, 4.67, 5.0, 5.5, 6.0, 8.0, 10, 12, 16, 20, 24, 36 and 48 hours after administration of the products.

The overall study design is acceptable considering the absorption rate and half-lives. Also the washout period is acceptable. As these products can be taken regardless food intake, studies under fasting conditions are justified.

Results

Three subjects were withdrawn on medical grounds in period II. 45 subjects were included for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 40 mg rosuvastatin calcium under fasted conditions.

Treatment N=45	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	467.612 ± 217.0808	484.097 ± 221.0926	63.001 ± 34.6682	2.67 (0.67 - 5.00)
Reference	447.759 ± 244.9063	464.440 ± 247.3231	58.108 ± 36.2610	4.33 (0.67 - 5.00)
***Ratio (90% CI)**	1.06 (1.00 - 1.12)	1.06 (1.00 - 1.11)	1.08 (1.00 - 1.17)	--
CV (%)	16.1	15.6	22.5	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Rosuvastatine Accord 5 mg and 40 mg film-coated tablets are considered bioequivalent with respectively Crestor 5 mg and 40 mg film-coated tablets.

The MEB has been assured that the bioequivalence studies has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Rosuvastatine Accord.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Rhabdomyolysis • Myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathy) • Increased transaminases, hepatitis, jaundice • Pancreatitis • Memory loss • Proteinuria • Stevens-Johnson syndrome and toxic epidermal necrolysis • Diabetes mellitus • Depression • Sleep disorders (including insomnia and nightmares) • Immune-mediated necrotizing myopathy • Thrombocytopenia/decreased platelet count • Tendon disorders • Drug-drug interactions including, ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, itraconazole, warfarin, other vitamin K antagonists and ezetimibe
Important potential risks	• Renal failure (including acute and chronic renal failure) and renal impairment • Hepatic failure: including hepatic necrosis and fulminant hepatitis • Peripheral neuropathy • Amyotrophic lateral sclerosis • Interstitial lung disease • Drug-drug interaction with fibrates (other than gemfibrozil)
Missing information	• Severe hepatic impairment • Elderly subjects • Paediatric subjects • Severe renal impairment • Pregnant or lactating women • Asian population: increased plasma exposure • Very low LDL-C levels • Genetic polymorphisms: increased plasma exposure

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

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Crestor film-coated tablets. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) regarding the content has been performed on the basis of a bridging report making reference to Crestor 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets. Regarding the lay out and design the MAH refers to the package leaflet of Solifenacin succinate 5 mg and 10 mg film-coated tablets. According to the MAH the lay out and design (font and font size, headings and sub-headings, dimension, colours uses for both package leaflets) are the same. The user test for the package leaflet of Solifenacin succinate 5 mg and 10 mg film-coated tablets was approved through procedure DK/H/2339/001-002/DC. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rosuvastatine Accord 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Crestor 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets. Crestor is a well-known medicinal product with an established favourable efficacy and safety profile.

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

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 essential similarity has been demonstrated for Rosuvastatine Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 July 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Repeat-use procedure to register the product in Poland.	NL/H/3255/E/001	E	18-11-2015	11-12-2015	Approval	No
Replacement or addition of a manufacturer responsible for importation and/or batch release; Including batch control/testing	NL/H//3255/001-004/IA/001	IA	4-3--2016	3-4-2016	--	--