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CBG MEB

Public Assessment Report

Scientific discussion

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

(rosuvastatin calcium)

NL/H/3367/001-004/DC

Date: 20 January 2017

This module reflects the scientific discussion for the approval of Rosuvastatine ELC 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets. The procedure was finalised on 3 February 2016. 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
CHMP	Committee for Medicinal Products for Human Use
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
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

I. INTRODUCTION

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

The product is indicated for:
Treatment of hypercholesterolaemia
Adults, adolescents and children aged 10 years or older with primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia) 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 hypercholesterolemia 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 product Crestor 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets (NL License RVG 26872-26874, 30823), which has been registered in the Netherlands by AstraZeneca since 6 November 2002 (10 mg, 20 mg, 40 mg) and 20 July 2004 (5 mg). Subsequently, an MRP was finalised with Crestor (NL/H/0343/001-004).

The concerned member states (CMS) involved in this procedure were Germany, Denmark, Italy, Sweden and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

- Rosuvastatine ELC 5 mg is a yellow, round, biconvex, film-coated tablet debossed with ‘5’ on one side and ‘B’ on the other side. Each tablet contains 5 mg rosuvastatin (as rosuvastatin calcium).
- Rosuvastatine ELC 10 mg is a pink, round, biconvex, film-coated tablet debossed with ’10’ on one side and ‘B’ on the other side. Each tablet contains 10 mg rosuvastatin (as rosuvastatin calcium).
- Rosuvastatine ELC 20 mg is a pink, round, biconvex, film-coated tablet debossed with ’20’ on one side and ‘B’ on the other side. Each tablet contains 20 mg rosuvastatin (as rosuvastatin calcium).
- Rosuvastatine ELC 40 mg is a pink, oval, biconvex, film-coated tablet debossed with ’40’ on one side and ‘B’ on the other side. Each tablet contains 40 mg rosuvastatin (as rosuvastatin calcium).

The film-coated tablets are packed in OPA/Al/PVC-Al blisters or white clear HDPE bottles with a white clear PP cap containing a silica gel desiccant.

The excipients are:
tablet core - calcium hydrogen phosphate dehydrate, Type 2 cellulose microcrystalline (E460), lactose monohydrate, Type A crospovidone (E1202), magnesium stearate (E572).

tablet coating – lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin (E1518), yellow iron oxide (E172), red iron oxide (E172).

The 10 mg strength and 20 mg strength are dose proportional.

II.2 Drug Substance

The active substance is rosuvastatin (as calcium salt), an established active substance described in the European Pharmacopoeia (Ph.Eur.). The substance is white to off white powder and hyproscopic in nature. It is slightly soluble in water, acetone and methanol and soluble in dimethylformamide, dimethyl sulfoxide and acetonitrile. Rosuvastatin is amorphous in nature and is an optically active molecule with two chiral centres. It was demonstrated that the polymorphic form of this active substance does not change or converse during the manufacture process or during storage.

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
Rosuvastatin calcium is manufactured in 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, and the active substance has been adequately characterised.

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. Batch analytical data demonstrating compliance with this specification have been provided for 6 batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 commercial batches in accordance with applicable European guidelines for 35 months at 5°C, 36 months at 25°C/60% RH and 6 months at 40°C/75% RH. All stability results were in accordance with the set drug substance specification. Based on the data submitted, a retest period could be granted of 36 months when stored in the proposed packaging 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 choice of excipients is justified and their functions explained.
The formulation was developed by a quality by design approach, and was optimised for the used excipients and their quantities to obtain a formulation that was essentially similar with the reference product Crestor. Three bioequivalence studies were submitted, conducted with the 5 mg, 20 mg and 40 mg strengths. The batches used in the bioequivalence studies were manufactured according to the proposed manufacturing process and were shown to have a similar impurity profile as the reference product.
In addition to the comparative dissolution profiles of the 5, 20 and 40 mg test bio-batches, also comparative dissolution studies with the 10 mg strength have been performed. All involved dissolution results are considered acceptable: either results > 85% after 15 min, or f2 values (between 10 mg batches and 20 mg test bio-batch or 10 mg innovator batch) > 50.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines and involves co-sifting, pre-blending, lubrication, compression and film-coating. Process validation data on the product have been presented for 3 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
The excipients, except for the used film coating mixtures, comply with the Ph. Eur. For the film-coating mixture, in house specifications have been provided and the individual components of the film coating mixture comply with the Ph. Eur. or relevant Food legislation. 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 description, related substances, water content, assay, uniformity of dosage units, dissolution and microbiological quality. 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 3 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 3 small scaled batches of each strength stored at 25°C/60% RH (6 months), and 40°C/75% RH (6 months) and, only for the 5 mg strength, 30°C/65% RH (6 months). The conditions used in the stability studies were according to the ICH stability guideline. The products were stored in the proposed packaging (bottles and blisters). Photostability studies showed that the product is not sensitive to light.
Based on availability of 18 months long-term stability data meeting the requirements, significant changes at accelerated condition and satisfactory 12 months intermediary stability results, support an extrapolation of X + 3 months, in line with ICH Q1E / Appendix A with Decision Tree. Herewith the claimed shelf-life of 21 months for the drug product packed in proposed blisters with the storage condition ‘Do not store above 30°C’, is accepted.
Based on availability of 18 months long-term stability data meeting the requirements and satisfactory accelerated stability data, support an extrapolation of X + 12 months. Herewith the claimed shelf-life of 30 months for the drug product in packed in the proposed bottles without a specific storage temperature condition, is accepted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
None of the materials used in the manufacture of the product, except lactose monohydrate, are of animal and/or human origin. TSE-BSE free certificates of all the raw materials, including lactose monohydrate, used in the manufacturing have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rosuvastatine ELC 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 ELC 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 three bioequivalence studies and requested one biowaiver, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test products Rosuvastatine ELC 5 mg, 20 mg and 40 mg film-coated tablets (ELC GROUP., CZ) is compared with the pharmacokinetic profile of the reference products Crestor 5 mg, 20 mg and 40 mg film-coated tablets (AstraZeneca B.V., NL). All studies were conducted under fasted conditions. As rosuvastatin can be taken regardless food intake, this is justified.

The choice of the reference product in the bioequivalence studies is accepted. The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

Biowaiver
A biowaiver was requested for the 10 mg tablets based on the established bioequivalence of the 20 mg tablets. With respect to the requirements for a biowaiver of strengths, all issues mentioned in the guideline are fulfilled for the 10 mg tablets. The dissolution tests at pH 4.5 and 6.8 showed similar profiles. An additional dissolution test at pH 1.2 was also performed. The MAH claims comparable dissolution based on an f2 value between 50 and 100. However, the conditions for the similarity factor calculation have not been met. For one batch, the similarity factor could not be calculated but drug release was only slightly faster than from the biobatch. For two other batches comparable dissolution was demonstrated. This is considered sufficient overall evidence for comparable dissolution between the biobatch and the biowaiver strength. A biowaiver for the 10 mg tablets can be granted.

Bioequivalence studies
Bioequivalence study I: 5 mg strength
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, aged 20-44 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 an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days..

Blood samples were collected pre dose and at 0.25, 0.5, 1.0, 2.0, 2.5, 3.00, 3.5, 4.0, 4.5, 5.00 6.0, 8.0,10.0, 12.0, 16, 24, 36, 48, 72 and 96 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable.
Analytical/statistical methods

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

Results
One subject withdrew from the study on his own accord. Therefore, a total of 49 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=49	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	67.01 ± 30.7	69.49 ± 31.0	8.39 ± 3.97	4.5 0.5 - 6.0
Reference	64.2 ± 29.4	66.9 ± 30.1	7.90 ± 3.67	4.5 0.5 - 5.0
***Ratio (90% CI)**	1.05 (1.00 - 1.09)	1.06 (1.00 - 1.12)	--	--
CV (%)	11.8%	16.3%	--	--

$AUC_{0-\infty}$ 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: 20 mg strength
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, aged 21-42 years. Each subject received a single dose (20 mg) of one of the 2 rosuvastatin calcium formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre dose and at 0.25, 0.5, 1.0, 2.0, 2.5, 3.00, 3.5, 4.0, 4.5, 5.00 6.0, 8.0,10.0, 12.0, 16, 24, 36, 48, 72 and 96 hours after administration of the products.

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

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject withdrew from the study due to an adverse event. Therefore, a total of 49 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=49	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	282 ± 128	287 ± 129	35.2 ±17.1	4.5 0.5 - 5.0

Reference	278 ± 143	282 ± 144	34.4 ± 19.4	4.5 1.0 - 5.0
***Ratio (90% CI)**	1.03 (0.97 - 1.10)	1.04 (0.96 - 1.13)	--	--
CV (%)	17.8	25.0	--	--

$AUC_{0-\infty}$ 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 III: 40 mg strength

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, aged 21-43 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 an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre dose and at 0.25, 0.5, 1.0, 2.0, 2.5, 3.00, 3.5, 4.0, 4.5, 5.00 6.0, 8.0,10.0, 12.0, 16, 24, 36, 48, 72 and 96 after administration of the products.

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

Analytical/statistical methods

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

Results

All 50 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rosuvastatin under fasted conditions.

Treatment N=50	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	510 ± 248	515 ± 249	67.0 ± 46.1	4.5 0.5 - 4.5
Reference	498 ± 196	502 ± 198	62.1 ± 29.3	4.5 0.5 - 4.6
***Ratio (90% CI)**	0.99 (0.94 - 1.05)	1.01 (0.94 - 1.08)	--	--
CV (%)	16.7	20.4	--	--

$AUC_{0-\infty}$ 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} and $AUC_{0-\infty}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Rosuvastatine ELC is considered bioequivalent with Crestor.

The MEB has been assured that the bioequivalence studies have 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).

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 ELC.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Rhabdomyolysis - Myopathy, myositis, myalgia, creatine kinase 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 night mares) - Immune-mediated necrotising myopathy - Thrombocytopenia/decreased platelet count - Tendon disorders - Drug interaction: drug-drug interactions including cyclosporine, 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 interactions: drug-drug interactions with fibrates (other than gemfibrozil)
Missing information	- Severe hepatic impairment - Elderly patients - Paediatric patients - Severe renal impairment - Pregnant and lactating women - Asian population: increased plasma exposure - Very low LDLC-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.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Crestor. 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

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 study consisted of a questionnaire which contained 19 questions specific to Rosuvastatin ELC and 3 specific to the format of the package leaflet. The questions addressed all the key safety issues and concerns of Rosuvastatin ELC. 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

Rosuvastatine ELC 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 ELC with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 February 2016.

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
Submission of a European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph; New certificate from an already approved manufacturer	NL/H/3367/ 1-4/IA/001	IA	06-12-2016	20-12-2016	Approved	No