CBG MEB

Public Assessment Report

Scientific discussion

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

(rosuvastatin calcium)

NL/H/3557/001-004/DC

Date: 18 September 2017

This module reflects the scientific discussion for the approval of Rosuvastatine SUN 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets. The procedure was finalised on 9 November 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
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 SUN 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets, from Sun Pharmaceutical Industries Europe B.V.

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 Italy 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 SUN is a film-coated tablet in 4 different strengths:
- 5 mg - round, light yellow to yellow coloured tablets debossed with ‘RT1’ on one side and plain on the other side.
- 10 mg - round, light pink to pink coloured tablets, debossed with 'RT2' on one side and plain on the other side.
- 20 mg - round, light pink to pink coloured tablets, debossed with 'RT3' on one side and plain on the other side.
- 40 mg – oval, light pink to pink coloured tablets, debossed with 'RT4' on one side and plain on the 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 oriented ployaminde/aluminium foil/polyvinyl chloride film/aluminium foil.

The excipients are:
tablet content – lactose monohydrate, microcrystalline cellulose (E460), crospovidone type A (E1202), magnesium stearate (E572) and sodium citrate
film-coating – hypromellose, titanium dioxide (E171), macrogol 400, only for the 5 mg strength yellow iron oxide (E172) and for the 10 mg, 20 mg and 40 mg red iron oxide (E172).

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 microcrystalline cellulose. The same is the case for the 20 mg and the 40 mg tablets. The 10 mg and the 20 mg are weight and 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 more than five stages. 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 characterized.

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 3 batches.

Stability of drug substance
Stability data on the active substance have been provided for 6 batches in accordance with applicable European guidelines stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (up to 6 months). No trends or changes were seen under any of the conditions. Based on the data submitted, a retest period could be granted of 36 months when stored in the proposed packaging without special requirements.

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. One bioequivalence study was submitted, conducted with the 40 mg strength for the other strengths, a biowaiver was applied for. A justification for the waiver for the bioequivalence study of the lower strengths has been provided based on in vitro dissolution data. The development of the dissolution method is considered adequate. The dissolution was tested in three buffers (pH 6.6 citrate, pH 4.5 acetate and pH 2 potassium chloride) and f2 values were calculated when necessary. The results demonstrated that the profiles of the test product can be considered similar to the profiles of the reference product.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. Process

validation data on the product have been presented for 3 commercial batches of each strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients
All excipients used, except opadry, comply with the requirements of the Ph.Eur. In-house specification for the opadry coating mixtures is provided, including statements regarding quality references of the individual components is the mixture. 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, identification, polymorphic form, uniformity of dosage units, water, dissolution, assay, related substances and microbiological purity. 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 6 commercial 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 product scaled batches per strength stored at 25°C/60% RH (5/10/20 mg: 36 months, 40 mg: 48 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. No significant changes were found either in the physical or in the chemical test characteristics of the product. Photostability studies have been performed and indicate that the drug product is not sensitive to light. The proposed shelf-life of 36 months can be accepted. No special storage conditions are required.

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rosuvastatine SUN 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 SUN 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 one bioequivalence study and requested for a biowaiver

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence studies in which the pharmacokinetic profile of the test product Rosuvastatine SUN 40 mg, film-coated tablets (Sun Pharmaceutical Industries Europe B.V., NL) is compared with the pharmacokinetic profile of the reference product Crestor 40 mg, film-coated tablets (AstraZeneca B.V., NL).

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

Biowaiver
Biowaiving for the 5 mg, 10 mg and 20 mg tablets based on the bioequivalence study with the 40 mg, strength can be granted as:

- The strengths have been manufactured by the same process and manufacturer.
- The qualitative composition of the different strengths is the same.
- The excipients included in the composition of the formulation are well established and no interaction with the pharmacokinetics of the active substance is expected.
- Dissolution tests resulted in similar dissolution profiles as compared to the other strengths at three different media (0.1N HCl, pH 4.5 and pH 6.8).

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 20-27 years. Each subject received a single dose (40 mg) of one of the 2 rosuvastatin calcium formulations. The tablet was orally administered after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 19 days.

Blood samples were collected at pre dose and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 20, 24, 36, 48 and 72 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
Three subjects withdrew from the study on their own accord. Therefore, a total of 37 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	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}	t_{max}

N=37	ng.h/ml	ng.h/ml	ng/ml	h
Test	218 ± 83	247 ± 85	26.9 ± 11.1	3.95 ± 1.14
Reference	198 ± 71	220 ± 79	26.2 ± 9.7	3.83 ± 1.18
***Ratio (90% CI)**	1.09 (1.00-1.18)	1.06 (0.94-1.20)	1.00 (0.90-1.12)	--
$AUC_{0-\infty}$ 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				

**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 SUN 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).

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 SUN.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Rhabdomyolysis • Myopathy, myositis, myalgia, creatinine 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 nightmares) • Immune-mediated necrotizing myopathy • Thrombocytopenia/decreased platelet count • Tendon disorders • Drug-drug interactions including ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, clopidogrel, eltrombopag, dronedarone, warfarin, fusidic acid and ezetimibe.
Important potential risks	• Renal failure (including acute and chronic renal failure) and renal impairment • Hepatic failure: including hepatic necrosis and fulminant hepatitis • Amyotrophic lateral sclerosis • Interstitial lung disease • Drug-drug interaction with fibrates (other than gemfibrozil)

Missing information	• Exposure in children < 6 years of age • Exposure in pregnant or lactating women

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

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) 61(1) of Directive 2001and /83/EC The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. Furthermore, the questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The user test is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rosuvastatine SUN 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 SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 November 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
Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier) Replacement or addition of a manufacturer responsible for importation and/or batch release; Not including batch control/testing	NL/H/3557/IA/001/G	IA	16-03-2017	15-04-2017	Approved	No