COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rosuvastatine Sun 5 mg, 10 mg, 20 mg and 40 mg hard capsules
(rosuvastatin calcium)

NL/H/5150/001-004/DC

Date: 27 September 2021

This module reflects the scientific discussion for the approval of Rosuvastatine Sun 5 mg, 10 mg, 20 mg and 40 mg hard capsules. The procedure was finalised at 29 April 2021. 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
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
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 Sun 5 mg, 10 mg, 20 mg and 40 mg hard capsules, from Sun Pharmaceutical Industries Europe B.V..

The products are 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.

  Adults, adolescents and children aged 6 years or older with 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 (see section 5.1 of the SmPC), 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 hybrid application claiming essential similarity with the innovator product Crestor film-coated tablets. Crestor 10 mg, 20 mg and 40 mg film-coated tablets have been registered in the Netherlands by AstraZeneca B.V. since 2002 (RVG 26872-4). The 5 mg strength is authorised in the Netherlands since 2004 (RVG 30823). In the Netherlands, Crestor has been registered by the mutual recognition procedure NL/H/0343/001-004/MR.

The concerned member states (CMS) involved in this decentralised procedure were France (only the 5 mg, 10 mg and 20 mg strengths), Romania and the United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as the products differ in terms of pharmaceutical form and method of administration of the reference medicinal products. Rosuvastatine Sun products can be:

- ingested as such (intact capsule), or
- sprinkled on soft food (applesauce or chocolate/vanilla flavoured pudding) before administration
- administered via nasogastric tubing to the patients who have a nasogastric tubing in place such as in a hospital setting.

The reference medicinal products can only be digested as such (intact film-coated tablet).

Scientific Advice
Scientific Advice was given by the Netherlands (CBG-MEB) in August 2017 and in September 2019. The United Kingdom (MHRA) also gave scientific advice in June 2018.

II. QUALITY ASPECTS

II.1 Introduction

Rosuvastatin Sun are opaque, hard gelatine capsules. The four different strengths can be distinguished by the colours of the cap and the capsule size:

- The 5 mg capsule with size “3”, peach cap and off white body.
- The 10 mg capsule with size "3", cool grey cap and off white body.
- The 20 mg capsule with size "1", pink cap and off white body.
- The 40 mg capsule with size “0el”, blue cap and off white body.

All four different strengths are imprinted with two bar lines with 360 degrees band on cap and body in black ink, and all capsules are filled with spherical/semi spherical yellow coloured pellets. Each capsule contains 5 mg, 10 mg, 20 mg or 40 mg of the active substance rosuvastatin (as rosuvastatin calcium).

The capsules are packed in OPA/Al/PVC-Al blisters or white round HDPE bottles with white PP child resistance cap containing a silica gel canister.

The excipients are:
Capsule content - microcrystalline cellulose, crospovidone, mannitol (E421), magnesium oxide (E530), ferric oxide (E172), sodium citrate (E331), hypromellose, polyethylene glycol 4000 (E1521) and colloidal hydrated silica (E551).
Capsule shell - gelatine, sodium lauryl sulfate, titanium dioxide (E171) and

- 5 mg: iron oxide yellow and iron oxide red (E172)
- 10 mg: iron oxide black (E172)
- 20 mg: iron oxide red (E172)
- 40 mg: FD & C Blue 1 (E133)

Printing Ink - shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide and purified water.

The contents of the four capsule strengths are dose proportional.

II.2 Drug Substance

The active substance is rosuvastatin calcium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The substance is a white to off white powder and hygroscopic in nature. It is slightly soluble in water, freely soluble in methylene chloride and

practically insoluble in anhydrous ethanol. Rosuvastatin is an optically active molecule with two chiral centres. It stays amorphous during the manufacturing process.

The CEP procedure is used for the active substance. 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 Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur, although more stringent limits have been adopted for some of the impurities. The specification is also set in accordance with the requirements of the CEP and with additional requirements for identity (X-ray diffraction, XRD), content of crystalline Form A (XRD), residual solvents (gas chromatography, GC), particle size and bulk density. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The products are an established pharmaceutical form and their 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 and manufacturing process to obtain a formulation that was essentially similar with the reference product Crestor. Studies adequately supporting the claims in the SmPC that the capsule contents can be mixed with soft foods and can be administered through nasogastric tubes have been provided. One bioequivalence study was submitted, conducted with the 40 mg strength, for the other strengths a biowaiver was applied for.

Manufacturing process
The manufacturing process consists of, among other things, granulation, extrusion-spheronisation and drying. All steps included have been validated according to relevant

European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product have been presented for three full scaled batches of each strength (including three batches of the pellets) in accordance with the relevant European guidelines.

Control of excipient

All excipients used, except for the capsule shell, comply with the requirements of the Ph.Eur or National Formulary. In-house specification for the capsule shell is provided, including statements regarding quality references of the individual components. 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, average fill weight, variation from standard fill weight, identification, dissolution, uniformity of dosage units, assay, related substance, residual solvents, disintegration time, water content and microbiological purity. Except for related substances and assay, the release and shelf-life limits are identical. The drug product specification is acceptable. 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 full scaled batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification. Adequate risk assessments on elemental impurities and nitrosamines have been provided.

Stability of drug product

Stability data on the products have been provided for three production scaled batches per strength stored at 25°C/60% RH (12 months), 30°C/65% RH (12 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 commercial container closure system (OPA/Al/PVC-Al blisters and HDPE bottles with PP cap with silica gel canister). No significant changes were found either in the physical or in the chemical test characteristics of the product. Photostability studies have been performed according to ICH Q1B showing that the product is sensitive to light exposure. On basis of the data submitted, a shelf life was granted of two years. The labelled storage conditions are ‘Store below 30°C’ and ‘Store in original pack in order to protect from light and moisture’.

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 gelatine. Certificate of suitability from the manufactures of the gelatine are provided.

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 hybrid 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 a hybrid formulation of Crestor 5 mg, 10 mg, 20 mg and 40 mg hard capsules, which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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 hybrid application, the MAH has submitted one bioequivalence study, which is discussed below. The bioequivalence study has been carried out with the 40 mg strength. For the lower strengths, a biowaiver was applied for.

IV.2 Pharmacokinetics

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

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the reference product in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH applied for a biowaiver for the 5 mg, 10 mg and 20 mg capsules. The qualitative composition of the strengths is the same and the composition of the strengths is quantitatively proportional with dose. The strengths are manufactured by the same manufacturing process. According to the SmPC of the reference product Crestor, the pharmacokinetics of rosuvastatin are linear. To support the biowaiver, dissolution studies were performed in accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). At pH 4.5 and 6.8, more than 85% of the drug was dissolved within 15 minutes for all strengths. At pH 1.2, similarity factor (f2) values were >50; the relative standard deviation (RSD) values were acceptable.
In conclusion, the biowaiver for the strengths 5 mg, 10 mg and 20 mg was agreed.

Bioequivalence study

Design

A single-dose, randomised, balanced, three-period, three-treatment (A-C), six-sequence, three-way crossover bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 22-44 years. Each subject received a single dose (40 mg) of one of the three rosuvastatin formulations. For treatments A (intact capsule – test product) and C (Crestor tablet – reference product), the tablets were orally administered with 240 ml water after a fasting period of at least 10 hours before their scheduled start time of dosing and 0.4 hours after dosing in each period. Drinking water was not allowed from one hour before dosing till one hour post-dose. For treatment B (contents of capsule – test product), the capsule was opened and its contents were sprinkled on a teaspoon (5 ml) of applesauce and swallowed within 5 min after scheduled dosing time by the subjects, followed by 240 ml of drinking water. There were three dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.50, 6, 8, 12, 16, 24, 36, 48 and 72 hours after dosing. Rosuvastatin was analysed in plasma. The design of the study is acceptable.

Rosuvastatin can be taken with or without food. From the literature it is known that food does not interact with the absorption of rosuvastatin. Therefore, a food interaction study is not

deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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
In the end, 47 subjects out of the 54 completed all three periods of the study. Four subjects were withdrawn from the study: one subject withdrew his consent, one was withdrawn because of an adverse event, the third subject tested positive in an alcohol test and the fourth subject tested positive in a drug abuse test. Furthermore, not all subjects completed the three periods of a treatment. Therefore, for the comparison of treatment A versus treatment C, data of 50 subjects were used for pharmacokinetic analysis and data of 49 subjects were used for statistical analysis. For the comparison of treatment B versus treatment C, data of 51 subjects were used for pharmacokinetic analysis and data of 48 subjects were used for statistical analysis.

Table 1. Pharmacokinetic parameters treatment A (Rosuvastatine Sun, as intact capsule) versus treatment C (Crestor) (non-transformed values; arithmetic mean ± SD, t_{max} median, range) of rosuvastatin under fasted conditions.

Treatment	AUC_{0-t} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/ml)	t_{max} (h)
Test	586 ± 277	596 ± 278	72.1 ± 40.3	2.0 0.7 – 6.0
Reference	576 ± 311	588 ± 314	66.0 ± 38.6	2.7 0.3 – 5.0
***Ratio (90% CI)**	1.03 (0.97 – 1.20)	1.03 (0.97 – 1.09)	1.09 (1.02 – 1.17)	-

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

**ln-transformed values*

Table 2. Pharmacokinetic parameters treatment B (content of capsule Rosuvastatine Sun, sprinkled on applesauce) versus treatment C (Crestor) (non-transformed values; arithmetic mean ± SD, t_{max} median, range) of rosuvastatin under fasted conditions.

Treatment	AUC_{0-t} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/ml)	t_{max} (h)
Test	605 ± 320	616 ± 321	78.4 ± 56.4	2.0 0.3 – 5.0
Reference	576 ± 311	588 ± 314	66.0 ± 38.6	2.7 0.3 – 5.0
***Ratio (90% CI)**	1.07 (0.95 – 1.09)	1.02 (0.95 – 1.09)	1.09 (1.00 – 1.19)	-

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

**ln-transformed values*

Conclusion on bioequivalence study

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 study, Rosuvastatin Sun 40 mg hard capsules, if taken as intact capsules, or taken following sprinkling the content of the capsule to a teaspoon of applesauce followed by ingestion of water, are considered bioequivalent with Crestor 40 mg film-coated tablets. The results of the bioequivalence study with 40 mg formulation can be extrapolated to other strengths 5, 10 and 20 mg, according to conditions in Guideline on the Investigation of Bioequivalence. Stability of the product in both applesauce and pudding was within acceptable range. Administration with pudding was therefore also acceptable. Administration via nasogastric tube was also acceptable, since it was shown that no blockage occurs in various types of tubes.

The MEB has been assured that the bioequivalence study 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).

Clinical efficacy / clinical safety

The proposed products differ in terms of method of administration of the reference medicinal product, as the proposed products can be:

1. ingested as such (intact capsule) or
2. sprinkled on soft food (applesauce or chocolate/vanilla flavoured pudding) before administration.
3. administered via nasogastric tubing to the patients who have a nasogastric tubing in place such as in a hospital setting.

The reference product can only be ingested as such (intact film-coated tablet).

From a clinical point of view, the proposed additional methods of administration, i.e. sprinkled on soft food before administration and administration via nasogastric tubing, are welcomed. Theoretically, these offer the potential of continuing or initiating therapy when swallowing is difficult and sprinkling rosuvastatin on soft food before administration may especially be useful with small children (the product is indicated in children from 6 years of age). However, the practical value of these methods for rosuvastatin, i.e. a preventive medicinal product (statin), may be limited. Very often patients who have a nasogastric tubing in place (such as in a hospital setting) or patients with difficulties in swallowing, also have other (serious) acute or chronic conditions and they are therefore often also taking other medicinal products. In hospitalisation of these patients for acute situations, the risk of interactions with other medicinal products and the risk of complications leading to myopathy may trigger treatment interruptions. In such acute situations, it may be difficult to attribute any adverse effect to a specific medicinal product and interrupting the preventive statin during treatment of the acute condition may facilitate clinical assessment. Also, in many chronic conditions associated with difficulty swallowing, for example Parkinson disease, the potential benefits of cardiovascular protection may be limited. Although the practical value may thus be limited, this issue is not pursued.

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 Rosuvastatin Sun.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the products are similar to the pharmacokinetic profile of this reference products. Risk management is adequately addressed. These hybrid medicinal products can be used instead of the reference products.

V. USER CONSULTATION

The package leaflet (PL) 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 language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with three participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL 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 Sun 5 mg, 10 mg, 20 mg and 40 mg hard capsules have a proven chemical-pharmaceutical quality and are hybrid 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 CMDh. 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 29 April 2021.

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/5150/001-4/IA/001	Type IAin: C.I.3. a) Implementation of wording agreed by the competent authority, to implement the outcome of a procedure concerning PSUR of Rosuvastatine (PSUSA/00010271/202007).	Yes; PL and SmPC	11 September 2021	Approved	