COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(rosuvastatin calcium)

NL/H/4582/001-004/DC

Date: 19 November 2019

This module reflects the scientific discussion for the approval of Rosuvastatine MSN 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets. The procedure was finalised at 22 October 2019. 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 MSN 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets, from Vivanta Generics s.r.o.

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.

Adults, adolescents and children aged 6 years or older with 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 (see SmPC section 5.1), 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 Czech Republic, Hungary, Poland, Romania and the Slovak Republic.

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

II. QUALITY ASPECTS

II.1 Introduction

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

- 5 mg – off-white to white, round, biconvex film-coated tablets, debossed with “R5” on one side.
- 10 mg - off-white to white, round, biconvex film-coated tablets, debossed with “R10” on one side.
- 20 mg - off-white to white, round, biconvex film-coated tablets, debossed with “R20” on one side.
- 40 mg – off-white to white, oblong, biconvex film-coated tablets, debossed with “R40” on one side.

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

The film-coated tablets are packed in Al/Al blisters and/or HDPE containers with child-resistant plastic caps with induction sealing wad and bag silica gel desiccant. Test data has been provided for the child resistant cap according to US CPSC (Consumer Product Safety Commission) CFR title 16, which is virtually same as to ISO 8317:2015 (Child-resistant packaging -- Requirements and testing procedures for reclosable packages). Based on the test results the claim “child-resistant” can be used.

The excipients are:
Tablet core - microcrystalline cellulose (E460), crospovidone (Type B), pregelatinised starch, meglumine, mannitol (E421) and magnesium stearate (E572)
Film-coating - OPADRY II 32K580000 White (containing HPMC 2910/hypromellose, lactose monohydrate, titanium dioxide (E171) and triacetin).

The four strengths 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.). Rosuvastatin calcium is a white to almost white powder and slightly soluble in water and practically insoluble in anhydrous ethanol. The active substance shows polymorphism and the amorphous form is used.

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.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality. An additional in-house specification on particle size is used. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
Assessment of the stability of the drug substance was part of granting the CEP and has been granted by the EDQM.

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. Data have been provided showing that the amorphous form of the drug substance is preserved in drug product batches of all 4 strengths, after manufacturing and long-term storage. An excipient compatibility study has been performed with satisfactory results. A bracketing approach is applied by performing bioequivalence studies using 5 mg and 40 mg test bio batches. A biowaiver for the additional 10 mg and 20 mg product strengths has been adequately justified based on *in vitro* dissolution data. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of sifting, preparation of binder solution, dry mixing and wet granulation, drying, milling, pre-lubrication and lubrication, compression, coating, inspection and packaging. The process is considered a standard process and has been validated according to relevant European guidelines. Process validation data on the product have been presented for a batch per strength in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. monographs for each of the tablet core excipients. Some functionality-related requirements have been included for crospovidone, magnesium stearate, microcrystalline cellulose, and pregelatinised starch. The in-house specifications for the two film-coat mixtures are based on long-term experience of the supplier, and herewith considered acceptable. 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 description, identity, average weight, KF water content, dissolution, uniformity of dosage units, related compounds and assay. 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 from three pilot scaled 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 full scaled batches of each strength stored at 25°C/60% RH (36 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 an Alu-Alu blister strip or a HDPE containers with a polypropylene cap and silica gel desiccant canister. A photostability study showed that the product is photo stable.
Based on the stability data a shelf life could be granted of 3 years without any special precautions for storage. The 5 mg, 10 mg and 20 mg strengths should be used within 90 days from opening when stored in the container. The 40 mg strength tablets should be used within 60 days from opening the container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Sufficient information has been provided on TSE/BSE risk of materials. For lactose monohydrate an adequate TSE/BSE statement is provided, and magnesium stearate is made from stearic acid which is from vegetable source.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rosuvastatine MSN 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 MSN 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

This product is a generic formulation 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 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, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test products Rosuvastatine MSN 5 mg and 40 mg, film-coated tablets (Vivanta Generics s.r.o., Czech Republic) is compared with the pharmacokinetic profile of the reference products Crestor 5 mg and 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 reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver for the 10 mg and 20 mg strengths can be granted based on the following:

- The formulations of all strength have a similar qualitative form and are of proportional composition. All strengths have the same blend with proportional formulation across the strengths. The proposed tablets are all film coated tablets.
- All strengths of the product are manufactured at the same site utilizing the same manufacturing process
- Pharmacokinetic data has demonstrated to be linear across the complete dosage range from 5 mg to 40 mg
- In vitro dissolution profiling to demonstrate immediate drug release. Comparative dissolution profiles have demonstrated that all strength are comparable at 0.01 N HCl, 4.5 Acetate buffer & 6.8 Phosphate buffer and observed that release is more than 85% at 20 min time point

Bioequivalence studies

Design

The design of the studies is acceptable. Rosuvastatin may be taken without reference to food intake. 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.

Bioequivalence study I – 5 mg under fasted conditions
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy subjects, aged 19-42 years. Each subject received a single dose (5 mg) of one of the 2 rosuvastatin 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 12 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.00, 1.33, 1.67, 2, 2.33, 2.67, 3.00, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results
Three subjects were withdrawn from the study as they did not turn up for the second period. Therefore, 39 subjects completed the study and 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=39	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	79030 ± 39710	81310 ± 39946	9606 ± 4803	4.33 (0.67 – 4.67)	16.84 ± 8.81
Reference	766230 ± 37082	78660 ± 37334	9735 ± 4852	4.33 (0.33 – 5.00)	15.07 ± 4.52
***Ratio (90% CI)**	1.02 (0.96 – 1.09)	1.02 (0.96 – 1.09)	1.00 (0.92 – 1.09)	--	--
CV (%)	16.6	16.3	21.8	--	--

$AUC_{0-\infty}$	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
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Bioequivalence study II – 40 mg under fasted conditions

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy subjects, aged 19-45 years. Each subject received a single dose (40 mg) of one of the 2 rosuvastatin 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 14 days.

Blood samples were collected pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00 and 96.00 hours after administration of the products.

Results
All 42 subjects completed the study and 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=42	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	386.8 ± 180	398.7 ± 182	54.7 ± 31	4.33 (0.50 - 4.67)
Reference	388.4 ± 155	399.3 ± 156	54.9 ± 22	4.33 (0.50 – 4.67)
***Ratio (90% CI)**	0.99 (0.92 – 1.07)	1.00 (0.93 – 1.07)	0.96 (0.88 – 1.05)	--

$AUC_{0-\infty}$ 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 MSN is considered bioequivalent with Crestor.

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).

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 MSN.

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 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 (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 study was previously used for an earlier approved and similar product (procedure NL/H/4158/001-004/DC). The test consisted of: a pilot test with 2 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 MSN 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Crestor 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 MSN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 October 2019.

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