CBG MEB

Public Assessment Report

Scientific discussion

Rosuvastatine Genericon 10 mg, 20 mg and 40 mg, film-coated tablets

(rosuvastatin calcium)

NL/H/3584/001-003/DC

Date: 21 April 2017

This module reflects the scientific discussion for the approval of Rosuvastatine Genericon 10 mg, 20 mg and 40 mg, film-coated tablets. The procedure was finalised on 20 October 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
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 Genericon 10 mg, 20 mg and 40 mg, film-coated tablets from GENERICON PHARMA Gesellschaft m.b.H.

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 product Crestor 10 mg, 20 mg and 40 mg film-coated tablets (NL License RVG 26872-26874), which has been registered in the Netherlands by AstraZeneca since 6 November 2002. Subsequently, an MRP was finalised with Crestor (NL/H/0343/001-003).

The concerned member states (CMS) involved in this procedure were Austria and Croatia.

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

II. QUALITY ASPECTS

II.1 Introduction

Rosuvastatine Genericon 10 mg is a white or almost white, round, biconvex film-coated tablet, with “10” engraved on one side and with breaking line on the other side.
Rosuvastatine Genericon 20 mg is a white or almost white, round, biconvex film-coated tablet, with “20” engraved on one side and with breaking line on the other side.
Rosuvastatine Genericon 40 mg is a white or almost white, oblong, biconvex film-coated tablets with breaking line on one side.

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

The film-coated tablets are packed in Al// OPA/Al/PVC foil blisters.

The excipients are:
Tablet core - lactose monohydrate, cellulose microcrystalline (E460), sodium citrate (E331), crospovidone type B, silica colloidal anhydrous (E551), magnesium stearate (E572)
Tablet coating - Opadry II White 33G28523 composition: hypromellose 2910 (6 cP) (E464), lactose monohydrate, macrogol 3350, triacetin (E1518), titanium dioxide (E 171)

The tablet cores of the rosuvastatin tablets are dose-proportional.

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 and very slightly soluble in water and insoluble in ethyl ether and ethyl acetate. Rosuvastatin calcium has two chiral centres, thus theoretically four diastereoisomers exist. Rosuvastatin calcium manufactured by the involved ASMs has a R, S geometry. Both manufacturers produce the amorphous form.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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 from both sources of rosuvastatin calcium cover several synthetic steps. 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 drug substance specification of the drug product manufacturer is according to the Ph.Eur. with additional test for the drug substance produced by the ASMF holders. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for at least three batches from both sources of rosuvastatin calcium.

Stability of drug substance
Several batches from the first manufacturer have been stored for 12-60 months at 25°C/60% RH and for 6 months at 40°C/75% RH. All stability results were in accordance with the set drug substance specification. Based on the provided stability data the claimed re-test period can be accepted: 36 months, without special storage conditions.

For the second manufacturer, three full scale batches have been stored for 6 months at 25°C/60% RH and 12 months at 2-8°C. All stability results were in accordance with the set drug substance specification. Based on the provided stability data the claimed re-test period can be accepted: 18 months, between 2-8°C.

II.3 Medicinal Product

Pharmaceutical development
The description of the pharmaceutical development is considered adequate. A bioequivalence study between the proposed Rosuvastatin Genericon 40 mg and the originator product Crestor 40 mg from Belgium has been conducted. The reference product is acceptable. A justification for the waiver for the bio-equivalence studies of the rosuvastatin calcium 10 mg and 20 mg tablets has been provided based on *in vitro* dissolution data and is acceptable.
The development of the dissolution method is described and acceptable.

Manufacturing process
The manufacturing process has been adequately described and validated for the lower batch size. A summary of the in-process information during manufacture has been provided. All parameters and attributes were found to be within acceptable ranges and according to acceptance criteria. The product is manufactured using conventional manufacturing techniques.

Control of excipients
All excipients, including components of the Opadry coating, meet the requirements of Ph. Eur. The specifications for the excipients are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, assay, related substances, dissolution, uniformity of dosage units, water content and microbiological purity. The limits for control of impurities were tightened and are acceptable. The limit for dissolution is in line with the release characteristics of the biobatch.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided for two full scaled batches of the 10 mg and 20 mg and three batches of the 40 mg strength, demonstrating compliance with the release specification.

Stability of drug product
Four pilot scaled batches for the 10 mg and the 20 mg strength of the drug product and two pilot scaled and two full scaled batches for the 40 mg strength of the drug product using both sources of the active substance were stored at 30°C/75% RH (24 – 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 Al/OPA/Al/PVC foil blisters. The stability results show slight but steady increase of impurities at all storage conditions. The proposed shelf-life of 24 months if stored below 30°C is acceptable.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
The only component of animal origin used for the manufacture of rosuvastatin tablets is lactose monohydrate. TSE-safety statements have been provided. Magnesium stearate is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

Rosuvastatine 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Rosuvastatine Genericon 40 mg (GENERICON PHARMA Gesellschaft m.b.H., Austria) is compared with the pharmacokinetic profile of the reference product Crestor 40 mg film-coated tablets (AstraZeneca B.V., Belgium).

The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver has been granted for the 10 mg and 20 mg strengths as the following conditions are fulfilled:

- The composition of all strengths of the test product is directly proportional.
- All strengths of test product are manufactured by the same manufacturer and process.
- Rosuvastatin pharmacokinetics is linear and dose-proportional between 5 and 80 mg.
- Comparable dissolution is sufficiently shown between different strengths.

Bioequivalence studies

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy subjects (41 males, 3 females), mean age ± SD: 39 ± 10 years. Each subject received a single dose (40 mg) of one of the 2 rosuvastatin formulations, under fasted conditions. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0 and 96.0 hours after administration of the products.

The design of the study is acceptable and the study has been performed in compliance with GCP. There is an adequate wash-out period and a long enough sampling period.

Analytical/statistical methods
In general, the analytical method is adequately validated and considered acceptable for analysis of the plasma samples. An acceptable justification for the absence of Incurred Sample Reanalysis was provided. Additionally, when comparing rosuvastatin pharmacokinetics in literature, rosuvastatin levels seem to fluctuate more than expected. The MAH provided information on the interconversion between lactone and acid forms of statins, justifying that the impact of back-conversion is limited.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
From the 44 subjects included in the study, 1 subject withdrew consent after period 1 due to personal reasons. The remaining 43 subjects were included in the pharmacokinetic and statistical analyses.

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

Treatment N=43	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	222 ± 149	228 ± 150	24.3 ± 19.7	4.50 (2.00-5.00)	--
Reference	227 ± 150	233 ± 151	25.5 ± 21.5	4.50 (2.00-5.50)	--
***Ratio (90% CI)**	0.98 (0.93-1.04)	0.98 (0.93-1.04)	0.97 (0.89-1.05)	--	--

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

**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 Rosuvastatine Genericon 40 mg is considered bioequivalent Crestor 40 mg film-coated tablets.

Safety

A total of 28 treatment-emerged adverse events (TEAEs) were reported by 9 of the 44 subjects who received at least one dose of the study medication. The most commonly reported TEAEs were 'inject site react' reported by 9.1% (n=4) and 'pain inject site' reported by 6.8% (n=3). Of the TEAEs reported, 25 were graded as mild and 3 were graded as moderate. The relationship of 7 TEAEs was judged as 'possible', 4 as 'remote', and 17 as 'unrelated'. No deaths, serious, or significant adverse events were reported. The results from the subjects who completed post-study procedures, confirmed the absence of significant changes in the subjects' state of health. Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations.

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 Genericon.

Summary of safety concerns	
Important identified risks	• Rhabdomyolysis • Myopathie, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathie) • Increased transaminases, hepatitis, jaundice • Pancreatitis • Memory loss • Proteinuria • Diabetes mellitus • Depression • Sleep disorders (including insomnia and nightmares) • Immune mediated necrotising myopathy (IMNM) • Thrombocytopenia / decreased platelet count • Stevens-Johnson syndrome / Toxic epidermal necrolysis (SJS / TEN) • Tendon disorders • Peripheral neuropathy • Drug interactions: ciclosporin, various protease inhibitor combinations with ritonavir, clopidogrel, gemfibrozil, eltrombopag, dronedarone, warfarin and other vitamin K-antagonists, fusidic acid and ezetimibe
Important potential risks	• Renal failure (including acute and chronic renal failure) and renal impairment • Hepatic failure including hapatic necrosis and fulminant hepatitis • Amyothrophic lateral sclerosis (ALS) • Interstitial lung disease (ILD)
Missing information	• Children <6 years of age • DDI studies in the paediatric population

The MAH described the pharmacovigilance activities for all important identified and potential risks as well as missing information. This is in line with the RMP of the reference product. Furthermore, the MAH performs similar additional risk minimisation activities as those of the reference product.

To enhance the safety use and to mitigate the risk of serious muscle side effects and to mitigate the risk of serious liver side effects, the following additional RMMs will be performed by the MAH:

- Review of rosuvastatin usage
- Restriction of samples
- Educational activities

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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. Between the pilot round and the test

rounds, the PL was not adjusted. The test was performed in English. The developed questionnaire contained 20 questions addressing the key safety issues and presentation of information.
There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. Four additional questions were formulated with regards to positive and negative and feedback about the readability of the PL. The data show all questions met the passing criteria in both rounds. The results of the test were satisfactory. The readability test has been adequately performed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rosuvastatine Genericon 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 Genericon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 October 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
Changes in scoring/break lines intended to divide into equal doses.	NL/H/3584/ 001-003/IB/ 001	IB	18-1-2017	8-2-2017	Approval	N