CBG MEB

Public Assessment Report

Scientific discussion

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

(rosuvastatine calcium)

NL/H/3517/001-004/DC

Date: 17 November 2016

This module reflects the scientific discussion for the approval of Rosuvastatine Hetero 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets. The procedure was finalised on 11 August 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

ALS	Amyotrophic Lateral Sclerosis
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CK	Creatine Kinase
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
DDI	Drug-Drug Interaction
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
ILD	Interstitial Lung Disease
IMNM	Immune Mediated Necrotising Myopathy
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 Hetero 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets, from Hetero Europe S.L.

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 (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 Germany (all strengths), Spain (all strengths) and France (5 mg, 10 mg and 20 mg strengths).

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

II. QUALITY ASPECTS

II.1 Introduction

Rosuvastatine Hetero is a film-coated tablet in 4 different strengths:
- 5 mg - Round, light yellow to yellow coloured tablets, debossed with 'H' on one side and 'R3' on the other side.
- 10 mg - Round, light pink to pink coloured tablets, debossed with 'H' on one side and 'R4' on the other side.
- 20 mg - Round, light pink to pink coloured tablets, debossed with 'H' on one side and 'R5' on the other side.
- 40 mg - Oval, light pink to pink coloured tablets, debossed with 'H' on one side and 'R6' on the other side.

Each tablet contains 5 mg, 10 mg, 20 mg or 40 mg of the active substance rosuvastatin, as 5.2 mg, 10.4 mg, 20.8 mg and 41.6 mg rosuvastatin calcium.

The film-coated tablets are packed in:
- Blisters of aluminium laminate/aluminium foil (for 5mg, 10 mg, 20 mg and 40 mg).
- HDPE tablet container with a polypropylene child-resistant closure and a silica gel desiccant (for 5 mg, 10 mg and 20 mg).

- HDPE tablet container with a polypropylene child-resistant closure and a silica gel desiccant (for 40 mg).

The excipients are:
Tablet content
- Lactose monohydrate
- Cellulose microcrystalline (E460)
- Crospovidone (E1202)
- Hydroxypropyl cellulose (E463)
- Sodium hydrogen carbonate (E500(ii))
- Talc (E553B)
- Magnesium stearate (E572)

Film coating
- Hypromellose (E464)
- Lactose monohydrate
- Titanium dioxide (E171)
- Triacetin (E1518)
- Tartrazine aluminum lake (E102) (5 mg tablet)
- Allura Red AC aluminum lake (E129) (5 mg tablet)
- Indigo carmine aluminum lake (E132) (5 mg tablet)
- Sunset yellow FCF aluminum lake (E110) (10 mg, 20 mg and 40 mg tablets)
- Allura red AC aluminum lake (E129) (10 mg, 20 mg and 40 mg tablets)
- Indigo carmine aluminum lake (E132) (10 mg, 20 mg and 40 mg tablets)

The four strengths are dose proportional.

II.2 Drug Substance

The active substance rosuvastatin calcium is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to almost white powder. It is freely soluble in methylene chloride, slightly soluble in water and practically insoluble in anhydrous ethanol. Rosuvastatin calcium is an optically active molecule, having two stereogenic centres and hence 4 possible stereoisomers. The substance used is the 3R,5S isomer. The amorphous form is produced.

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
The manufacturing of rosuvastatin calcium is a sixteen step convergent process. The structure of the active substance is completely characterised. Acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 full scaled batches stored at 5°C (24 months), 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). At the 5 month time point under accelerated conditions (40°C/75% RH) the level of a specified impurity is above the proposed specification limit for two batches. Under all other storage conditions the drug

substance remains stable. No specific up or downward trends are observed. Based on the EMA guideline on stability testing of existing active substances and the submitted stability data the proposed retest period of 30 months can be granted. The storage conditions are in line with the Ph.Eur. monograph of the drug substance.

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 main development studies consist of binary stress tests of the drug substance with the excipients, comparison of the composition with the reference product Crestor and variation in blending times, speeds and the amounts of excipients. The choices of the packaging are justified by the results of the stability studies.

The 40 mg batch used in the bioequivalence study is manufactured according to the final manufacturing process. The batches used in the bioequivalence study have the same composition and are manufactured in the same way as the future commercial batches. The bioequivalence batches are of sufficient size in relation to the intended commercial batch size. Comparative *in vitro* dissolution tests at pH 1, 4.5, 6.6 and 6.8 in support of a biowaiver for additional strengths have been performed. The dissolution profiles are similar and the requested biowaiver of strengths is considered acceptable (see also section IV.2 'Pharmacokinetics).
The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is a dry granulation process followed by compression and film-coating. It has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches of common tabletting mixture, which were divided into three full scale batches for each 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. The excipients in the film-coating comply with the Ph.Eur. or have an E-number according to EU 1130/2011 on food additives. 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, identity, average weight, water content, dissolution, content uniformity, related compounds, assay and microbiological quality. Identity of the colourant will be tested upon special request only and tablet dimensions are not part of routine testing but will comply if tested. The release and shelf life parameters and limits are almost identical, except for water content and related compounds. 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 full 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 has been provided for three full scaled batches of each strength stored at 25°C/60% RH (24 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 packagings. The photostability of the tablets was tested on three batches each of the 5 mg and 40 mg strengths. The in-use stability of the tablets packaged in HPDE containers was tested on three batches of the 5 mg strength for 90 days and on three batches of the 40 mg strength for 30 days.
Under all storage conditions (including in-use and photostability) and in all packaging forms the drug product used in the stability studies remains within the acceptance limits. In all cases a small increase in the levels of two related substances is observed which is within the range determined by the release and shelf-life limits of the drug product specification.

The proposed shelf life of 24 months in the blister and HDPE container can be granted. The labelled storage conditions are “does not require any special storage conditions”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is of animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rosuvastatine Hetero 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 Hetero 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 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, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Rosuvastatine Hetero 40 mg film-coated tablets (Hetero Europe S.L., Spain) is compared with the pharmacokinetic profile of the reference product Crestor 40 mg film-coated tablets (AstraZeneca Österreich GmbH, Austria).

The choice of the reference product
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 for the 5 mg, 10 mg and 20 mg tablets based on the bioequivalence study with the highest strength of 40 mg has been granted as:

- The strengths have been manufactured by the same process and manufacturer.
- The pharmacokinetics of rosuvastatin can be considered linear.
- The compositions are qualitatively similar and dose proportional (the differences in film-coating are not relevant).
- Dissolution tests resulted in similar dissolution profiles as compared to the 40 mg strength at three different media (0.1N HCl, pH 4.5 and pH 6.8).

Design
A single-dose, open-label, randomised, two-treatment, partial replicate, three-period cross-over bioequivalence study was carried out under fasted conditions in 51 healthy male subjects, aged 24-44 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. There were three dosing periods, separated by a washout period of 7 days. The test formulation was administered once, and the reference product was given twice to each subject.

Blood samples were collected before dosing and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 10, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. As rosuvastatin can be taken regardless of food, a study under fasting conditions is acceptable. The half-life of rosuvastatin is about19 hours. Therefore plasma levels should be measured over a period of at least 72 hours. The wash-out period of 7 days is sufficient.

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.

A partial-replicate design was applied to use the observed intra-subject variability for C_{max} of the reference for scaling the 90% confidence intervals (CI). The bioequivalence acceptance criteria were based on intra-subject variability of reference product as follows:

- If the intra-subject coefficient of variability (CV) for C_{max} parameter was >30% for reference product in the study, then the product was considered as highly variable and the limit for bioequivalence for C_{max} was applied based on scaled average bioequivalence approach. However, in this case the point estimate (test/reference) should fall between 0.80-1.25.
- If the intra-subject CV for C_{max} parameter was <30% for reference product in the study, then the conventional bioequivalence limit was considered for C_{max}. In that case, the test product was considered to be bioequivalent to the reference product if the 90% CI for the ratio of the geometric least square means of natural log transformed C_{max} of test and reference formulations fall within 0.80-1.25.

In any case, the conventional average bioequivalence criteria using 90% CI was to be considered as 0.80-1.25 for AUC_{0-t}.

Results
One subject was withdrawn from the study on grounds of protocol non-compliance in period 3, so 50 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 (N=50 for test and N=100 for reference).

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	431 ± 290	442 ± 292	56.5 ± 47.5	3.0 (0.5 – 4.7)	8.9 ± 3.6
Reference	400 ± 270	410 ± 271	54.2 ± 49.0	3.8 (0.5 – 5.0)	8.9 ± 3.8
***Ratio (90% CI)**	1.08 (1.03 - 1.13)	1.08 (1.03 - 1.13)	1.04 (0.98 - 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
$t_{1/2}$	half-life

**ln-transformed values*

Conclusion on bioequivalence study

A partial replicate design was applied to use the observed intra-subject variability of the reference for C_{max} for scaling the acceptance range. As the observed intra-subject variability was below 30%, scaling did not have to be applied. The 90% CI 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 Hetero 40 mg film-coated tablets is considered bioequivalent with Crestor 40 mg film-coated tablets.

For 2% of the test treatments and 4% of the reference treatments, C_{max} was observed at the first point of the concentration-time curve (in six subjects (8 observations)). The sampling schedule based on the SmPC of rosuvastatin, which reports that t_{max} is about 5 hours, was considered adequate. Based on the study results it is agreed that this does not invalidate the outcome of this study.

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 Hetero.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Rhabdomyolysis and Myopathy; myositis, myalgia; CK 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 necrotising myopathy • Thrombocytopenia/decreased platelet count • Tendon disorders • Drug-drug interactions including ciclosporin, various

	protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, itraconazole, warfarin, other vitamin K antagonists, ezetimibe, fusidic acid and clopidogrel
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
Missing information	• Children less than 6 years of age • Drug-drug interaction studies in the paediatric population

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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report.
Regarding the content of the PL the MAH refers to the PL of Crestor (NL/H/0343/001-004). The content of the PL is nearly in line with the PL of Crestor, except for the product-specific information.
Regarding the layout reference is made to the user test and report of Levetiracetam Hetero film-coated tablets (PT/H/0515/001-004/DC). The MAH submitted the public assessment report of this procedure to prove that the PL of these products have been tested and approved.
The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rosuvastatine Hetero 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 Hetero with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 August 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