Public Assessment Report

Scientific discussion

Rosuvastatin "Sigillata"

Rosuvastatin calcium

DK/H/2681/001-003/DC

Date: 19-01-2018

This module reflects the scientific discussion for the approval of Rosuvastatin "Sigillata". The procedure was finalised on 18-01-2017 on day 210. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for **Rosuvastatin "Sigillata"**, film-coated tablets 5mg, 10mg, 20mg and 40mg, from Rosuvastatin "Sigillata".

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 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.

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

The active substance is not considered a new active substance.

With respect to the legal basis in the RMS and the CMSs all applications have been made according to EU-directive 2001/83/EC article 10 (1) generic application.

The original product Crestor® 5 mg, 10 mg, 20 mg & 40 mg film-coated tablets (brand leader) and the reference product are approved by the mutual recognition procedure and was registered 2003-03-24. The safety/efficacy profile is thus claimed to be identical to the brand leader.

The applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the product 40mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Crestor® 40 mg film-coated tablets (AstraZeneca UK Ltd) and also with Rosuvastatin 5 mg film-coated tablets vs. Crestor® 5 mg film-coated tablets (AstraZeneca UK Ltd). This generic product can be used instead of its reference product.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is film-coated tablets, is packed in alu/alu blister, nature of container as described in the SmPC/PL, pack sizes according to approved SmPC). However, not all pack-sizes may be marketed.

Rosuvastatin "Sigillata", 5 mg, 10 mg, 20 mg or 40 mg film-coated tablets contain as active substance either 5 mg, 10 mg, 20 mg or 40 mg rosuvastatin (as rosuvastatin calcium).

Description of visual appearance:

5 mg tablets:
Yellow, round, 7 mm, biconvex with “RU5” engraved on one side and blank on the other side.

10 mg tablets:
Pink, round, 7 mm, biconvex with “RU10” engraved on one side and blank on the other side.

20 mg tablets:
Pink, round, 9 mm, biconvex with “RU20” engraved on one side and blank on the other side.

40 mg tablets:
Pink, oval, 15.5 mm x 8 mm, biconvex with “RU40” engraved on one side and blank on the other side.

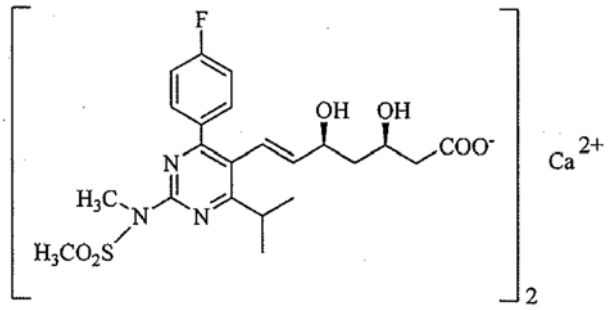
The excipients are: *tablet core:* lactose monohydrate, microcrystalline cellulose, crospovidone type A, sodium carbonate monohydrate sodium laurilsulfate, magnesium stearate, *tablet coat [5mg] Opadry II 85F62533 Yellow:* polyvinyl alcohol part hydrolised, titanium dioxide (E171), polyethylene glycol, talc, iron oxide yellow (E172), [*10mg, 20mg, 40mg] Opadry II 85F64743 Pink:* polyvinyl alcohol part hydrolised, titanium dioxide (E171), polyethylene glycol, talc, iron oxide yellow (E172), iron oxide red (E172), Allura red AC (E129), Indigo carmine (E132).

Compliance with Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

Active Substance
The active substance, rosuvastatin calcium, is described in the European Pharmacopoeia. It is a white or almost white powder. It is slightly soluble in water, freely soluble in methylene chloride, practically insoluble in anhydrous ethanol. It is optically active.
Polymorphism: rosuvastatin calcium shows polymorphism. The amorphous form is produced by the ASM.

Physical and pharmaceutical properties
Name (INN): Rosuvastatin calcium
Molecular formula: $(C_{22}H_{27}FN_3O_6S)_2Ca$
Molecular structure:



Molecular weight: 1001.14 g/mol
Chemical names: Calcium bis[(3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl (methylsulfonyl)amino]pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoate]
CAS registry: 147098-20-2
Appearance: White or almost white powder.

The ASM manufactures the active substance. The documentation on the active substance was initially provided as an ASMF but has been replaced by a CEP.

The active substance is described in Ph. Eur. and the specifications have been set based on the Ph. Eur. monograph and additional in-house requirements.
The re-test period is according to the CEP

The finished product manufacturer's specification on the drug substance includes all tests as included in the ASM's specification and additional test for particle size. Certificates of analysis of the active substance issued by the finished product manufacturer are presented.

II.3 Medicinal Product

The finished product is conventional film-coated tablet to be marketed in alu/alu blisters. The strengths applied for are 5, 10, 20 and 40 mg. The 10, 20 and 40 mg strengths are dose proportional, whereas the 5 mg strength is not proportional to the other strengths, but it has the same tablet core weight as the 10 mg strength. The development of the product has been adequately described, the choice of excipients is justified and their functions explained.

The finished product specifications cover appropriate parameters for this dosage form. The limit for dissolution testing reflects the dissolution profiles obtained with the biobatches. The analytical methods used to control the finished product has been adequately validated. Batch analysis results are provided showing that the finished products meet the specifications proposed.

A photostability study has been carried out where it was demonstrated that the finished product is not sensitive to light.
The proposed shelf-life of 36 months is acceptable based on the primary and supportive stability studies.
No special storage conditions are proposed, which is acceptable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of Rosuvastatin calcium are well known. As Rosuvastatin calcium is a widely used well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers numerous publications up to year 2015. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Rosuvastatin "Sigillata" 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rosuvastatin calcium is a well-known active substance with established efficacy and tolerability. As Rosuvastatin calcium is a widely used, well-known active substance, the applicant has not provided additional studies (apart from supportive bioequivalence studies referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical report refers 586 publications up to 2015. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Rosuvastatin "Sigillata" is compared with the pharmacokinetic profile of the reference product Crestor® 40 mg film-coated tablets (AstraZeneca UK Ltd) and Crestor® 5 mg film-coated tablets (AstraZeneca UK Ltd).

Bioequivalence studies

Bioequivalence
To support the application, the applicant has submitted as report two bioequivalence studies; single dose, fasting conditions for the 5 and 40 mg strength. All studies were 2 way cross over studies.

First study
The single centre, open label, randomized, 2-period, 2-sequence, single dose, crossover bioequivalence study was performed under fasting conditions. The treatment periods were separated by a washout period of 10 days. A single oral dose of rosuvastatin as one 40 mg tablet was administered in each study period.

Bioequivalence between the test and the reference product was demonstrated since 90% confidence intervals for the log-transformed AUC_{0-t} and C_{max} were within the acceptance range of 80-125%:

Table 21: Summary of Statistical Results for Rosuvastatin

Parameters	Geometric LSM Test	Geometric LSM Reference	DF	MSE	LSM Difference	Test/ Reference Ratio (%)	Lower 90% Confidence Limit	Upper 90% Confidence Limit	Intra-Subject CV (%)	Power (%)
$LnAUC_{0-t}$ (ng.hr/mL)	209.30	203.08	28	0.05666	0.030163	103.06	92.83	114.42	24.14	93.76
$LnAUC_{0-inf}$ (ng.hr/mL)	225.48	207.89	23	0.06022	0.081228	108.46	96.29	122.17	24.91	86.78
LnC_{max} (ng/mL)	25.61	26.59	28	0.12813	-0.037714	96.30	82.29	112.69	36.97	64.14

Second study
The single centre, open label, randomized, 2-period, 2-sequence, single dose, crossover bioequivalence study was performed under fasting conditions. The study included Rosuvastatin 5 mg film coated tablets and Crestor 5 mg film coated tablets. The treatment periods were separated by a washout period of 10 days. Bioequivalence between the test and the reference product was demonstrated since 90% confidence intervals for the log-transformed AUC_{0-t} and C_{max} were within the acceptance range of 80-125%:

Results

Table 1 - Summary of Pharmacokinetic Data for Rosuvastatin

Crestor (Reference Product)

Pharmacokinetic parameter	Geometric mean	Arithmetic mean	Standard deviation
AUC_{0-t} (ng.h/mL)	63.19	68.07	27.685
C_{max} (ng/mL)	7.53	8.13	3.405

Rosuvastatin (Test Product)

Pharmacokinetic parameter	Geometric mean	Arithmetic mean	Standard deviation
AUC_{0-t} (ng.h/mL)	70.44	77.04	34.437
C_{max} (ng/mL)	8.37	9.16	4.002

Table 2 - Ratio and 90% Confidence Intervals of Test Product versus Reference Product

Pharmacokinetic parameter	Ratio (%)	90% Confidence Intervals		Intra Subject Variability (%)
		Lower 90% CI (%)	Upper 90% CI (%)	
AUC_{0-t}	112.49	105.53	119.91	14.59
C_{max}	112.11	104.35	120.44	16.40

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Rosuvastatin ”Sigillata” is considered bioequivalent with Crestor.

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 ”Sigillata”.

The agreed summary list of safety concerns with no additional pharmacovigilance or risk minimisation measures is as follows:

Summary of safety concerns	
Important identified risks	• Rhabdomyolysis • Myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathy) • Increase transaminases, hepatitis, jaundice • Pancreatitis • Memory loss • Proteinuria • Diabetes mellitus • Depression • Sleep disorders (including insomnia and nightmares) • Immune Mediated Necrotizing Myopathy (IMNM) • Thrombocytopenia/decreased platelet count

	• SJS/TEN (Stevens-Johnson syndrome and toxic epidermal necrolysis) • Tendon disorders • Peripheral neuropathy • Drug interaction: ciclosporin, various protease inhibitor combinations with ritonavir, clopidogrel, gemfibrozil, eltrombopag, dronedarone, warfarin, other vitamin K antagonists, fusidic acid, ezetimibe and simeprevir.
Important potential risks	• Renal failure (including acute and chronic renal failure) and renal impairment • Hepatic failure (including hepatic necrosis and fulminant hepatitis) • Interstitial lung disease (ILD) • Amyotrophic lateral sclerosis (ALS) • Drug-drug interaction with fibrates (other than gemfibrozil)
Missing information	• Children < 6 years of age • DDI studies in the paediatric population

V. USER CONSULTATION

The package leaflet has been evaluated via a bridging report to a former 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 PIL was English.
The results show that the package leaflet 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

Rosuvastatin ”Sigillata”, film-coated tablets 5mg, 10mg, 20mg and 40mg, has a proven chemical-pharmaceutical quality and is a generic form of Crestor. 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.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Rosuvastatin ”Sigillata” with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 18-01-2017. Rosuvastatin ”Sigillata”, was authorised in DK on 21-09-2017.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), no routine PSURs are required for this product.

The date for the first renewal will be: 18-01-2022.

There were no post-approval commitments made during the procedure.