

Public Assessment Report

Scientific discussion

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

(rosuvastatin zinc)

NL/H/3059/001-004/DC

Date: 4 March 2015

This module reflects the scientific discussion for the approval of Rosuvastatine Resochem 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets. The procedure was finalised on 24 October 2014. 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 Rosuvastatine Resochem 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets, from Resolution Chemicals Limited.

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 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets (NL License RVG 26872-26874, 30823), which has been registered in the Netherlands by AstraZeneca since 6 November 2002 (10 mg, 20 mg, 40 mg) and 20 July 2004 (5 mg). Subsequently, an MRP was finalised with Crestor (NL/H/0343/001-004).

The concerned member state (CMS) involved in this procedure was Malta.

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

II. QUALITY ASPECTS

II.1 Introduction

Rosuvastatine Resochem 5 mg is a round, slightly biconvex, white or almost white, 6.0 mm diameter tablet, with a stylized 'E' engraving on one side and '591' on the other side.

Rosuvastatine Resochem 10 mg is a round, slightly biconvex, white or almost white, 7.0 mm diameter tablet, with a stylized 'E' engraving on one side and '592' on the other side.

Rosuvastatine Resochem 20 mg is a round, slightly biconvex, white or almost white, 9.0 mm diameter tablet, with a stylized 'E' and '593' engraved on one side and no engraving on the other side.

Rosuvastatine Resochem 40 mg is a Oval, slightly biconvex, white or almost white, 8.0 x 15.5 mm diameter tablet, with 'E 594' engraved on one side and no engraving on the other side.

The film-coated tablets are packed in polyamide/aluminium/PVC/aluminium blisters.

The excipients are lactose monohydrate, povidone, crospovidone and magnesium stearate. The Opadry film-coating material contains polyvinyl alcohol, talc, polyethylene glycol 3350 and titanium dioxide.

The different strengths are dose-proportional.

II.2 Drug Substance

The active substance rosuvastatin zinc is not described in any pharmacopoeia. It is a white powder, which is freely soluble in ethanol, methylene chloride and dimethylformamide and slightly soluble in water and 2-propanol. Rosuvastatin zinc has two chiral centers, thus theoretically four diastereoisomers exist. Rosuvastatin zinc salt produced by the manufacturer has a 3R,5S geometry. Polymorphic form I is used. The substance is hygroscopic, and sensitive to light and humidity.

The Active Substance Master File (ASMF) procedure is used for rosuvastatin zinc. 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 rosuvastatin tert-butylammonium salt intermediate covers several synthetic steps. Sufficient information on the manufacturers and specifications has been provided. Specifications of the intermediates, critical process parameters and in-process control tests from the starting materials have been laid down. The carry over of potential impurities and residual solvents has been adequately discussed.

Quality control of drug substance

The drug substance specification has been established in-house. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches of rosuvastatin zinc.

Stability of drug substance

Three pilot-scale batches have been stored for 24 months at 2 – 8°C and 6 months at 25°C/60%RH. Three full-scale batches have been stored for 6 months at 25°C/60% RH and 12 months at 2 – 8°C. The MAH has demonstrated that the polymorphic form of the drug substance does not change during storage. All stability results were in accordance with the set drug substance specification. Based on the provided stability data a re-test period of 18 months if stored in the proposed packaging at 2-8°C can be accepted.

II.3 Medicinal Product

Pharmaceutical development

The description of the pharmaceutical development is considered adequate. The MAH chose to use rosuvastatin zinc instead of rosuvastatin calcium, the active substance of the reference product. The particle size of the drug substance has been kept constant, and this can be accepted as such.

Two bio-equivalence studies have been performed:

The bio-equivalence study between the proposed 40 mg rosuvastatin zinc product and the originator product (Crestor 40 mg) from Hungary and the bio-equivalence study between the proposed 20 mg rosuvastatin zinc product and the originator product (Crestor 20 mg) from France. The latter bio-equivalence study has been assessed for this application. Crestor 10-20-40 mg has been registered by MRP in 2002. A justification for the waiver for the bioequivalence studies of the rosuvastatin zinc 5 mg & 10 mg tablets has been provided based on *in vitro* dissolution data.

The development of the dissolution method is considered adequate. At pH 1 (0.1 N HCl) and pH 2 (0.01 N HCl) the shape of the dissolution profiles during the first 10 minutes between the test product and originator products (Crestor) is different. However, after 15 min all profiles are comparable between corresponding strengths of proposed and originator tablets. At pH 4.5 and pH 6.6 all results for proposed and originator products were > 85% in 15 minutes.

The description of manufacturing process development is acceptable; for the chosen direct compression processing the setting of parameters (blending time, lubrication time, hardness of the compressed tablets), has been established.

Manufacturing process

The manufacturing process consists of the usual steps of weighing and sieving, blending (homogenizing), lubrication, compression, preparation of aqueous film-coat dispersion and film-coating. The process has been adequately described. For rosuvastatin tablets for the 5 mg, 10 mg & 20 mg tablets three full-scale batches and for the 40 mg tablets two full-scale batches have been prospectively validated, and all prospective validation results were satisfactory and meeting the acceptance criteria.

The product is manufactured using conventional manufacturing techniques. Process validation for full-scaled batches will be performed post authorisation.

Control of excipients

The specifications for the excipients are acceptable. Low-substituted hydroxypropylcellulose is in accordance with USP. All other excipients, or components of excipients, meet the requirements of Ph. Eur. The individual components of the Opadry II White 85F 14822 film-coating material comply with the Ph.Eur.

Quality control of drug product

The product specification includes tests for appearance, odour, size, average mass, uniformity of mass, identification, dissolution, uniformity of dosage units, water content, related substances, assay, resistance to crushing and microbiological purity. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided for three full-scale batches of the 5 mg, 10 mg and 20 mg strengths and two full-scale batches of the 40 mg strength, demonstrating compliance with the release specification.

Stability of drug product

Three pilot scaled batches for each strength of drug product, three full-scale batches for the 5 mg, 10 mg and 20 mg strengths and two full-scale batches of the 40 mg strength of drug product were stored at 25°C/60% RH (pilot scale: 36 months; full scale: 9-24 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 OPA/Al/PVC/Al-blisters. No significant changes were found either in the physical or in the chemical test characteristics of the product. The drug product is sensitive to light. The shelf life as claimed in the SmPC of 36 months with no special requirement except "Store in the original package in order to protect from light" is justified and suitable for the rosuvastatin film-coated tablets.

Specific measures concerning 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. The milk used for the production of this excipient is sourced from healthy animals in the same conditions as milk collected for human consumption and the lactose is prepared without the use of other ruminant materials than calf rennet. The lactose anhydrous is in accordance to NfG on minimizing risk of transmissible animal spongiform encephalopathy via human & veterinary products (i.e. EMEA/410/01 Rev-02).

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rosuvastatine Resochem 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets have 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 Resochem 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. The first study was performed using a pilot scale test formulation batch (40 mg strength) and the bioanalytical method was not in compliance with the guidelines in force at the moment of the marketing authorization application. This study can be regarded as a pilot study. Therefore only the second study, conducted with the 20 mg tablet is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Rosuvastatine Resochem 20 mg (Resolution Chemicals Limited, United Kingdom) is compared with the pharmacokinetic profile of the reference product Crestor 20 mg film-coated tablets (AstraZeneca, France).

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

The MAH applied for a waiver of the bioequivalence studies for 5 mg, 10 mg and 40 mg strengths, based on the following:

- linear pharmacokinetics for rosuvastatin
- the same qualitative composition for all the strengths
- the same ratio between amount of active substance and excipients for all the strengths
- similar dissolution for 5 mg, 10 mg and 40 mg compared to the 20 mg strength
- same manufacturing process of 10 mg, 20 mg and 40 mg strengths

The bioequivalence study was conducted with the 20 mg strength based on linear pharmacokinetics and high solubility of the drug substance. The 5 mg strength was manufactured at a different site and with a slightly different manufacturing process. However, comparative dissolution confirmed there are no reasons to suspect differing bioavailability characteristics of the 5 mg. The MAH chose to conduct the study only with the 20 mg strength, instead of the highest strength which is in general the choice for the bioequivalence study. However the MAH in compliance with the guideline justified this design because rosuvastatin demonstrates linear pharmacokinetics over the therapeutic dose range and because of the high solubility of rosuvastatin. A biowaiver was granted for the 5 mg, 10 mg and 40 mg strengths.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 18-63 years. Each subject received a single dose (20 mg) of one of the 2 rosuvastatin formulations. The tablet was orally administered after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

This standard design for a bioequivalence investigation is acceptable. The wash-out between periods is long enough, the sampling period is long enough and the sampling scheme adequate to estimate pharmacokinetic parameters.

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

A total of 56 healthy male subjects of the white race were included in the study, a total of 54 subjects received both formulations and were included in pharmacokinetic and statistical analysis. Two subjects withdrew due to a adverse events (headache and vomiting). Two subjects did not show up for samples at either the 36 and 48 hour point or the 48 and 72 hour point. These subjects were included in the statistical analysis only for C_{max} and T_{max} .

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

Treatment N=54	AUC ₀₋₇₂ ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	93.86 \pm 43.04	100.28 \pm 44.80	10.01 \pm 4.83	4.5 (2.0-5.0)	--
Reference	95.60 \pm 45.71	100.82 \pm 46.28	10.62 \pm 5.44	4.5 (1.5-5.0)	--
*Ratio (90% CI)	0.99 (0.95-1.03)	1.00 (0.95-1.04)	0.95 (0.89-1.00)	--	--
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC₀₋₇₂ area under the plasma concentration-time curve from time zero to 72 hours C_{max} maximum plasma concentration t_{max} time for maximum concentration t_{1/2} half-life					

**In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC₀₋₇₂, AUC_{0-∞} and C_{max} are within the bioequivalence acceptance range of 0.80-1.25. Based on the submitted bioequivalence study Rosuvastatine Resochem 20 mg is considered bioequivalent with Crestor 20 mg film-coated tablets.

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 Resochem.

- Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Rhabdomyolysis • Myopathy, myositis, myalgia, creatine kinase 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, and ezetimibe.
Important potential risks	<ul style="list-style-type: none"> • Renal failure (including acute and chronic renal failure) and renal impairment • Hepatic failure including hepatic necrosis and fulminant hepatitis

Summary of safety concerns	
	<ul style="list-style-type: none"> • Peripheral neuropathy • Amyotrophic lateral sclerosis • Interstitial lung disease • Drug-drug interaction with fibrates (other than gemfibrozil)
Missing information	<ul style="list-style-type: none"> • Severe hepatic impairment • Elderly subjects • Paediatric subjects • Severe renal impairment • Pregnant or lactating women • Asian population (increased plasma exposure) • Very low LDL-C levels • Genetic polymorphisms (increased plasma exposure)

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 test consisted of a pilot (5 participants) and two rounds with 10 participants each. Inclusion and exclusion criteria of the test persons were specified in the protocol. The test was performed in Hungarian. Questions were designed to determine whether users can identify key information that is necessary for appropriate use.

There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. The test included 15 questions related to the content of the PL. Five questions were related to the design and layout of the PL. A satisfactory outcome was achieved when 90% of the participants were able to find information and when 90% was able to show that they could understand the information. All questions met the criteria. No further changes were required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rosuvastatine Resochem 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 Resochem 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 October 2014.

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