CBG MEB

Public Assessment Report

Scientific discussion

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

(rosuvastatin calcium)

NL/H/3696/001-004/DC

Date: 22 March 2018

This module reflects the scientific discussion for the approval of Rosuvastatine Denk 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets. The procedure was finalised on 19 April 2017. 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
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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
USP/NF	United States Pharmacopoeia/National Formulary

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rosuvastatine Denk 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets, from Denk Pharma Europe GmbH.

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 Germany and Poland.

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

II. QUALITY ASPECTS

II.1 Introduction

Rosuvastatine Denk is a film-coated tablet in 4 different strengths:
- 5 mg – white or almost white, round, biconvex film-coated tablets, debossed with “5” on one side.
- 10 mg - white or almost white, round, biconvex film-coated tablets, debossed with “10” on one side.
- 20 mg - white or almost white, round, biconvex film-coated tablets, debossed with “20” on one side.
- 40 mg – white or almost white, oblong, biconvex film-coated tablets, debossed with “40” on one side.

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

Tablets are packed in Al/OPA/Al/PVC foil blisters.

The excipients are:
tablet content – lactose monohydrate, microcrystalline cellulose (E460), sodium citrate (E331), crospovidone (type B), anhydrous silica colloidal (E551) and magnesium stearate (E572).
film-coating – hypromellose (E464), lactose monohydrate, macrogol 3350, triacetin (E1518) and titanium dioxide (E171).

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, 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.

For the active drug substance, both the CEP and Active Substance Master File (ASMF) procedure are used. The main objective of the CEP procedure is that 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 European Pharmacopoeia.
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
Rosuvastatin calcium is manufactured in several synthetic steps. The choice of starting materials has been adequately justified. 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, and the active substance has been adequately characterised.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur with additional tests from the ASMF and the CEP. Batch analytical data demonstrating compliance with this specification have been provided for at least 3 batches from both sources.

Stability of drug substance
Manufacturer 1 - The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.
Manufacturer 2 - Stability data on the active substance have been provided for 3 full scaled batches in accordance with applicable European guidelines stored at 25°C/60% RH (6 months) and 2-8°C (12 months). No trends or changes were seen under any of the conditions. Based on the data submitted, a retest period could be granted of 18 months when stored in the proposed packaging stored in the refrigerator (2-8°C).

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 formulation was developed by a quality by design approach, and was optimised for the used excipients and their quantities to obtain a formulation that was essentially similar with the reference product Crestor. One bioequivalence study was submitted, conducted with the 40 mg strength. For the other strengths, a biowaiver was applied for. A justification for the waiver for the bioequivalence study of the lower strengths has been provided based on in vitro dissolution data. The development of the

dissolution method is considered adequate. The dissolution was tested in three buffers (pH 6.6 citrate, pH 4.5 acetate and pH 2 potassium chloride) and f2 values were calculated when necessary. The results demonstrated that the profiles of the test product can be considered similar to the profiles of the reference product.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The manufacturing process has been adequately described and validated for the lower batch size. A summary of the in-process information during manufacture is provided to confirm that the proposed film-coated tablets can be manufactured according to the proposals in the dossier. 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 meet the requirements of the Ph. Eur. 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, identification, assay, related substances, dissolution, uniformity of dosage units, water content and microbiological purity. The release and shelf life parameters 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 on 2 full scaled batches of the 5mg, 10 mg and 20 mg and three batches of the 40 mg 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 on 4 pilot scaled batches of the 5 mg, 10 mg and the 20 mg strength and 2 full scaled batches for the 40 mg strength stored at 30°C/75% RH (24 – 36 months) and 40°C/75% RH (6 months). Both sources of the active substance were used. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. The stability results show a slight but steady increase of impurities at all storage conditions. The photostability study showed that the product is slightly sensitive to light, however the results remained well within the specification limits. On basis of the data submitted, the proposed shelf-life ’24 months if stored below 30°C’ can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
None of the materials used is of animal or human origin except for lactose monohydrate. A statement of the manufacturer, regarding the safety and compliance of the production and marketing of products from milk or milk ingredients manufactured, has been included in the dossier.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

These products are generic formulations 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 and requested for a biowaiver.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Rosuvastatine Denk 40 mg, film-coated tablets (Denk Pharma Europe GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Crestor 40 mg, film-coated tablets (AstraZeneca B.V., NL).

The choice of the reference product in the bioequivalence study is accepted. The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

Biowaiver
A biowaiver has been requested for the 5, 10 and 20 mg strengths. The following argumentation has been provided for the acceptability of this biowaiver:

- 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.

The criteria for a biowaiver of additional strengths have been met.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male (41) and female (3) subjects, aged 22-55 years. Each subject received a single dose (40 mg) of one of the 2 rosuvastatin calcium formulations. The tablet was orally administered 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 at pre dose and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 16, 24, 36, 48, 72, and 96 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable.

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
One subject withdrew from the study due to personal reasons. Therefore, a total of 43 subjects were eligible for pharmacokinetic analysis.

Table 3. 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
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				

**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 studies Rosuvastatine Denk is considered bioequivalent with Crestor.

The MEB has been assured that the bioequivalence studies have 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 Denk.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Rhabdomyolysis • Myopathy, myositis, myalgia, creatinine 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 necrotizing myopathy • Thrombocytopenia/decreased platelet count • Tendon disorders • Drug-drug interactions: ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, clopidogrel, eltrombopag, dronedarone, warfarin, fusidic acid and ezetimibe.

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	• Exposure in children < 6 years of age • Drug-drug interaction studies in the paediatric population

Since the reference product Crestor has additional Risk Minimisation Measures (RMM), the MAH will implement, where applicable, similar additional RMMs as those of the reference product. The following additional risk minimisation activities are included in the RMP:

- Review of rosuvastatin usage: Active review for evidence of off-label use with appropriate follow-up action (this concerns review of ICSRs with info on dose). Where possible, the MAH representatives will target physicians with high use of 40 mg rosuvastatin to reiterate prescribing advice. In those markets that have implemented active monitoring of off-label use, the MAH will actively monitor rosuvastatin off-label use for at least 5 years from the date of first sale in those markets.
- Restriction of samples: Provision of physician samples should be restricted to the approved start dose(s). Restriction of physician samples to the approved start dose(s) should continue as long as the MAH continues to provide physician samples.
- Educational activities: This only applies in situation where the MAH will approach HCPs when attending meetings and symposia etc.: During meetings, symposia, and educational roundtable events regarding the product, the MAH will target physician speakers, including key opinion leaders, and will brief these HCPs on the recommended start dose, and the impact of the individual patient's benefit-risk profile on the choice of start dose. This activity will continue for at least 5 years from the date of first sale in a market that has implemented this activity. Since activities aimed towards healthcare providers and patients are normally conducted on a country-by-country basis, these may be modified or adapted by each country, depending upon local needs and the regulatory requirements. However, the MAH is not requested to participate in meetings or symposia as additional risk minimisation activity by itself.

The MAH indicated they will not provide product samples. No educational activities are proposed, which is accepted since these activities are voluntary activities of the reference product.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Crestor film-coated tablets. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies 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 MAH did not perform a user testing but submitted a bridging statement. The MAH claims that due to the usage of the already tested and approved package leaflet text of another rosuvastatin product of Farmaprojects S.A.U. (Rosuvastatina Farmaprojects 40 mg comprimidos recubiertos con película EFG) and implementation of the user-tested lay-out of the same package leaflet, the proposed package leaflet is compliant with Article 59(3) of Directive 2001/83/EC and therefore, an additional user-test is not required. This justification is acceptable since the tested and approved PL for Rosuvastatina Farmaprojects 40 mg comprimidos recubiertos con película EFG of Farmaprojects S.A.U has been submitted in a national procedure in Spain (procedure number assigned by AEMPS is: 2015045470), meaning it has been assessed and approved based on the same standards. Therefore, overall the bridging report submitted has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rosuvastatine Denk 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 Denk with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 April 2017.

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