COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rosuvastatine Interdos 5 mg, 10 mg, 20 mg, 40 mg film-coated tablets

(rosuvastatin calcium)

NL/H/4195/001-004/DC

Date: 7 March 2019

This module reflects the scientific discussion for the approval of Rosuvastatine Interdos 5 mg, 10 mg, 20 mg, 40 mg film-coated tablets. The procedure was finalised at 26 November 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
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 Interdos 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets from Interdos Pharma BV.

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 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, Spain, France (except for the 40 mg strength), and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Rosuvastatine Interdos is a film-coated tablet in four different strengths:

- The 5 mg strength is a pink, round, biconvex, bevelled edge, film-coated tablet debossed with 'R5' on one side.
- The 10 mg strength is a pink, round, biconvex, bevelled edge, film-coated tablets debossed with 'R10' on one side.
- The 20 mg strength is a pink, round, biconvex, film coated tablets, debossed with ' R20' on one side.
- The 40 mg strength is a pink, oval, biconvex, film coated tablets, debossed with ' R40' on one side

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

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

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), sodium hydrogen carbonate powdered (E500), crospovidone (E1202), and magnesium stearate (E572).
Tablet coat - lactose monohydrate, hypromellose (E464), triacetin (E1518), titanium dioxide (E171), and iron oxide red (E172).

The four tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is Rosuvastatin calcium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is slightly soluble in water. Rosuvastatin calcium, is amorphous in nature. Rosuvastatin calcium is an optically active molecule, having two chiral centres. The required stereochemistry of the drug substance is 3R,5S.

The CEP procedure is used for the active substance. 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 Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

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. It includes additional tests on residual solvents, identification, particle size distribution, calcium content, specific optical rotation and microbial contamination. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for three years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 proposed packaging and manufacturing process are justified.

The 40 mg strength batch used in the bioequivalence studies was manufactured according to the proposed manufacturing process, and was shown to have a similar impurity profile as the reference product. The products used in the bioequivalence study are acceptable. The biowaiver for the additional 5 mg, 10 mg and 20 mg strengths has been justified based on comparative *in vitro* dissolution studies.

Manufacturing process
The tablets are prepared by direct blending and compression. The manufacturing process involves the following operations: co-sifting, blending, lubrication, compression, and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production scaled batches per strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients and film-coating mixture comply with the Ph.Eur. with additional tests for functionality related characteristics. The film-coating mixture is controlled according to an in-house specification. The individual components of the film-coating mixture are of Ph.Eur. quality. 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, uniformity of mass, water content, disintegration time, uniformity of dosage units by content uniformity, dissolution, assay, related substances and microbiological quality. Limits in the specification

have been justified and are considered appropriate for adequate quality control of the product. The product is not photosensitive.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches per 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 on three batches per strength that were stored at 25°C/60% RH (18 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 packaging. No clear trends or changes were observed in any of the tested parameters. The proposed shelf-life of two years with storage condition 'This medicinal product does not require any special storage conditions' is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
None of the materials used in the manufacture of the rosuvastatin film-coated tablets, except lactose monohydrate, are of animal and/or human 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 Interdos 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 Interdos 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Rosuvastatine Interdos 40 mg film-coated tablets (Interdos Pharma BV, the Netherlands) is compared with the pharmacokinetic profile of the reference product Crestor 40 mg tablets (AstraZeneca Limited, United Kingdom).

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.

<u>Biowaiver</u>
A biowaiver is granted for the 5 mg, 10 mg and 20 mg strengths. The biowaiver was based on the following conditions:

- The qualitative and quantitative composition of the different strengths are dose proportional.
- All strengths of rosuvastatin Interdos are manufactured by the same process.
- Rosuvastatin has linear pharmacokinetics over the therapeutic dose range.
- The tablets are completely dose proportional.
- The MAH has performed comparative dissolution studies in 0.1N HCl (pH 1.2), pH 4.5 and pH 6.8 medium between the 40 mg and additional three strengths (5 mg, 10 mg and 20 mg). In pH 4.5 and pH 6.8 media similarity can be concluded based on the very rapid dissolution of all strengths in these media. In pH 1.2 medium, for the 5 mg and 20 mg strengths the underlying dissolution data were suitable, and similarity was confirmed. Similarity between the 40 mg bioequivalence study test batch versus the 10 mg strength has also been adequately demonstrated (f2 >50).

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy subjects, aged 20-44 years. Each subject received a single dose (40 mg) of one of the two rosuvastatin calcium formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and 0.167, 0.50, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 24 and 48 hours after administration of the products.

The design of the bioequivalence study is acceptable and in accordance with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). The washout period is sufficient. A washout period of seven days is sufficient. The sampling scheme is adequate to estimate the pharmacokinetic parameters of interest. The study is conducted at the highest strength under fasting conditions, which is in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**).

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

All subjects completed the study. Therefore, 48 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=48	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	784.9 ± 322.4	826.2 ± 329.1	88.8 ± 42.4	2.3 (0.5 – 4.5)
Reference	775.6 ± 300.9	811.8 ± 304.8	88.5 ± 42.0	2.3 (0.5 – 4.5)
***Ratio (90% CI)**	0.99 (0.94 – 1.05)	--	1.00 (0.93 – 1.07)	--

$AUC_{0-\infty}$ 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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Rosuvastatine Interdos is considered bioequivalent with Crestor.

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 Interdos.

Table 2. Summary table of safety concerns as approved in RMP

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 Necrotising Myopathy (IMNM) • Thrombocytopenia/decreased platelet count • SJS/TEN (Stevens-Johnson syndrome and toxic epidermal necrolysis) • Tendon disorders • Peripheral neuropathy • Drug-drug interactions including 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 • 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

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 three participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Rosuvastatine Interdos 5 mg, 10 mg, 20 mg, 40 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Crestor 5 mg, 10 mg, 20 mg, 40 mg 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 Interdos with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 November 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse