Public Assessment Report

Scientific discussion

Rosuvastatine Torrent 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets (rosuvastatin calcium)

NL/H/2854/001-004/DC

Date: 11 June 2014

This module reflects the scientific discussion for the approval of Rosuvastatine Torrent film-coated tablets. The procedure was finalised on 10 December 2013. 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 Torrent 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets from Torrent Pharma GmbH.

The product is indicated for:

Treatment of hypercholesterolaemia
Adults, adolescents and children aged 10 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 states (CMS) involved in this procedure were Germany, Lithuania, Romania 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 Torrent 5 mg is a yellow coloured, round, biconvex, film-coated tablet, debossed with “135” on one side and “5” on the other side.
Rosuvastatine Torrent 10 mg is a Light pink coloured, round, biconvex, film-coated tablet, debossed with break line on both sides, separating “11” and “36” on one side and “10” on the other side. The tablet can be divided into equal doses.
Rosuvastatine Torrent 20 mg is a light pink coloured, round, biconvex, film-coated tablet, debossed with break line on both sides, separating “11” and “37” on one side and “20” on the other side. The tablet can be divided into equal doses.
Rosuvastatine Torrent 40 mg is a light pink coloured, oval shape, biconvex, bevelled edge, film-coated tablet, with break line on both sides. The tablet can be divided into equal doses.

The film-coated tablets are packed in OPA/Aluminium/PVC-Aluminium blisters or HDPE bottles.

The excipients are: lactose monohydrate, microcristalline cellulose, crospovidone, magnesium stearate, hypromellose, triacetin, titanium dioxide (E 171); 5 mg only - ferric oxide yellow (E 172); 10 mg, 20 mg 40 mg – ferric oxide red (E172)

The 5 mg, 10 mg and 20 mg core strengths are fully dose-proportional. The 40 mg strength differs in the content of the active ingredient, which is 6.7% (5-10-20 mg tablets) versus 12.6% (40 mg tablets).

II.2 Drug Substance

The active substance is rosuvastatin calcium, an established active substance however not described in any pharmacopoeia. It is an off-white to light yellow colored powder, which is soluble in N, N-dimethyl formamide, acetone and acetonitrile, and insoluble in water. Rosuvastatin calcium consists of two asymmetric carbon atoms; hence two pairs of isomers are possible. The substance used is the R,S isomer, and it is an amorphous form.

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 process is a complex process with two manufacturing sites. All steps have been described in full detail. The starting materials are acceptable and have been adequately specified. The manufacturing process has been adequately described.

Quality control of drug substance

In general adequate in-house drug substance specifications are applied. The MAH's specifications are in line with those of the DMF holder, with an additional specification for particle size.
The MAH provided batch analysis results for two batches of drug substance, demonstrating compliance with the specification.

Stability of drug substance

Three validation and three additional commercial batches have been stored for 60 months at 25°C/60% RH and 6 months at 40°C/75% RH. All results met the set requirements.
One batch with intermediates has been stored for 3 years at 25°C/60% RH and 6 months at 40°C/75% RH.
In addition another batch has been stored for 2 years at 25°C/60% RH and 6 months at 40°C/75% RH, and finally a high scale process validation batch for 12 months at long term conditions.
In general the claimed re-test period of 3 years without specific storage condition can be accepted.

II.3 Medicinal Product

Pharmaceutical development

The proposed formulation is highly based on that of the innovator product. The innovator's excipient calcium phosphate has not been included in the formulation. However, here are no indications that the absence of this excipient would have any negative impact on the performance of the proposed product.
The description of the pharmaceutical development is considered adequate. The particle size of the drug substance is adequately controlled. Sufficient data have been provided demonstrating that the nature of the amorphous character of the drug substance does not change into another crystalline form during utilization of the drug substance in the drug product manufacturing and during drug product storage. The effects of the crucial excipients crospovidone (disintegrant) and magnesium stearate (lubricant) have been adequately investigated.
The development of the dissolution method is considered adequate. Breakability of the 10 mg, 20 mg and 40 mg tablets has been demonstrated.
Two bioequivalence studies have been performed: one with the 20 mg strength in comparison with the German reference product, and another with the 40 mg strength with the UK reference product.
The justification for a biowaiver for the 5 mg and 10 mg strengths is considered acceptable on pharmaceutical-chemical grounds. All dissolution profiles of the 5mg, 10 mg and 20 mg strengths of the proposed product (including test bio-batch) and the 20 mg reference bio-batch show dissolution of >85% within 15 minutes. Therefore the dissolution profiles are considered equivalent. For the 40 mg formulation the comparative dissolution profiles at pH 3.0 and 6.8 were found to be similar, but not at pH 4.5 and pH 6.6. However, since the 40 mg tablets are bioequivalent with the 40 mg innovator product, the equivalence of the *in-vitro* profile is not relevant.

Manufacturing process
The manufacturing process consists of the usual steps of weighing and sifting, blending, lubrication, compression, film-coating and packing. A flow-chart of the manufacturing process including the in-process controls is provided for each strength. The manufacturing steps are described in detail. The in-process controls for the tableting and film-coating steps are usual and acceptable. The manufacturing process involved is a standard process comprising operations such as sieving, blending, lubrication, compressing and coating. Sufficient validation data on lower production-scale batches have been provided.

Control of excipients
All excipients are tested in accordance with their corresponding Ph. Eur. monograph, except for ferric oxide yellow and red, which are tested according to USP-NF and EC Directive 2009/35/EC. The specifications and the analytical procedures of the other excipients used are as per the current edition of Ph. Eur. The specifications are acceptable.

Quality control of drug product
The MAH has laid down adequate drug product specifications. These include tests for description, identification, average weight, dissolution, uniformity of dosage units, water content, related substances, assay, microbiological limit and uniformity of mass in subdivided tablets (10 mg, 20 mg and 40 mg tablets). In general the specification is based on pharmacopoeial requirements and relevant guidelines. The methods for the testing and analysis of the drug product are described in detail and are considered appropriate. Batch analysis results of the two validation batches per strength, demonstrating compliance with the specification.

Stability of drug product
The claimed shelf-life is 3 years if stored in Alu–Alu blisters or HDPE containers without any specific storage condition. Two batches of each strength have been placed on stability: 36 months normal (25°C/60% RH) and 6 months accelerated (40°C/75%) data are available. At all conditions no specific or significant changes are noted. The available stability results meet the shelf life specifications. The product was demonstrated to be photostable.
The following shelf life, packaging and storage conditions were granted:
36 months for Alu-Alu pack (all strengths) and HDPE pack (5, 10 and 20 mg tablets).
The shelf life for 40 mg tablets in HDPE pack is 12 months. No specific storage conditions are required.
Sufficient data have been provided to justify a shelf life after first opening of the HDPE bottles: 90 days.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is prepared without the use of other ruminant materials than milk and calf rennet. The manufacturer also certifies that the milk is sourced from the healthy animals in same conditions as milk collected for human consumption. The production of calf rennet complies with the applicable EU regulation. Magnesium stearate is of vegetable origin. Triacetin is produced using raw materials from vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rosuvastatine Torrent 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets 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 Torrent 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, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test products Rosuvastatine Torrent 20 mg and 40 mg (Torrent Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference products Crestor 20 mg tablets (AstraZeneza GmbH, Germany) and 40 mg tablets (AstraZeneza, UK).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The following argumentation has been provided for the acceptability of the biowaiver for the 5 mg and 10 mg strength, based on the study with the 20 mg tablet:
- The different strengths (5, 10 & 20 mg) are manufactured by the same manufacturer and by same manufacturing process.
- The qualitative composition of Rosuvastatine Torrent 5 mg, 10 mg and 20 mg is the same.
- Rosuvastatin 5, 10 & 20 mg tablets are developed as a dose proportional formula (scale down). The ratio between the amounts of excipients is similar.
- The pharmacokinetic profile of orally administered rosuvastatin is dose proportional over the dose range of 10 to 80 mg.
- The dissolution profile of Rosuvastatine Torrent 5 mg tablets and 10 mg tablets is similar to the 20 mg tablets.

Bioequivalence studies

Study I – 20 mg tablets
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 20-44 years. Each subject received a single dose (20 mg) of one of the 2 rosuvastatin formulations. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.75, 1.0, 1.5, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is acceptable. There is an adequate wash-out period and a long enough sampling period. Food does not interact with the absorption of rosuvastatin. Therefore, a food interaction study is not deemed necessary.

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 his consent at the start of the second period. Therefore a total of 47 subjects were included in the pharmacokinetic and statistical analysis.

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

Treatment N=47	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	159 ± 81	170 ± 81	19 ± 9.0	4.5 (0.33-4.5)	--
Reference	167 ± 72	176 ± 73	20 ± 8.2	4.5 (0.33-5)	--
***Ratio (90% CI)**	0.95 (0.89-1.00)	--	0.93 (0.87-1.01)	--	--

$AUC_{0-\infty}$ 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*

A total of 7 adverse events were reported, all post study laboratory investigation abnormalities, creatine kinase (4) and random blood sugar (3). All events were judged to be mild in nature and resolved without intervention.

Study II – 40 mg tablets
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 21-44 years. Each subject received a single dose (40 mg) of one of the 2 rosuvastatin formulations. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.75, 1.0, 1.5, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is acceptable. There is an adequate wash-out period and a long enough sampling period. Food does not interact with the absorption of rosuvastatin. Therefore, a food interaction study is not deemed necessary.

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 did not report to the facility for the second period. Two subjects withdrew their consent at the start of the second period. Another subject was withdrawn due to a positive urine drug screen (THC). Therefore a total of 44 subjects were included in the pharmacokinetic and statistical analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rosuvastatin under fasted conditions.

Treatment N=44	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	557 ± 256	571 ± 257	69 ± 37	2.88 (0.33-5.5)	--999
Reference	569 ± 250	583 ± 252	72 ± 39	2.38 (0.33-5.0)	--
***Ratio (90% CI)**	0.96 (0.91-1.02)	--	0.95 (0.87-1.04)	--	--

$AUC_{0-\infty}$ 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*

In total, a number of 8 adverse events were described; all post study laboratory investigation abnormalities, serum potassium (3), WBC (2), random blood sugar (2) and creatine kinase (1). All these were judged mild, not serious and resolved without treatment.

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80-1.25. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t} as is the case in these studies for immediate-release products. Based on the submitted bioequivalence studies, Rosuvastatine Torrent 20 mg and 40 mg are considered bioequivalent with Crestor 20 mg and 40 mg tablets respectively.

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 Torrent.

Important identified risks	- Rhabdomyolysis - 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 - 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	- Renal failure (including acute and chronic renal failure) - Renal impairment - Hepatic failure: including hepatic necrosis and fulminant hepatitis - Peripheral neuropathy - Amyotrophic lateral sclerosis - Interstitial lung disease - Drug-drug interaction with fibrates (other than gemfibrozil)
Important missing information/special patient population	- 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

Pharmacovigilance actions
Routine pharmacovigilance will be applied for all important identified and potential risks, as well as missing information. Targeted follow-up questionnaires will be utilized to elicit additional detailed follow-up to enhance the quality and completeness of information for adverse event reports of rhabdomyolysis with a fatal outcome.
Targeted follow-up questionnaires will be utilized to elicit detailed follow-up to enhance the quality and completeness of information for the following reported adverse event reports: Renal failure, renal impairment, hepatic failure, amyotrophic lateral sclerosis and interstitial lung disease.
Targeted follow-up questionnaires will be utilized to elicit detailed follow-up to enhance the quality and completeness of information for reports in paediatric subjects related to the specified identified and potential risks. Follow-up will be performed on all reports of pregnancy with a delivery date.

Risk minimisation measures
For the identified risk rhabdomyolysis and the potential risks renal failure (including acute and chronic renal failure) and renal impairment, the MAH will follow the activities of the originator and adopt their risk minimisation measures.
To minimize the risk of off-label use, the MAH will actively review rosuvastatin usage for evidence of off-label use with appropriate follow-up action. 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. In addition, the MAH will restrict samples: provision of physician samples should be restricted to the approved start dose(s). Restriction of physician samples to the approved start dose(s) will continue as long as the MAH continues to provide physician samples.

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 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 package leaflet 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 testing process involved one pilot test on two participants, followed by two main tests on ten participants each.
Eighteen questions about the most critical parts of the package leaflet and three general questions about the package leaflet were used. There were sufficient questions about the critical sections. Taking into account the results, for each question more than 90% of the participants was able to find the section and answered the question correctly. The conclusions are clear, concise and clearly presented.

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

Rosuvastatine Torrent 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 Torrent 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 10 December 2013.

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

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