Public Assessment Report

Scientific discussion

Name of the Product:
Rosuvastatin-Teva film-coated tablets

Rosuvastatin Calcium 5, 10, 20, 40 mg

Procedure numbers:
HU/H/0218/001-004/DC

Applicant:
Teva Hungary

Date: 29 August 2012

**This module reflects the scientific discussion for the approval of Rosuvastatin-Teva tablets.
The procedure was finalised at 06 December 2009.
For information on changes after this date please refer to the module 'Update'**

Content

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, implemented by the Act CXV of 2005 *on Medicinal Products for Human Use and on the Amendment of Other Regulations Related to Medicinal Products* as well as by the Decree 52/2005 (IX. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary, an application has been submitted to the reference and competent authorities of the Member State concerned.

In this Decentralised Procedure application the Reference member state, RMS was Hungary, while the concerned member states, CMS were Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Greece, Ireland, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, Slovenia and Spain.

This application is submitted according to Article 10(1) and Article 10(3) (in Bulgaria and the Czech Republic) of Directive 2001/83/EC.

The application concerned the generic version of rosuvastatin 5 mg, 10, mg, 20 mg and 40 mg film-coated tablets. The Applicant: Teva Hungary stated that this product has been developed to be essentially similar to the original product Crestor, 5 mg, 10 mg, 20 mg, and 40 mg film-coated tablets of Astra Zeneca. Crestor film-coated tablets have been marketed in Hungary since 2004.

Rosuvastatin is indicated for:

- primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolemia) 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 hypercholesterolemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL aphaeresis) or if such treatments are not appropriate.

The 10 mg and 20 mg dose tablets are proportional and the mass of 5 mg and 10 mg and mass of 20 mg and 40 dose tablets are equal. Bioequivalence studies were performed on the 5 mg, 20 mg, and 40 mg strength product.

Since the application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application) it contained no new clinical or preclinical data, other than the bioequivalence study as well as the supporting literature where necessary.

II. QUALITY ASPECTS

II.1 Introduction

The Applicant stated that these products had been developed to be essentially similar to the original products Crestor 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets of the innovator company AstraZeneca. Crestor film-coated tablets have been marketed in Hungary since 2004.

The products are formulated as film-coated tablets. The 10 mg and 20 mg dose tablets are proportional and the mass of 5 mg and 10 mg and mass of 20 mg and 40 dose tablets are equal. Bioequivalence studies were performed on the 5 mg, 20 mg, and 40 mg strength product.

II.2 Drug Substance

INN name: rosuvastatin calcium
Chemical name: (*E*)-(3*R*,5*S*)-7-{4-(4-Fluorophenyl)-6-isopropyl-2 [methyl(methylsulfonyl) amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid calcium (2:1)

The active substance is a white to light yellow powder and is soluble in dimethylformamide, acetone and acetonitril and is insoluble in water. It shows polymorphism.

The molecule has 2 chiral centres; the manufacturer consistently produces the correct isomer and the same polymorphic form.

The proposed manufacturing process has been adequately described; critical steps and accompanying in-process controls have been defined to ensure quality of the final compound. In-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials, solvents and reagents have been established.

Evidence of the structure has been confirmed by various methods.

Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed in relation to their origin and potential carry-over into the final drug substance. Residual solvents and heavy metals are routinely controlled.

The substance complies with the requirements of the EMA guideline on genotoxic impurities.

The substance is not official in the European Pharmacopoeia (Ph. Eur.) Therefore, an in-house specification has been set for rosuvastatin calcium, that are in accordance with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods are adequately drawn up and sufficiently validated. In house reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies performed on the rosuvastatin calcium justify for the proposed retest period without any particular storage precautions.
Or
Stability data have been obtained. The data show the substance to be stable. Based on the data submitted appropriate retest periods and storage conditions have been set.

GMP compliance of the API manufacture is demonstrated by the Applicant.

II.3 Medicinal Product

The aim of the pharmaceutical development was to produce immediate release film-coated tablets containing 5 mg, 10 mg, 20 mg or 40 mg rosuvastatin calcium as active substance, pharmaceutically equivalent and bioequivalent to the product Crestor® tablets marketed by AstraZeneca.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.

As a result of development studies product with the following composition, appearance and packaging was obtained. The used excipients were: microcrystalline cellulose, crospovidone, lactose anhydrous, povidone K-30 and sodium stearyl fumarate. The orange and pink film-coating mixture contained partially hydrolyzed poly(vinyl-alcohol), titanium dioxide, talc, macrogol 3350 and colourings. All excipients used comply with their respective Ph. Eur. monographs, with the exception of film-coating, which complies with a satisfactory in-house monograph. Compliance of the products with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the Applicant.

Rosuvastatin 5 mg film-coated tablets are orange, round, standard convex coated tablet, debossed with "N" on one side and with "5" on the other side of the tablet.

Rosuvastatin 10 mg film-coated tablets are light pink to pink, round, standard convex coated tablet, debossed with "N" on one side and with "10" on the other side of the tablet.

Rosuvastatin 20 mg film-coated tablets are light pink to pink, round, standard convex coated tablet, debossed with "N" on one side and with "20" on the other side of the tablet.

Rosuvastatin 40 mg film-coated tablets are light pink to pink, oval shaped film coated tablets debossed with"N" on one side and with "40" on the other side of the tablet.

The film-coated tablets are packaged in OPA/Al/PVC foil fastened with Aluminium foil and box.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented.
GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. The acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented. Certificates of analysis were also provided for the working standard used.

The container closure system of the product is as follows: in OPA/Al/PVC// Al blisters. The same blisters as those proposed for routine storage were used for the stability studies. The selected primary packaging material complies with the relevant Ph. Eur. monograph, directive 2002/72/EC and foodstuff legislation.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results a shelf-life of 24 months with storage conditions: “do not store above 30°C, store the medicinal product in the original package in order to protect from light and moisture” is considered only acceptable for 10 mg, 20 mg and 40 mg strengths. For 5 mg film-coated tablets the storage condition for temperature has been modified to “do not store above 25°C store the medicinal product in the original package in order to protect from light and moisture”.

The SmPC, Patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It has been concluded that the product has been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative content of the active substance and pharmaceutical form until the end of the approved shelf-life. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This is a generic/hybrid application made under Article 10(1) and Article 10(3) of EC Directive 2001/83/EC. Pharmacodynamic, pharmacokinetic and toxicological properties of rosuvastatin are well known. The non-clinical dossier is based on a review of published literature.

III.2 Pharmacology

No new data have been submitted.

III.3 Pharmacokinetics

No new data have been submitted.

III.4 Toxicology

No new data have been submitted.

III.5 Ecotoxicity/environmental risk assessment

Since Rosuvastatin TEVA 5 mg, 10mg, 20mg and 40 mg film-coated tablets are intended to substitute other similar products on the market, its storage, distribution, use and disposal will not result in an increase of risk to the environment.

III.6 Discussion on the non-clinical aspects

No new preclinical data have been submitted and therefore the application has not been subjected to a pre-clinical assessment. This is acceptable for this type of application.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application has been made under Article 10(1) and Article 10(3) of the Directive 2001/83/EC. Pharmacodynamic, pharmacokinetic and toxicological properties of rosuvastatin are well known.

The Applicant adequately summarized the clinical experience with rosuvastatin. To support the application the Applicant submitted three bioequivalence studies conducted in accordance with the *Guideline on Bioequivalence* (CHMP/EWP/QWP/1401/98).

IV.2 Pharmacokinetics

IV.1.1 Literature data

Rosuvastatin is rapidly absorbed after oral administration. The peak concentration in the plasma is reached between 3 and 5 hours after dosing. The absolute bioavailability of rosuvastatin is approximately 20% and a repeated dose does not result in accumulation. The pharmacokinetic properties of rosuvastatin are dose-proportional. Administration of rosuvastatin with food decreased the rate of drug absorption by 20%.

This active principle is widely distributed in the body. Rosuvastatin undergoes first pass extraction in the liver. Plasma protein binding is 88%, involving mostly albumin. The mean volume of distribution at steady state of rosuvastatin is approximately 134 litres. Rosuvastatin undergoes very limited metabolism (app. 10%) primarily via cytochrome P450 (CYP) 2C9. The metabolite N-desmethyl rosuvastatin having 50% less activity of the parent compound. Rosuvastatin is predominantly excreted *via* bile and leaves the body mostly in the faeces together with its metabolites (including absorbed and non-absorbed molecules). This route of excretion accounts for 90% of the total excretion. The remaining part is excreted in the urine. The plasma elimination half-life is approximately 19 hours. There were no clinically relevant changes in the pharmacokinetics of rosuvastatin with differences in patient age or gender, time of administration, or mild to moderate renal impairment. However, plasma concentrations of rosuvastatin were increased in patients with severe renal impairment. In a study with subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

IV.1.2 Bioequivalence studies

In order to demonstrate pharmacokinetics of rosuvastatin in the developed tablets and to establish bioequivalence with the reference products, three bioequivalence (BE) studies were conducted with Teva Pharmaceutical Industries Ltd. as sponsor between January and June 2008. The studies utilised the following dose forms: 40 mg, 20 mg and 5 mg rosuvastatin. The Applicant requested a biowaiver for the 10mg strength.

The conduct of the studies was satisfactory and the results comply with the acceptance criteria for bioequivalence as detailed in the relevant CHMP guideline.

1st study: A Single-Dose, Comparative Bioavailability Study of Three Formulations of Rosuvastatin 5 mg Tablets Under Fasting Conditions

Design

The objective of this study was to evaluate the comparative bioavailability between Rosuvastatin 5 mg Tablets (Teva Pharmaceutical Industries Ltd.- – Treatment A) and two formulations of Crestor® 5 mg Tablets (AstraZeneca Canada Inc., Canada- Treatment B and NV AstraZeneca SA, Belgium – Treatment C) after a single-dose in healthy subjects under fasting conditions.

This was a blinded, single-dose, randomized, three-period, three-sequence, three-treatment, crossover study, designed to evaluate the comparative bioavailability of three formulations of rosuvastatin 5 mg tablets administered to healthy male subjects under fasting conditions. Subjects were randomly assigned to one of the three dosing sequences ABC, BCA or CAB. Concentrations of rosuvastatin were measured from the samples collected over a 72-hour interval after dosing in each period.

One tablet was administered orally to each subject with 240 ml water after an overnight fast of at least 10 hours. A single oral dose of rosuvastatin as a 1 x 5mg tablet was administered in each study period. The dose phases were separated by a washout period of 14 days.

In each period, 22 blood samples from 21 time points were obtained. Blood samples were collected prior to study drug administration and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after the drug administration in each period.

The study design is appropriate. The number of measurements around the C_{max} and the duration of sample-collection are sufficient.

Since a European marketing authorisation requires the comparison with a European originator product, the Canadian originator has no importance in this case.

Bioanalytics

Plasma concentrations of rosuvastatin were determined in plasma samples of volunteers using a Liquid Chromatography / Tandem Mass Spectrometry Method (LC-MS/MS).

Statistics, statistical methods

Pharmacokinetics: parametric ANOVA was applied to log-transformed AUC_{0-t}, C_{max}, AUC_{0-inf}, and untransformed K_{el} and $T_{1/2}$, geometric confidence intervals were calculated for AUC_{0-t}, AUC_{0-inf} and C_{max}; and non-parametric test was applied to T_{max}.

Statistical analysis was applied to quality assured data from all subjects in the final data set. The PROC GLM procedure from SAS® was used.

- Treatment A (Test Product) vs. Treatment C (Reference Product):
  - The 90% confidence intervals of the relative mean plasma rosuvastatin AUC_t and AUC_{inf} of the test to reference product should be between 80-125%.
  - The 90% confidence interval of the relative mean plasma rosuvastatin C_{max} of the test to reference product should be between 75-133%.

Results

Table 1. *Descriptive statistics of pharmacokinetic parameters for rosuvastatin (n=25) (Only the results of Test Product vs. Reference Product are presented and assessed)*

Parameters (Units)	**Geometric mean**	
	Test Product (A)	**Reference Product (C)**
C_{max} (ng/ml)	2.909	2.957
AUC_{o-t} (ng.h/ml)	24.621	24.554
$AUC_{0-\infty}$ (ng.h/ml)	27.908	28.094
t_{max} (h)	4.08	4.32
K_{el} (1/h)	0.0564	0.0500
$t_{1/2}$ (h)	18.20	20.31

The conventional CI for Log transformed AUCt, AUCinf and Cmax are within the [80; 125]% acceptance range. No significant difference in Tmax was evidenced by the non parametric test. Therefore, the BE of the test and reference drug products could be concluded"

ANOVA detected a significant sequence effect in the analysis of AUC_t (p=0.0138), AUC_{inf} (p=0.0126) and C_{max} (p=0.0025) parameters. Since the study was a single-dose design which included only healthy volunteers, rosuvastatin is not an endogenous entity, the washout period was sufficiently long, all pre-dose levels from the second and third periods were zero and the assay was a validated procedure, it may be possible that the observed sequence effect was a random occurrence, without clinical significance.

Safety:

A total of 23 adverse events involving 9 subjects were reported. 16 of the 23 adverse events were judged as non-related. Two adverse events required medical intervention. All the adverse events were mild and were resolved. No deaths, serious or significant other adverse events occurred in this study.

2nd study: A Single-Dose, Comparative Bioavailability Study of Two Formulations of Rosuvastatin 20 mg Tablets Under Fasting Conditions.

Design

The objective of this study was to evaluate the comparative bioavailability between Rosuvastatin 20 mg Tablets (Teva Pharmaceutical Industries Ltd. – Treatment A) and Crestor® 20 mg Tablets (NV AstraZeneca SA, Belgium – Treatment B) after a single-dose in healthy subjects under fasting conditions.

This was an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study, designed to compare the bioavailability of two formulations of rosuvastatin 20 mg tablets administered to healthy male subjects under fasting conditions. Subjects were randomly assigned to one of two dosing sequences AB or BA. Concentrations of rosuvastatin were measured from the samples collected over a 72-hour interval after dosing in each period.
One tablet was administered orally to each subject with 240 ml water after an overnight fast of at least 10 hours. A single oral dose of rosuvastatin as a 1 x 20mg tablet was administered in each study period. The dose phases were separated by a washout period of 14 days.

In each period, 22 blood samples from 21 time points were obtained. Blood samples were collected prior to study drug administration and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after the drug administration in each period.

The study design is appropriate. The number of measurements around the C_{max} and the duration of sample-collection are sufficient.

Bioanalytics

Plasma concentrations of rosuvastatin were determined in plasma samples of volunteers using a Liquid Chromatography / Tandem Mass Spectrometry Method (LC-MS/MS).

Statistics, statistical methods

Pharmacokinetics: parametric ANOVA was applied to log-transformed AUC_{0-t}, C_{max}, AUC_{0-inf}, and untransformed K_{el} and $T_{1/2}$, geometric confidence intervals were calculated for AUC_{0-t}, AUC_{0-inf} and C_{max}; and non-parametric test was applied to T_{max}.

Statistical analysis was applied to quality assured data from all subjects in the final data set. The PROC GLM procedure from SAS® was used.

Criteria for Bioequivalence for rosuvastatin
Test Product vs. Reference Product:

- The 90% confidence intervals of the relative mean plasma rosuvastatin AUC_t and AUC_{inf} of the test to reference product should be between 80-125%.
- The 90% confidence interval of the relative mean plasma rosuvastatin C_{max} of the test to reference product should be between 75-133%.

Results

Table 3. *Descriptive statistics of pharmacokinetic parameters for rosuvastatin (n=27)*

Parameters (Units)	**Geometric mean**	
	Test Product (A)	**Reference Product (B)**
C_{max} (ng/ml)	11.931	11.974
AUC_{o-t} (ng.h/ml)	118.322	117.028
$AUC_{0-\infty}$(ng.h/ml)	126.777	122.431
t_{max}(h)	3.78	3.89
K_{el} (1/h)	0.0420	0.0441
$t_{1/2}$(h)	19.02	16.67

The conventional CI for Log transformed AUCt, AUCinf and Cmax are within the [80; 125]% acceptance range. No significant difference in Tmax was evidenced by the non parametric test. Therefore, the BE of the test and reference drug products could be concluded"

Safety

A total of 28 adverse events involving 13 subjects were reported. 15 of the 23 adverse events were judged as non-related. One adverse event required medical intervention. No deaths, serious or significant other adverse events occurred in this study.

3rd study: A Single-Dose, Comparative Bioavailability Study of Three Formulations of Rosuvastatin 40 mg Tablets Under Fasting Conditions

Design

The objective of this study was to evaluate the comparative bioavailability between Rosuvastatin 40 mg Tablets (Teva Pharmaceutical Industries Ltd.- Treatment A) and two formulations of Crestor® 40 mg Tablets (AstraZeneca Canada Inc., Canada – Treatment B and NV AstraZeneca SA, Belgium – Treatment C) after a single-dose in healthy subjects under fasting conditions.

This was a blinded, single-dose, randomized, three-period, three-sequence, three-treatment, crossover study, designed to evaluate the comparative bioavailability of

three formulations of rosuvastatin 40 mg tablets administered to healthy male subjects under fasting conditions. Subjects were randomly assigned to one of the three dosing sequences ABC, BCA or CAB. Concentrations of rosuvastatin were measured from the samples collected over a 72-hour interval after dosing in each period.
One tablet was administered orally to each subject with 240 ml water after an overnight fast of at least 10 hours. A single oral dose of rosuvastatin as a 1 x 40mg tablet was administered in each study period. The dose phases were separated by a washout period of 14 days.
In each period, 22 blood samples from 21 time points were obtained. Blood samples were collected prior to study drug administration and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after the drug administration in each period.

The study design is appropriate. The number of measurements around the C_{max} and the duration of sample-collection are sufficient. The number of samples per period/subject is 22.

Since the European marketing authorization requires the comparison with a European originator product the American originator has no importance in this case.

Bioanalytics

Plasma concentrations of rosuvastatin were determined in plasma samples of volunteers using a Liquid Chromatography / Tandem Mass Spectrometry Method (LC-MS/MS).

Statistical methods

Pharmacokinetics: parametric ANOVA was applied to log-transformed AUC_{0-t}, C_{max}, AUC_{0-inf}, and untransformed K_{el} and $T_{1/2}$, geometric confidence intervals were calculated for AUC_{0-t}, AUC_{0-inf} and C_{max}; and non-parametric test was applied to T_{max}.

Statistical analysis was applied to quality assured data from all subjects in the final data set. The PROC GLM procedure from SAS® was used.

- Test Product (Treatment A) vs. Reference Product (Treatment C):
  - The 90% confidence intervals of the relative mean plasma rosuvastatin AUC_t and AUC_{inf} of the test to reference product should be between 80-125%.
  - The 90% confidence interval of the relative mean plasma rosuvastatin C_{max} of the test to reference product should be between 75-133%.

Results

Table 5. *Descriptive statistics of pharmacokinetic parameters for rosuvastatin (n=29) (Only the results of Test Product vs. Reference Product are presented and assessed)*

Parameters (Units)	**Geometric Mean**	
	Test Product (A)	**Reference Product (C)**
C_{max} (ng/ml)	18.486	18.790
AUC_{o-t} (ng.h/ml)	180.153	183.650
$AUC_{0-\infty}$(ng.h/ml)	189.946	195.029
t_{max}(h)	3.43	3.76
K_{el} (1/h)	0.0427	0.0417
$t_{1/2}$(h)	17.94	19.53

The conventional CI for Log transformed AUCt, AUCinf and Cmax are within the [80; 125]% acceptance range. No significant difference in Tmax was evidenced by the non parametric test. Therefore, the BE of the test and reference drug products could be concluded**.**

A statistically significant difference ($\alpha = 0.05$) was detected between the three periods of the study in the analysis of the K_{el} ($p=0.0336$) parameter. The Applicant states that all clinical procedures were under strict control and kept the same between the three periods of the study. Hence, it is possible that the observed effect is due solely to chance. The least-squares means of the formulation effect were adjusted for the period effect. Therefore, the final results are not influenced by the statistically significant period effect noticed for the K_{el} parameter.

Safety

A total of 41 adverse events involving 18 subjects were reported. 17 of the 41 adverse events were judged as non-related. All 41 adverse events were judged as mild. There were no deaths or other serious or significant adverse events reported during this study.

Conclusion of the three bioequivalence studies

The results of the bioequivalence studies comply with the requirements of the CPMP/EWP/QWP/1401/98 *Note for Guidance on the Investigation of Bioavailability and Bioequivalence*. Therefore essential similarity for the Applicant's product rosuvastatin and the originator Crestor® (AstraZeneca) tablets has been established.

Biowaiver

For the 10mg strength of Rosuvastatin Teva additional dissolution studies were performed to confirm the adequacy of waiver of additional bioequivalence studies. Accordingly, dissolution was investigated at different pH values and similarity of dissolution was demonstrated at all conditions within the applied product series. As pharmacokinetics of rosuvastatin is linear and all the stipulated biowaiver criteria are fulfilled (CPMP/EWP/QWP/1401/98) additional in vivo studies for the bioequivalence assessment of 10mg rosuvastatin tablets may be waived.

IV.3 Pharmacodynamics

Rosuvastatin is a potent competitive inhibitor of HMG-CoA reductase, belonging to the statins. The HMG-CoA reductase catalyzed reaction is the rate-limiting step of the cholesterol synthesis. Rosuvastatin increases clearance of plasma low-density lipoprotein-cholesterol (LDL-C) by up-regulation of hepatic LDL-C receptors and affects LDL production by decreasing hepatic production of very low-density lipoprotein (VLDL). Rosuvastatin demonstrated dose-dependent effects in reducing low-density lipoprotein cholesterol, total cholesterol, and apolipoprotein (apo) B. Rosuvastatin has also been shown to be highly effective in reducing LDL-C, increasing high-density lipoprotein cholesterol (HDL-C), and producing favourable modifications of other elements of the atherogenic lipid profile. Rosuvastatin is selectively taken up by hepatic cells in vitro and in vivo, with minimal uptake by nonhepatic cells. Rosuvastatin has a high affinity for the predominantly hepatic organic anion transport protein C.

IV.4 Clinical efficacy

The efficacy of rosuvastatin has already been demonstrated during the clinical development of the reference product. No new data have been submitted.

IV.5 Clinical safety

The clinical safety of rosuvastatin has been well established. The bioequivalence studies did not raise any safety concerns.

IV.6 Discussion on the clinical aspects

The application concerns a generic/hybrid application of rosuvastatin. The suggested indications are identical with those of the originator Crestor® (AstraZeneca).

To support the application the Applicant has adequately demonstrated bioequivalence between rosuvastatin Teva and Crestor® (AstraZeneca).

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application concerns a generic version of rosuvastatin. This active substance is widely and safely used, the application of the present product does not pose any new risk.

The submitted documentation is formally adequate and scientifically sound. The benefit/risk assessment is positive.

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for **Rosuvastatin TEVA 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets**, in the treatment of

- primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia) or mixed dyslipidemia (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 hypercholesterolemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL aphaeresis) or if such treatments are not appropriate could be approvable.

V.1 Conditions for the marketing authorisation

V.1.1 Requirements for specific post-marketing obligations

Not needed.

V.1.2 Pharmacovigilance system

The RMS considers that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reactions suspected of occurring either in the Community or in a third country.

V.1.3 Legal status

Prescription-only medicine.

V.2 Summary of Product Characteristics (SmPC)

The SmPC is acceptable.

V.3 Package Leaflet and 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 language used for the purpose of user testing the PIL was Hungarian.

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. UPDATE. STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
New batch release (including control testing) site IA	HU/H/0218/001-004/001	N	16. 06. 2010	15. 07. 2010	Approval	N
Alternative packaging material source IB	HU/H/0218/001-004/002	N	21. 07. 2010	20. 08. 2010	Approval	N
New active substance manufacturer IB	HU/H/0218/001-004/004	N	06. 07. 2011	06. 08. 2011	Approval	N
New active substance specification (acceptance limits decreased) IA	HU/H/0218/001-004/005	N	01. 08. 2011	31. 08. 2011	Approval	N
New active substance identification test method IB	HU/H/0218/001-004/006	N	01. 08. 2011	31. 08. 2011	Approval	N
Harmonisation with the SmPC of the reference product IB	HU/H/0218/001-004/007	Y	18. 02. 2011	20. 03. 2011	Approval	N
Updating the product information in line with the Core Safety Profile of rosuvastatin Teva, IB	HU/H/0218/001-004/0010	Y	03. 11. 2011	03. 12. 2011	Approval	N
Change in the polymorphism testing method IB	HU/H/0218/001-004/012	N	31. 01. 2012	31. 01. 2012	Approval	N
Change in the SmPC within an MRP procedure IB	HU/H/0218/001-004/013	Y	30.06. 2012	29. 06. 2012	Approval	N