Public Assessment Report

Scientific discussion

Rovasyn
5 mg, 10 mg, 20 mg and 40 mg
Film-coated tablets
(Rosuvastatin)

DK/H/2232/001-004/DC

22 March 2014

This module reflects the scientific discussion for the approval of Rovasyn. The procedure was finalised on 4 September 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 Rovasyn 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets, from Codal Synto Ltd.

The product is indicated for treatment of hypercholesterolaemia and prevention of cardiovascular events.
A comprehensive description of the indications and posology is given in the SmPC.

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Crestor 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets which has been registered in Denmark by AstraZeneca A/S since 2003 (10 mg, 20 mg and 40 mg) and 2005 (5 mg).

The reference products used for the bioequivalence studiess are Crestor 10 mg and 40 mg film-coated tablets, AstraZeneca UK, sourced from Cyprus.

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

II. QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 5 mg, 10 mg, 20 mg or 40 mg of rosuvastatin as rosuvastatin calcium, respectively.

The 5 mg tablets are yellow, round, biconvex, coated tablets, embossed ‘ROS’ over ‘5’ on one side and nothing on the other, with diameter 7 mm.
The 10 mg tablets are pink, round, biconvex, coated tablets, embossed ‘ROS’ over ‘10’ on one side and nothing on the other, with diameter 7 mm.
The 20 mg tablets are pink, round, biconvex, coated tablets, embossed ‘ROS’ over ‘20’ on one side and nothing on the other, with diameter 9 mm.
The 40 mg tablets are pink, oval, biconvex, coated tablets, embossed ‘ROS’ on one side and ‘40’ on the other side, with dimensions 6.8 x 11.4 mm.

The tablets are packed in OPA-Al-PVC/Al blisters in pack sizes of: 14, 20, 28, 30, 56, 60, 84, 90 and 100 film coated tablets. However, not all pack sizes may be marketed.

The excipients in the tablet core are: cellulose microcrystalline PH-101; silica colloidal anhydrous; crospovidone type A; cellulose microcrystalline PH-102; lactose monohydrate; and magnesium stearate.
The film-coating consists of: hypromellose; titanium dioxide (E171); lactose monohydrate; triacetin; iron oxide yellow (E172) (5 mg tablets only); and iron oxide red (E172) (10 mg, 20 mg and 40 mg tablets only).

The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The documentation concerning the active substance, rosuvastatin calcium, is presented as an Active Substance Master File.

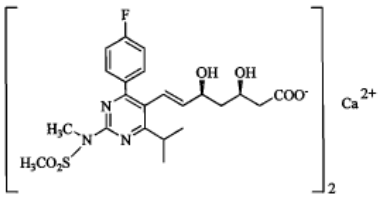
The active substance rosuvastatin calcium is not described in the European Pharmacopoeia.

Rosuvastatin calcium is an off-white to light yellow coloured amorphous powder. It is insoluble in water and soluble in N, N-dimethyl formamide, acetone and acetonitrile. It is optically active.

INN: Rosuvastatin calcium

- Chemical name(s): 3R,5S)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-3,5-dihydroxy-6(E)-heptenoic acid calcium salt (2:1)
- 6-Heptanoic acid-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-,calcium salt (2:1), (3R,5S,6E)
- Bis[(E)-7[4-(4-fluorophenyl)-6-isopropyl-2-(methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt

Molecular structure:



Molecular formula: $C_{44}H_{54}F_2N_6O_{12}S_2 * Ca$
Molecular mass: 1001.14

Rosuvastatin calcium consists of two asymmetric carbon atoms; hence two pairs of isomers are possible.

No European Pharmacopeia monograph exists for rosuvastatin calcium and the control tests and specifications for drug substance have been set according to Ph.Eur. general requirement to active substance and EU guidance.

Based on the solubility of the active substance the MAH's active substance specification includes a test for particle size distribution to ensure a finished product of consistent quality.

Stability studies have been performed with the drug substance in accordance with general ICH requirements. No significant changes in any parameters were observed for the periods investigated.
The proposed re-test period is justified and acceptable.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.
Two manufacturing sites are proposed for the manufacturing and control of the product and manufacturing processes at both sites have been described.

The product specification cover appropriate parameters for this dosage form. Acceptable validations of the analytical methods according to EU/ICH requirements have been presented.

The applied acceptance criteria have been acceptably justified according to EU/ICH requirements, batch results and stability data.

Batch analysis has been performed of 21 batches (of both manufacturing sites). The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 30 months with the storage statement "store in the original package in order to protect from light" is justified and accepted.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of rosuvastatin are well known. As rosuvastatin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers 8 publications up to year 2012. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Rovasyn 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rosuvastatin is a well-known active substance with established efficacy and tolerability. As rosuvastatin is a widely used, well-known active substance, the applicant has not provided additional studies (apart from supportive bioequivalence studies referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical overview report refers 9 publications up to year 2012. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

To support the application, the MAH has submitted as report 2 bioequivalence studies in which the pharmacokentic profile of the test product Rovasyn 10 mg and 40 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Crestor 10 mg and 40 mg film-coated tablets, AstraZeneca UK, sourced from Cyprus.

Biowaiver

Based on the bioequivalence studies performed on the 10 mg and 40 mg strengths it is proposed to waive studies on the 5 mg and 20 mg strengths.

The qualitative composition is the same for all strengths.
The products are manufactured in the same manufacturing site and by the same manufacturing process.
Rosuvastatin has linear pharmacokinetics over the proposed dosage range.
The 10 mg and 20 mg strengths are quantitatively proportional. In case of the 5 mg and 10 mg strengths, the amount of core excipients are the same and the amount of filler (lactose monohydrate) is changed to account for the change in amount of active substance. Therefore, the 10 mg strength was considered suitable to cover the 20 mg and the 5 mg strengths.
The 40 mg strength is not proportional in composition and waiving of the 5 mg and 20 mg is therefore based on the 10 mg strengths.

Bioequivalence studies

10 mg study
The study was a two-stage, open-label, randomized, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 14 days between the two administrations. A 10 mg film-coated tablet of Rovasyn (Test) or one 10 mg film-coated tablet of Crestor (Reference) was administered in each period.
Blood samples were collected pre-dosing and at various time-points up to 72.0 hours post administration of a single-dose 10 mg film-coated tablet with 200 ml of water for the analyses of rosuvastatin.

36 healthy male and female volunteers (all Caucasian) were enrolled in the first stage of the study. The second stage was not initiated because of the results obtained in the first stage. All 36 subjects completed the study.

The primary pharmacokinetic parameters calculated for rosuvastatin were AUC_{0-72} and C_{max}.

Criteria for conclusion of bioequivalence:

Stage	Outcome	Action
1	80<LowerLimit CI-1* < UpperLimit CI -1*<125	Stop the trial and accept bioequivalence
	Geometric mean ratio T/R outside 80 -125	Stop the trial and reject bioequivalence Or Calculate sample size** and continue to Stage 2
2	80<LowerLimit CI-2* < UpperLimit CI -2*<125	Accept bioequivalence
	Geometric mean ratio T/R outside 80 -125	Reject bioequivalence

*CI-1 = 94.12% Confidence interval after the first stage;
*CI- 2 = Confidence interval of the combined stages; it's value shall be 94.12%.
** After stage 1 is completed the total sample size (stage 1 + final stage) will be evaluated based on the planned 95% geometric mean ratio, the intra-subject variability from the stage 1 of the most variable pharmacokinetic parameter and alpha=0.0294, rounded up to even number.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

n=36					
Treatment	**AUC_{0-72}** pg/ml/h	**$AUC_{0-\infty}$** pg/ml/h	**C_{max}** pg/ml	**t_{max}** h	**$T_{1/2}$** h
Test	70801.010 (±43225.740)	74925.300 (±43829.425)	6534.001 (±3895.380)	5.000 (0.500-7.000)	14.432
Reference	71497.506 (±43412.537)	74944.411 (±43887.593)	6290.629 (±3850.692)	4.250 (0.500–7.000)	14.546
***Ratio (94.12% CI)**	97.444 (88.126-107.747)	98.786 (89.984-108.450)	103.174 (89.894-118.415)	-	-
CV (%) (intra-subject)	22.070 %	-	30.575 %	-	-

AUC_{0-t}	Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t} in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max}	Maximum plasma concentration
t_{max}	**Time until Cmax is reached**

**ln-transformed values*

The results confirm bioequivalence between Rovasyn 10 mg film-coated tablets and Crestor 10 mg film-coated tablets according to the current regulatory requirements.
The products were well tolerated and the safety profiles of the two products are considered comparable.

40 mg study
The study was a two-stage, open-label, randomized, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 14 days between the two administrations. A 40 mg film-coated tablet of Rovasyn film-coated tablets (Test) or one 40 mg film-coated tablet of Crestor (Reference) was administered in each period.
Blood samples were collected pre-dosing and at various time-points up to 72.0 hours post administration of a single-dose 40 mg film-coated tablet with 200 ml of water for the analyses of rosuvastatin.

36 healthy male (20) and female (16) subjects were enrolled in the first stage as per the study protocol; as bioequivalence was already reached after the first stage, the second stage was not required. All subjects completed the study and were used for the statistical evaluation of the pharmacokinetic data.

The primary pharmacokinetic parameters calculated for rosuvastatin were AUC_{0-72} and C_{max}.

Criteria for conclusion of bioequivalence:

Stage	Outcome	Action
1	80<LowerLimit CI-1* < UpperLimit CI -1*<125	Stop the trial and accept bioequivalence
	Geometric mean ratio T/R outside 80 -125	Stop the trial and reject bioequivalence Or Calculate sample size** and continue to Stage 2
2	80<LowerLimit CI-2* < UpperLimit CI -2*<125	Accept bioequivalence
	Geometric mean ratio T/R outside 80 -125	Reject bioequivalence

*CI-1 = 94.12% Confidence interval after the first stage;
*CI- 2 = Confidence interval of the combined stages; it's value shall be 94.12%.
** After stage 1 is completed the total sample size (stage 1 + final stage) will be evaluated based on the planned 95% geometric mean ratio, the intra-subject variability from the stage 1 of the most variable pharmacokinetic parameter and alpha=0.0294, rounded up to even number.

Results

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

n = 36					
Treatment	**AUC_{0-72}** pg/ml/h	**$AUC_{0-\infty}$** pg/ml/h	**C_{max}** pg/ml	**t_{max}** h	**$T_{1/2}$** h
Test	227294.491 (±89041.855)	237955.391 (±94504.365)	20136.358 (±10013.562)	5.000 (0.500 – 7.000)	17.529 (±7.153)
Reference	243089.101	251562.901	22931.066	4.000	15.236
	(±94447.335)	(±100769.242)	(±15896.319)	(0.500 – 7.000)	(±5.250)
***Ratio (94.12% CI)**	93.867 (87.055- 101.212)	94.942 (88.139- 102.271)	93.233 (82.558- 105.288)	-	-
CV (%) (intra subject)	19.073%	-	31.233%	-	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t} in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} **Time until Cmax is reached**

**ln-transformed values*

The results confirm bioequivalence between Rovasyn 40 mg film-coated tablets and Crestor 40 mg film-coated tablets according to the current regulatory requirements.
The products were well tolerated and the safety profiles of the two products are considered comparable.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Rovasyn 10 mg and 40 mg film-coated tablets are considered bioequivalent with Crestor 10 mg and 40 mg film-coated tablets, respectively.
The results of the study with the 10 mg formulation can be extrapolated to the other strengths, 5 mg and 20 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The RMS 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

Rosuvastatin was first approved in 2002, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of rosuvastatin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described 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 identification and notification of any a potential risks occurring either in the Community or in a third country.

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 language used for the purpose of user testing the PIL was Czech.
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.

The test consisted of: a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rovasyn 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Crestor. 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Rovasyn with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 4 September 2013. Rovasyn was authorised in Denmark on 19 December 2013.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), no routine PSURs are required for this product.

The date for the first renewal will be: 4 September 2018.

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