Public Assessment Report

Decentralised Procedure

Rosuvastatin 5mg film-coated tablets
PL 17871/0215; UK/H/5702/001/DC

Rosuvastatin 10mg film-coated tablets
PL 17871/0216; UK/H/5702/002/DC

Rosuvastatin 20mg film-coated tablets
PL 17871/0217; UK/H/5702/003/DC

Rosuvastatin 40mg film-coated tablets
PL 17871/0218; UK/H/5702/004/DC

Rosuvastatin Zinc

Jenson Pharmaceutical Services Limited
LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) Rosuvastatin 5, 10, 20 & 40mg film-coated tablets (PL 17871/0215-0218; UK/H/5702/001-004/DC). Rosuvastatin 5, 10, 20 & 40mg film-coated tablets will be termed Rosuvastatin film-coated tablets throughout this PAR for ease of reading. It explains how Rosuvastatin film-coated tablets were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Rosuvastatin film-coated tablets, patients should read the Package Leaflet or contact their doctor or pharmacist.

What are Rosuvastatin film-coated tablets and what are they used for?
Rosuvastatin film-coated tablets are a ‘generic medicine’. This means that they are similar to a ‘reference medicine’, already authorised in the European Union (EU) called Crestor film-coated tablets.

Rosuvastatin film-coated tablets are used for the following in adults, adolescents and children 6 years and over:

- To treat high cholesterol levels, when there is a risk of a heart attack or stroke, and where changing diet and taking more exercise are not enough to correct the cholesterol levels
- To reduce the risk of heart attack, stroke or related health problems in patients with other risk factors. Heart attack, stroke and other problems can be caused by atherosclerosis, a build-up of fatty deposits in the arteries.

How do Rosuvastatin film-coated tablets work?
Rosuvastatin film-coated tablets belong to a group of medicines called statins.

Rosuvastatin is used to correct the levels of fatty substances in the blood called “lipids”, the most common of which is cholesterol. There are different types of cholesterol found in the blood – ‘bad’ cholesterol (LDL-C) and ‘good’ cholesterol (HDL-C). • Rosuvastatin can reduce the ‘bad’ cholesterol and increase the ‘good’ cholesterol. • It works by helping to block the body’s production of ‘bad’ cholesterol. It also improves the body’s ability to remove it from the blood.

For most people, high cholesterol does not affect the way they feel because it does not produce any symptoms. However, if it is left untreated, fatty deposits can build up in the walls of blood vessels causing them to narrow. Sometimes, these narrowed blood vessels can get blocked, which can cut off the blood supply to the heart or brain leading to a heart attack or a stroke. By lowering cholesterol levels, this reduces the risk of having a heart attack, a stroke or related health problems.

Each film-coated tablet contains 5, 10, 20 & 40mg rosuvastatin (as rosuvastatin zinc).

How are Rosuvastatin film-coated tablets used?
Rosuvastatin film-coated tablets should be taken once daily and swallowed whole with a drink of water. They can be taken any time of the day, with or without food; however, patients should try and take their tablets at the same time every day.

Please read Section 3 of the Package Leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.
This medicine can only be obtained with a prescription.

**How have Rosuvastatin film-coated tablets been studied?**
Because Rosuvastatin film-coated tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Crestor film-coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Rosuvastatin film-coated tablets?**
Because Rosuvastatin film-coated tablets are a generic medicine, their benefits and possible side-effects are taken as being the same as the reference medicine, Crestor film-coated tablets.

For further information, please see Section 4 the Package Leaflet.

**Why are Rosuvastatin film-coated tablets approved?**
It was concluded that, in accordance with EU requirements, Rosuvastatin film-coated tablets have been shown to have comparable quality and be bioequivalent to Crestor film-coated tablets. Therefore, the view was that, as for Crestor film-coated tablets, the benefits outweigh the identified risks and it was recommended that Rosuvastatin film-coated tablets can be approved for use.

**What measures are being taken to ensure the safe and effective use of Rosuvastatin film-coated tablets?**
A risk management plan (RMP) has been developed to ensure that Rosuvastatin film-coated tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Rosuvastatin film-coated tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Rosuvastatin film-coated tablets**
Iceland and the UK agreed to grant marketing authorisations for Rosuvastatin film-coated tablets on 11 January 2015. The marketing authorisations in the UK were granted on 30 January 2015.

The full PAR for Rosuvastatin film-coated tablets follows this summary.

For more information about treatment with Rosuvastatin film-coated tablets, read the Package Leaflet or contact your doctor or pharmacist.

This summary was last updated in March 2015.
TABLE OF CONTENTS

I  Introduction  Page 5
II Quality aspects  Page 7
III Non-clinical aspects  Page 8
IV  Clinical aspects  Page 9
V  User consultation  Page 13
VI Overall conclusion, benefit/risk assessment and recommendation  Page 13

Table of content of the PAR update for MRP and DCP  Page 17
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member State (CMS) considered that the applications for Rosuvastatin 5, 10, 20 & 40mg film-coated tablets (PL 17871/0215-0218; UK/H/5702/001-004/DC).could be approved.

These products are prescription-only medicines indicated for the:

- **treatment of hypercholesterolaemia**
  In 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.

- **prevention of cardiovascular events**
  The prevention of major cardiovascular events in patients who are estimated to have a high risk of a first cardiovascular event, as an adjunct to correction of other risk factors.

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. Rosuvastatin increases the number of hepatic low-density lipoprotein (LDL) receptors on the cell-surface, enhancing uptake and catabolism of LDL. It also inhibits the hepatic synthesis of very low-density lipoproteins (VLDL), thereby reducing the total number of VLDL and LDL particles.

These applications were made under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the reference medicinal product Crestor 5, 10, 20 & 40mg film-coated tablets, which were originally authorised to AstraZeneca in the Netherlands in November 2002. The reference products in the UK are Crestor 5, 10, 20 & 40mg film-coated tablets, which have been licensed to AstraZeneca UK Limited since 26 October 2005.

The RMS for these procedures was the UK and the CMS was Iceland.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being generic medicinal products of the originator products that have been licensed for over 10 years.

Since these products are intended for generic substitution, this will not lead to an increased exposure to the environment. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

With the exception of the two following bioequivalence studies, no new clinical data were provided with these applications:

- A bioequivalence study to compare the pharmacokinetics of the applicant’s Rosuvastatin 20mg film-coated tablets versus those of the reference product, Crestor 20mg film-coated tablets, in healthy subjects under fasting conditions.
• A bioequivalence study to compare the pharmacokinetics of the applicant’s Rosuvastatin 40mg film-coated tablets versus those of the reference product, Crestor 40mg film-coated tablets, in healthy subjects under fasting conditions.

Both bioequivalence studies were conducted in-line with current Good Clinical Practice.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, as certification that acceptable standards of GMP are in place at those non-Community sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

The RMS and CMSs considered that the applications could be approved at the end of procedure (Day 210) on 11 January 2015. After a subsequent national phase, a licence was granted in the UK on 30 January 2015.

II QUALITY ASPECTS
II.1 Introduction
These applications are submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The applicant has specified Crestor 5, 10, 20 & 40mg film-coated tablets (AstraZeneca) as the EU reference medicinal products.

Rosuvastatin film-coated tablets are white to almost white, film-coated tablets, as follows:
• 5mg - round, slightly biconvex tablet with a stylised “E” engraved on the one side and “591” on the other side
• 10mg - round, slightly biconvex tablet with a stylised “E” engraved on the one side and “592” on the other side
• 20mg - round, slightly biconvex tablet with a stylised “E” and “593”engraved on the one side and nothing on the other side
• 40mg – oval shaped, slightly biconvex tablet with a stylised “E” and “ 594”engraved on one side and nothing on the other side

Each tablet contains 5, 10, 20 or 40mg of the active substance rosuvastatin (as rosuvastatin zinc). The excipients in each tablet are lactose monohydrate, crospovidone, povidone, magnesium stearate, and Opadry White, which is composed of polyvinyl alcohol (E1203), talc (E553b), Macrogol 3350 and titanium dioxide (E171).

The tablets are presented in polyamide/polyvinylchloride (PVC)/aluminium blisters. These are packaged into cardboard boxes in pack sizes of 28 and 30 film-coated tablets. Not all pack sizes are marketed.
II.2 DRUG SUBSTANCE
rINN: Rosuvastatin zinc
Chemical Name: \((3R,5S,6E)-7-\{4-(4-Fluorophenyl)-6-(1-methylethyl)-2-methyl[methylsulfonyl]amino\}-5-pyrimidinyl\}-3,5-dihydroxy-6-heptenoic acid zinc salt (2:1)

Structure:

\[
\text{Structure Image}
\]

Molecular Formula: \(C_{44}H_{54}F_2N_6O_{12}S_2Zn\)

Molecular Weight: 1026.46

Appearance: A white to off-white crystalline powder

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT
Pharmaceutical development
The objective of the pharmaceutical development was to produce tablets containing 5, 10, 20 and 40mg rosuvastatin (as rosuvastatin zinc) that could be considered to be generic medicinal products of Crestor 5, 10, 20 & 40mg film-coated tablets (AstraZeneca). Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. Comparable dissolution and impurity profiles have been provided for these products versus their respective reference products.
All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry White which is controlled to a suitable in-house specification and complies with current EU regulations concerning colourants. The individual components of Opadry White comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of human origin are used in the final products. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals, under the same conditions as milk for human consumption.

None of the excipients are sourced from genetically modified organisms.

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale and has shown satisfactory results. The process validation protocol to be followed for full production-scale batches submitted is also satisfactory.

Finished Product Specification
The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years with the storage conditions “Store in the original package in order to protect from light”.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of rosvastatin are well-established. As rosvastatin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is, thus, appropriate.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment (ERA). As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the marketing authorisation for the proposed product.

IV Clinical aspects
IV.1 Introduction
With the exception of the below bioequivalence studies, no new clinical data have been submitted for these applications. The applicant’s clinical overview on the clinical pharmacology, efficacy and safety of the product has been written by an appropriately
II. 2 Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence studies:

An open-label, randomised, two-way, crossover, single-dose bioequivalence study to compare the pharmacokinetics of the test product Rosuvastatin 40mg film-coated tablets versus the reference product Crestor 40mg film-coated tablets (AstraZeneca) in healthy male subjects under fasted conditions.

Volunteers received the test or reference treatment after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. The two treatment periods were separated by a minimum 7-day washout period.

The main pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>INTRA-SUBJECT C.V. (%)</th>
<th>GEOMETRIC LSMEANS *</th>
<th>RATIO (%)</th>
<th>90% CONFIDENCE LIMITS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max</td>
<td>23.8</td>
<td>16.998</td>
<td>17.500</td>
<td>97.13</td>
</tr>
<tr>
<td>AUC_T</td>
<td>16.2</td>
<td>159.030</td>
<td>160.600</td>
<td>99.02</td>
</tr>
</tbody>
</table>

* units are ng/mL for C_max and ng h/mL for AUC_T

The 90% confidence intervals were within the acceptance criteria of 80.00%-125.00%.

Based on these results, the test product Rosuvastatin 40mg film-coated tablets can be considered to be bioequivalent with the reference product Crestor 40mg film-coated tablets.

This study was performed using a pilot scale formulation of Rosuvastatin 40 mg film-coated tablets and the bioequivalence of the test and reference formulations was proved. The study was performed in accordance with the actual European Guidelines on the Investigation of Bioequivalence and its results were judged by the authorities as an adequate proof of the bioequivalence between the test and the reference products. However, at the time of the execution of the study, in compliance with the existing guidelines, no incurred sample reanalysis was performed.

Although the bioanalytical method for the determination of rosuvastatin was carefully validated and the possible back-conversion of rosuvastatin lactone metabolite to rosuvastatin was evaluated and significant impact on the plasma/concentration data was excluded during the bioanalytical method validation, the applicant repeated the study complying with the present regulatory requirements for bio analytical validation using the 20mg formulation, which is presented below.
An open-label, randomised, two-way, crossover, single-dose bioequivalence study to compare the pharmacokinetics of the test product Rosuvastatin 20mg film-coated tablets versus the reference product Crestor 20mg film-coated tablets (AstraZeneca) in healthy male subjects under fasted conditions.

Volunteers received the test or reference treatment after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. The two treatment periods were separated by a minimum 7-day washout period.

The main pharmacokinetic results are presented below:

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<tr>
<th>PARAMETER</th>
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<th>GEOMETRIC LSMEANS *</th>
<th>RATIO (%)</th>
<th>90% CONFIDENCE LIMITS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEST</td>
<td>REFERENCE</td>
<td></td>
<td>LOWER</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>17.9</td>
<td>8.997</td>
<td>9.508</td>
<td>94.63</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt;</td>
<td>13.7</td>
<td>85.481</td>
<td>86.430</td>
<td>98.90</td>
</tr>
</tbody>
</table>

* units are ng/mL for C<sub>max</sub> and ng·h/mL for AUC<sub>T</sub>

The 90% confidence intervals were within the acceptance criteria of 80.00%-125.00%.

Based on these results, the test product Rosuvastatin 20mg film-coated tablets can be considered to be bioequivalent with the reference product Crestor 20mg film-coated tablets.

Considering the bioanalytical method used in both bioequivalence studies was identical and as the 5, 10, 20 and 40mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the extrapolation of results and conclusions from the bioequivalence study on the 20mg strength to the other strengths is justified. Therefore, bioequivalence has been shown between the 5, 10, 20 and 40mg strengths of product and their respective reference products.

**IV.3 Pharmacodynamics**

No new pharmacodynamic data are required for these applications and none have been submitted.

**IV.4 Clinical efficacy**

No new efficacy data were submitted with these applications and none were required.

**IV.5 Clinical safety**

With the exception of the safety data collected during the bioequivalence studies, no new safety data were submitted with these applications and none were required. No new unexpected treatment-related adverse events were observed during the trial.

**IV.6 Risk Management Plan (RMP)**

The marketing authorisation holder has submitted an RMP 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 Rosuvastatin film-coated tablets.
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below.

**Important identified risks**

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal liver function and use in patients with liver disease</td>
<td>The risk of abnormal liver function associated with the use of the medicinal product and risks associated with the use of the medicine in patients with liver disease are described in the SPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 and advise that rosuvastatin should not be used in patients with active liver disease and should be used with caution in patients with history of liver disease.</td>
<td>None</td>
</tr>
<tr>
<td>Effects on the kidney and use in patients with kidney impairment</td>
<td>Effects of the medicine on the kidneys and the risks associated with the use of the medicinal product in patients with severe kidney disease are described in the SPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 and state that no dose adjustment of rosuvastatin is necessary in patients with mild to moderate kidney problems and that rosuvastatin should not be used in patients with severe kidney problems.</td>
<td>None</td>
</tr>
<tr>
<td>Muscle injury (myopathy and rhabdomyolysis)</td>
<td>The risk of muscle injury (myopathy and rhabdomyolysis) associated with the use of the medicinal product is described in the SPC Sections 4.2, 4.3, 4.4, 4.5 and 4.8, and advise that rosuvastatin should not be used in patients with myopathy and in patients with pre-disposing factors for myopathy/rhabdomyolysis.</td>
<td>None</td>
</tr>
<tr>
<td>Simultaneous use with ciclosporin</td>
<td>The risk associated with the simultaneous use of the medicine with ciclosporin is described in the SPC Sections 4.2, 4.3, 4.4 and 4.5, and advise that rosuvastatin should not be</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<tr>
<td>Simultaneous use of warfarin</td>
<td>The risks associated with the simultaneous use of warfarin with the medicinal product are described in the SPC Section 4.5. Appropriate monitoring of INR is advised in patients treated simultaneously with warfarin.</td>
<td>None</td>
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<tr>
<td>Interstitial lung disease</td>
<td>The risk of interstitial lung disease associated with the use of the medicinal product is described in the SPC Sections 4.4 and 4.8. If it is suspected that a patient has developed interstitial lung disease statin therapy should be discontinued.</td>
<td>None</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>The risk of diabetes mellitus associated with the use of the medicinal product is described in the SPC Sections 4.4 and 4.8, and appropriate advice to monitor patients at risk is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Use in pregnancy</td>
<td>The risks associated with use of the medicinal product during pregnancy are described in the SPC Sections 4.3, 4.6 and 5.3, and advise that rosuvastatin should not be used in pregnant women.</td>
<td>None</td>
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**Important potential risks**

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<tr>
<th>Important potential risks</th>
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<tr>
<td>Severe skin reactions</td>
<td>The risks of severe skin reactions associated with use of the medicinal product are described in the SPC Section 4.8.</td>
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<td>None</td>
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**Missing information**

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<tr>
<td>Use in children</td>
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<td>The SPC Sections 4.2, 4.4, 4.5 and 4.8 state that limited information is available</td>
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<tr>
<td>Safety concern</td>
</tr>
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<td>--------------------------------------</td>
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<tr>
<td>Use in breastfeeding women</td>
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IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications.

V User consultation
A user consultation with target patient groups on the PIL has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The application includes an adequate review of published non-clinical and clinical data concerning the efficacy and safety of rosuvastatin. The test products Rosuvastatin 5, 10, 20 & 40mg film-coated tablets can be considered bioequivalent to the reference products Crestor 5, 10, 20 & 40mg film-coated tablets (AstraZeneca) film-coated tablets. The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

The currently approved labels are listed below:
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached Y/N (version)</th>
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