UK Public Assessment Report

Simvastatin 10 mg Film-coated Tablets
Simvastatin 20 mg Film-coated Tablets
Simvastatin 40 mg Film-coated Tablets

PL 24668/0156-0158

Caduceus Pharma Limited
Simvastatin 10 mg, 20 mg and 40 mg Film-coated Tablets

Lay Summary
Simvastatin 10 mg Film-coated Tablets
Simvastatin 20 mg Film-coated Tablets
Simvastatin 40 mg Film-coated Tablets
(simvastatin)

This is a summary of the Public Assessment Report (PAR) for Simvastatin 10 mg, 20 mg and 40 mg Film-coated Tablets (PL 24668/0156-0158). Simvastatin 10 mg, 20 mg and 40 mg Film-coated Tablets will be referred to as Simvastatin 10 mg, 20 mg and 40 mg Tablets throughout this report, for ease of reading. It explains how Simvastatin 10 mg, 20 mg and 40 mg Tablets were assessed and their authorisation 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 Simvastatin 10 mg, 20 mg and 40 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Simvastatin 10 mg, 20 mg and 40 mg Tablets and what are they used for?
These medicines are the same as Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 30306/0033-0036), which are already authorised. The company that makes Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 30306/0033-0036), Actavis Group PTC ehf, has agreed that its scientific data can be used as a basis for the grant of identical licences for Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 24668/0156-0158).

Simvastatin 10 mg, 20 mg and 40 mg Tablets are used:
- to lower cholesterol and triglycerides in the blood when a low fat diet and other measures (such as exercise, weight loss) have failed (primary hypercholesterolaemia or mixed hyperlipidaemia).
- to lower inherited high levels of cholesterol in your blood (homozygous familial hypercholesterolemia), together with dieting and other treatments (e.g. LDL-apheresis), or when such treatments are not appropriate.
- to reduce the risk of coronary heart disease if you have hardening of the arteries (arteriosclerosis) or diabetes, even if your cholesterol levels are normal, together with dieting and other treatments.

How do Simvastatin 10 mg, 20 mg and 40 mg Tablets work?
Simvastatin 10 mg, 20 mg and 40 mg Tablets contain the active substance simvastatin, which belongs to a group of medicines known as statins. These work by reducing the amount of total cholesterol, ‘bad’ cholesterol (LDL cholesterol), and certain fatty substances called triglycerides in your blood. In addition, simvastatin raises levels of ‘good’ cholesterol (HDL cholesterol). You should stay on a cholesterol-lowering diet while taking these medicines.

How are Simvastatin 10 mg, 20 mg and 40 mg Tablets used?
One Simvastatin 10 mg, 20 mg or 40 mg Tablet should be taken by mouth once a day, in the evening, with or without food. The prescribing doctor will determine the appropriate tablet strength for the patient and may adjust the dose after at least 4 weeks to a maximum of 80 mg a day. (The 80mg dose is only recommended in adult
patients with very high cholesterol levels and at high risk of heart disease problems who have not reached their cholesterol goal on lower doses).

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Simvastatin 10 mg, 20 mg and 40 mg Tablets can be only be obtained with a prescription.

**What benefits of Simvastatin 10 mg, 20 mg and 40 mg Tablets have been shown in studies?**
Simvastatin 10 mg, 20 mg and 40 mg Tablets are considered identical to the previously granted marketing authorisations for Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 30306/0033-0036), with the same benefits and risks. No new studies have been provided for Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 24668/0156-0158) but reference is made to the studies for Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 30306/0033-0036).

**What are the possible side effects from Simvastatin 10 mg, 20 mg and 40 mg Tablets?**
Like all medicines, these medicines can cause side effects, although not everybody gets them.

For information about side effects that may occur with using Simvastatin 10 mg, 20 mg and 40 mg Tablets, please refer to the package leaflet or the Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency website.

**Why are Simvastatin 10 mg, 20 mg and 40 mg Tablets approved?**
The MHRA decided that the benefits of Simvastatin 10 mg, 20 mg and 40 mg Tablets outweigh the risks, and recommended that these products be approved for use.

**What measures are being taken to ensure the safe and effective use of Simvastatin 10 mg, 20 mg and 40 mg Tablets?**
A Risk Management Plan (RMP) has been developed to ensure that Simvastatin 10 mg, 20 mg and 40 mg Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet for Simvastatin 10 mg, 20 mg and 40 mg 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 Simvastatin 10 mg, 20 mg and 40 mg Tablets**
Marketing authorisations were granted to Caduceus Pharma Limited, in the UK, for Simvastatin 10 mg, 20 mg and 40 mg Tablets on 05 May 2015.

For more information about taking Simvastatin 10 mg, 20 mg and 40 mg Tablets, read the package leaflet, or contact your doctor or pharmacist.
This summary was last updated in June 2015.

The full PAR for Simvastatin 10 mg, 20 mg and 40 mg Tablets follows this summary.
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I  Introduction

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations to Caduceus Pharma Limited for the medicinal products Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 24668/0156-0158) on 05 May 2015.

Simvastatin 10 mg, 20 mg and 40 mg Tablets are indicated for:

- **Hypercholesterolaemia**
  - Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate
  - Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

- **Cardiovascular prevention**
  - Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy.

Simvastatin 10 mg, 20 mg and 40 mg Tablets are prescription-only medicines (legal status POM).

These applications were submitted as abridged simple national applications, according to Article 10c of Directive 2001/83/EC, as amended. These applications cross-refer, and claim to be identical, to Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 30306/0033-0036), currently held by the marketing authorisation holder Actavis Group PTC ehf. These licences were granted to Actavis Group PTC ehf (PL 30306/0033-0036) in the UK on 15 September 2008, via a Mutual Recognition procedure with the Netherlands as RMS (NL/H/1177/01/MR).

These medicinal products contain the active substance simvastatin. Simvastatin has been shown to reduce both normal and elevated LD- C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases HDL C and reduces plasma TG. As a result of these changes the ratios of total- to HDL C and LDL- to HDL C are reduced.

No new data have been submitted and none are required for these simple applications, as the data are identical to those of the previously granted, cross-referred products.
II Quality aspects

II.1 Introduction
These are simple, piggyback (informed consent) applications for Simvastatin 10 mg, 20 mg and 40 mg Tablets submitted under Article 10c of Directive 2001/83/EC, as amended.

The applications cross-refer to Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 30306/0033-0036). The current applications are considered valid.

Simvastatin 10 mg Tablets are formulated as peach-coloured, oval, biconvex, film-coated tablets, scored on one side. The tablets can be divided into equal halves.

Simvastatin 20 mg Tablets are formulated as tan-coloured, oval, biconvex, film-coated tablet, scored on one side. The tablets can be divided into equal halves.

Simvastatin 40 mg Tablets are formulated as brick-red coloured, oval, biconvex, film-coated tablets, scored on one side. The tablets can be divided into equal halves.

Simvastatin 10 mg, 20 mg and 40 mg Tablets contain 10 mg, 20 mg and 40 mg, respectively, of the active substance simvastatin. The excipients present in the tablet core of each strength tablet are: lactose monohydrate, microcrystalline cellulose (E460), pregelatinised maize starch, butylhydroxyanisole (E320), ascorbic acid (E300), anhydrous citric acid (E330), colloidal anhydrous silica (E551), talc (E553b) and magnesium stearate (E470b). The excipients present in the tablet coat of each strength tablet are: hypromellose (E464), red iron oxide (E172), yellow iron oxide (E172), triethyl citrate (E1505), titanium dioxide (E171), talc (E553b) and povidone K-30. The qualitative and quantitative compositions of the excipients in Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 24668/0156-0158) are identical to those of the respective cross-reference products Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 30306/0033-0036).

Simvastatin 10 mg, 20 mg and 40 mg Tablets are packed into polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC)/aluminium (Al) blisters, which are further packed into cardboard cartons in pack sizes of 10, 20, 28, 30, 50, 60, 98 and 100 tablets.

This packaging is identical to that of the cross-reference products.

II.2 Drug Substance
Simvastatin
The drug substance specification is identical to that of the respective cross-reference products and is acceptable.

II.3 Medicinal Product
Pharmaceutical development
Caduceus Pharma Limited have confirmed that they have access to the complete chemical and pharmaceutical data of the cross-reference products Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 30306/0033-0036). The chemical and pharmaceutical
data supporting the applications for Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 24668/0156-0158) are, therefore, identical to those of the respective cross-reference products (PL 30306/0033-0036).

**Manufacture of the product**

The proposed manufacturing sites are consistent with those registered for the cross-reference products. Evidence of Good Manufacturing Practice (GMP) compliance has been provided, which is identical to that of the cross-reference products.

The proposed manufacturing process is identical to that of the cross-reference products and is acceptable.

None of the excipients, with the exception of lactose monohydrate, contain materials of animal or human origin. The supplier of lactose monohydrate and anhydrous lactose have certified that the pharmaceutical grade of these excipients is prepared in accordance with the relevant requirements laid down in the *Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (EMEA/410/01 rev 3).

**Finished Product Specification**

The proposed finished product specifications are identical to those of the respective cross-reference products and are acceptable.

**Stability of the product**

The proposed shelf-life for Simvastatin 10 mg, 20 mg and 40 mg Tablets is 3 years, with the following storage precautions: ‘Do not store above 30°C. Store in the original package, in order to protect from light and moisture’.

These shelf lives and storage conditions are identical to those of the respective cross-reference products.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**

The quality data for these applications are consistent with those previously assessed for the marketing authorisations for Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 30306/0033-0036) and, as such, have been judged to be satisfactory. The grant of marketing authorisations is recommended.

**III Non-clinical aspects**

As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Since Simvastatin 10 mg, 20 mg and 40 mg Tablets 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.
The grant of marketing authorisations is recommended.

IV   Clinical aspects
As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Risk Management Plan (RMP)
The applicant 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 Simvastatin 10 mg, 20 mg and 40 mg Tablets.

A summary of safety concerns and risk minimisation measures, as approved in the RMP, are listed below:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Myopathy/Rhabdomyolysis</th>
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<tr>
<td></td>
<td>Interaction with potent inhibitors of</td>
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<td>CY45A4 (gemfibrozil, ciclosporin and</td>
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<td>danozol)</td>
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<td></td>
<td>Interaction with calcium Channel</td>
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<td>blockers and other fibrates (except</td>
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<td>fenofibrate).</td>
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<td>Use in pregnancy</td>
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<td>Diabetes mellitus</td>
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<td>Interstitial lung disease</td>
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<td>Hepatic events</td>
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<tr>
<td>Important potential risks</td>
<td>N/A</td>
</tr>
<tr>
<td>Missing information</td>
<td>Use in children &lt; 10 years and use &gt; 48 weeks</td>
</tr>
</tbody>
</table>
Summary table of risk minimisation measures

Important identified risks

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Summary of Routine Risk Minimisation Activities</th>
<th>Summary of Additional Risk Minimisation Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathy/Rhabdomyolysis</td>
<td>Information is included in sections 4.4, 4.5 and 4.8 of the SmPC.</td>
<td>N/A</td>
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<tr>
<td>Interaction with potent inhibitors of CYP3A4 gemfibrozil, ciclosporin and danazol</td>
<td>Information is included in sections 4.3, 4.4 and 4.5 of the SmPC.</td>
<td>N/A</td>
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<tr>
<td>Interaction with calcium Channel blockers and other fibrates (except fenofibrate)</td>
<td>Information is included in sections 4.4 and 4.5 of the SmPC.</td>
<td>N/A</td>
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<td>Use in pregnancy</td>
<td>Information is included in sections 4.3 and 4.6 of the SmPC.</td>
<td>N/A</td>
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<tr>
<td>Diabetes mellitus</td>
<td>Information is included in sections 4.4 and 4.8 of the SmPC.</td>
<td>N/A</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Information is included in sections 4.4 and 4.8 of the SmPC.</td>
<td>N/A</td>
</tr>
<tr>
<td>Hepatic events</td>
<td>Information is included in sections 4.2, 4.4 and 4.8 of the SmPC.</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Discussion on the clinical aspects
The grant of marketing authorisations is recommended.

V  User consultation
The proposed package leaflet for Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 24668/0156-0158) is identical to the package leaflet approved for the cross-reference products Simvastatin 10 mg, 20 mg and 40 mg Tablets (PL 30306/0033-0036), with the exception of the product name, MA Holder name and date of approval. Further user-testing is, therefore, not required.

VI  Overall conclusion, benefit/risk assessment and recommendation
The quality of these products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the respective cross-reference products. The benefit/risk assessment is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPC), package leaflet and labelling are satisfactory, in line with current guidelines and consistent with the cross-reference products. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and package leaflet for these products are available on the Medicines and Healthcare products Regulatory Agency website.

The currently approved labelling text is listed below:
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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>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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