SIMVASTATIN 10MG TABLETS (PL 17907/0125)
SIMVASTATIN 20MG TABLETS (PL 17907/0126)
SIMVASTATIN 40MG TABLETS (PL 17907/0127)

UKPAR

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SIMVASTATIN 10MG TABLETS (PL 17907/0125)
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SIMVASTATIN 40MG TABLETS (PL 17907/0127)

LAY SUMMARY

The MHRA granted Bristol Laboratories Limited (licences) for the medicinal products Simvastatin 10mg, 20mg and 40mg Tablets (PL 17907/0125-7) on 13th September 2007. These are prescription-only medicines (POM) that reduce the amount of cholesterol and fatty substances called triglycerides in the blood.

Simvastatin 10mg, 20mg and 40mg Tablets contain the active ingredient simvatstain, which belongs to a group of medicines known as “statins” or “HMG-CoA reductase inhibitors”.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Simvastatin 10mg, 20mg and 40mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
SIMVASTATIN 10MG TABLETS (PL 17907/0125)
SIMVASTATIN 20MG TABLETS (PL 17907/0126)
SIMVASTATIN 40MG TABLETS (PL 17907/0127)

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Simvastatin 10mg, 20mg and 40mg Tablets to Bristol Laboratories Limited (PL 17907/0125-7) on 13th September 2007. The products are prescription-only medicines.

The applications were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, as amended, claiming essential similarity to the original products Zocor 10mg, 20mg and 40mg Tablets (PL 00025/0241-3), which have been authorised to Merck, Sharp and Dohme in the UK since April 1989.

The products contain the active ingredient simvastatin and are indicated for the treatment of hypercholesterolaemia and the reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus.

Simvastatin is derived synthetically from a fermentation product of Aspergillus terreus. It is a lipid-lowering agent that reduces concentrations of total cholesterol, low-density lipoprotein, very low-density lipoprotein and plasma triglycerides, while elevating concentrations of high-density lipoprotein. It is an inactive lactone that, after oral ingestion, is hydrolysed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that catalyses the conversion of HMG-CoA to mevalonate – an early, rate-limiting step in the biosynthesis of cholesterol.
PHARMACEUTICAL ASSESSMENT

Active Substance
INN: Simvastatin

Chemical Name: \((1S,3R,7S,8S,8aR)-1,2,3,7,8,8a\text{-Hexahydro-3,7-dimethyl-8-\{2-[(2R,4R)\text{-tetra-hydro-4-hydroxy-6-oxo-2H-pyran-2-yl}]\text{-ethyl}\}-1\text{-naphthyl}-2,2\text{-dimethylbutyrate}}\)

Molecular Formula: \(\text{C}_{25}\text{H}_{38}\text{O}_{5}\)

Chemical Structure:

![Simvastatin Chemical Structure]

Molecular Weight: 418.6

Appearance: White to off-white powder

Properties: Practically insoluble in water, freely soluble in ethanol, methanol and chloro-form; sparingly soluble in propylene glycol; very slightly soluble in hexane.

Simvastatin is the subject of a European Pharmacopoeia monograph.

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.

An appropriate specification is provided for the active substance simvastatin. Analytical methods are those of the European Pharmacopoeia, with addition tests for residual solvents that comply with the relevant ICH guidelines.

Appropriate proof of structure has been supplied for the active pharmaceutical ingredient.

All potential known impurities have been identified and characterised.
Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. The data support a retest period of 24 months with storage conditions “Store in original package” and “Keep drum tightly closed”.

**Other Ingredients**
Other ingredients consist of pharmaceutical excipients lactose anhydrous, cellulose microcrystalline, maize starch pregelatinised, butylhydroxyanisole E320, magnesium stearate, talc, hyprollose, hypromellose and titanium dioxide E171.

All excipients have a respective European Pharmacopoeia monograph.

Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph.

Lactose anhydrous is the only ingredient that comes from an animal source. The lactose used to produce lactose monohydrate is sourced from healthy animals under the same conditions as milk for human consumption.

**Pharmaceutical development**
The objective of the pharmaceutical development programme was to produce products with 10mg, 20mg and 40mg simvastatin that are tolerable and can be considered as generic products to the originator products Zocor 10mg, 20mg and 40mg Tablets.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative *in vitro* dissolution profiles have been generated for the proposed and originator products with satisfactory results. Comparative impurity studies have also been undertaken.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results at pilot-scale. Additionally, a commitment has been provided that the first full-scale commercial production batches will be validated.

**Finished Product Specification**
The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.
Container-Closure System
All strengths of tablet are packaged in either:
1. Polyethylene/polyvinylidene chloride/polyvinylchloride/aluminium blister strips in pack sizes of 14, 28, 30, 56, 60 and 100 tablets.
2. Polyester/aluminium/polyethylene sachets in pack sizes of 14, 28, 30, 56, 60 and 100 tablets.
3. High-density polyethylene containers with a child-resistant polypropylene closure and aluminium seal in pack sizes of 100 and 500 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations regarding materials for use in contact with food.

The applicant has stated that not all packaging will be marketed in the UK and has provided assurances that they will submit mock-ups before launching any packaging types into the market.

Stability of the product
Stability studies were performed on pilot-scale batches of all strengths of finished product and all packaging types, in accordance with current guidelines. All results from stability studies on pilot batches were within specified limits. These data support a shelf-life of 3 years, with storage conditions ‘Do not store above 25°C’ and ‘Store in original packaging’.

The applicant has committed to providing stability data for the first three production-scale batches of each strength of finished product.

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable.

CONCLUSION
It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution profiles have been demonstrated for the proposed and reference products.
PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Zocor 10mg, 20mg and 40mg Tablets (Merck, Sharp and Dohme), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.
CLINICAL ASSESSMENT

1. INTRODUCTION AND BACKGROUND
These are standard abridged national applications for Simvastatin 10mg, 20mg and 40mg Tablets submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applications cross-refer to Zocor 10mg, 20mg and 40mg Tablets (Merck, Sharp and Dohme), which have been authorised in the EU for more than 10 years.

2. INDICATIONS
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 (see section 5.1).

The indications proposed are consistent with those for the originator products and are, therefore, satisfactory.

3. DOSE & DOSE SCHEDULE
The dosage range is 5-80 mg/day given orally as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.

Hypercholesterolaemia
The patient should be placed on a standard cholesterol-lowering diet, and should continue on this diet during treatment with Simvastatin tablets. The usual starting dose is 10-20mg/day given as a single dose in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 20-40 mg/day given as a single dose in the evening. Adjustments of dosage, if required, should be made as specified above.

Homozygous familial hypercholesterolaemia
Based on the results of a controlled clinical study, the recommended dosage is Simvastatin tablets 40mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. Simvastatin tablets should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Cardiovascular prevention
The usual dose of Simvastatin tablets is 20 to 40 mg/day given as a single dose in the evening in patients at high risk of coronary heart disease (CHD, with or without hyperlipidaemia). Drug therapy can be initiated simultaneously with diet and exercise. Adjustments of dosage, if required, should be made as specified above.

Concomitant therapy
Simvastatin is effective alone or in combination with bile acid sequestrants. Dosing should occur either > 2 hours before or > 4 hours after administration of a bile acid sequestrant.
In patients taking cyclosporine, danazol, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses (≥ 1g/day) of niacin concomitantly with ‘Simvastatin tablets’, the dose of ‘Simvastatin tablets’ should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with Simvastatin tablets, the dose of Simvastatin tablets should not exceed 20mg/day. (See sections 4.4 and 4.5)

**Dosage in renal insufficiency**

No modification of dosage should be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance <30ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

**Use in the elderly**

No dosage adjustment is necessary

**Use in children and adolescents**

Efficacy and safety of use in children have not been established. Therefore Simvastatin is not recommended for paediatric use.

The dose and dose schedule proposed are consistent with those for the originator products and are, therefore, satisfactory.

4. **CLINICAL PHARMACOLOGY**

With the exception of the bioequivalence study comparing the proposed product to Zocor 40mg Tablets, no formal data are provided and none are required for these applications.

4.1 **Bioequivalence**

The bioavailability of the proposed simvastatin 40mg tablet (Test) was compared to the reference product Zocor 40mg tablet (Reference) from the German market by comparing the rate and extent of absorption of simvastatin hydroxy acid, the active metabolite formed in the body by conversion from the inactive lactone simvastatin after administration.

The study was a randomised, two-way, single-dose crossover design using healthy volunteers. The products were administered after a 10-hour supervised fast. Blood samples were collected over a 24-hour period.

The essential pharmacokinetic parameters of simvastatin hydroxy acid for the two preparations are summarised below (Table I: log-normal distribution; Table II: normal distribution), while in the following figure, the mean simvastatin hydroxy acid plasma levels are shown for both products over the 24-hour period.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference (R)</th>
<th>Test (T)</th>
<th>90% Confidence Interval (%)</th>
<th>Mean Ratio (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_{(0-t)}) (ng<em>h</em>mL(^{-1}))</td>
<td>GMEAN 14.075</td>
<td>14.530</td>
<td>95.48 – 111.62**</td>
<td>103.23</td>
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<tr>
<td>GSD</td>
<td>0.4768</td>
<td>0.5156</td>
<td>95.55 – 111.54***</td>
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<tr>
<td>%CVres</td>
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<td>AUC(_{(0-inf)}) (ng<em>h</em>mL(^{-1}))</td>
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<td>17.774</td>
<td>99.35 – 115.53**</td>
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<tr>
<td>GSD</td>
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<td>99.45 – 115.42***</td>
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</tr>
<tr>
<td>%CVres</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>C(_{max}) (ng*mL(^{-1}))</td>
<td>GMEAN 1.403</td>
<td>1.398</td>
<td>89.11 – 111.36**</td>
<td>99.62</td>
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<tr>
<td>GSD</td>
<td>0.5710</td>
<td>0.6153</td>
<td>89.00 – 111.50***</td>
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<tr>
<td>%CVres</td>
<td>33.02</td>
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<tr>
<td>C(<em>{max}/AUC(</em>{(0-inf)})) (h(^{-1}))</td>
<td>GMEAN 0.0846</td>
<td>0.0787</td>
<td>85.47 – 101.15**</td>
<td>92.98</td>
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<td>GSD</td>
<td>0.3059</td>
<td>0.3318</td>
<td>85.46 – 101.16***</td>
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<tr>
<td>%CVres</td>
<td>24.41</td>
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</table>

Notes:
- GMEAN = exp (mean of In transformed values)
- LSM values are the same as means because the study is balanced and there were no missing pharmacokinetic parameters values.
- GSD = standard deviation of In transformed values
- %CVres = \(100 \sqrt{\exp(\sigma^2)-1}\)
- \(\sigma\) = root MSE obtained in ANOVA calculation of In transformed values (cf. Appendix III) (In denotes loge logarithms)
- *: geometric mean of individual “test/reference” pair ratios
- **: \(\exp\) (Conventional confidence interval for the mean of individual “test/reference” pair ratios after logarithmic transformation of the data) expressed in % of the reference mean
- ***: confidence intervals calculated on the bases of reference and test means of In transformed data and root MSE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference (R)</th>
<th>Test (T)</th>
<th>90% Confidence Interval (%)</th>
<th>Mean Ratio (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_{(0-t)}) (ng<em>h</em>mL(^{-1}))</td>
<td>MEAN 15.792</td>
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<td>95.13 – 114.27</td>
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<tr>
<td>SD</td>
<td>8.522</td>
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<tr>
<td>%CV</td>
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<tr>
<td>AUC(_{(0-inf)}) (ng<em>h</em>mL(^{-1}))</td>
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<td>C(_{max}) (ng*mL(^{-1}))</td>
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<tr>
<td>SD</td>
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<tr>
<td>%CV</td>
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<td>t(_{max}) (h)</td>
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<tr>
<td>MIN</td>
<td>1.50</td>
<td>2.00</td>
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</tr>
<tr>
<td>MEDIAN</td>
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<td>4.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
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<td>012.80 – 134.62</td>
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<tr>
<td>SD</td>
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<td>%CV</td>
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<tr>
<td>K(_{el}) (h(^{-1}))</td>
<td>MEAN 0.11702</td>
<td>0.10254</td>
<td>74.47 – 100.78</td>
<td>87.63</td>
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<tr>
<td>SD</td>
<td>0.06026</td>
<td>0.06224</td>
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<tr>
<td>%CV</td>
<td>51.50</td>
<td>60.70</td>
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</tr>
</tbody>
</table>

Notes:
- MEAN – arithmetic mean
- LSM values are the same as means because the study is balanced and there were no missing pharmacokinetic parameters values.
- SD = standard deviation
- %CV = SD/MEAN * 100
Based on these results, it can be accepted that the Test and Reference products are bioequivalent with respect to rate and extent of absorption. Although the German version of the originator product (Zocor 40mg Tablets) was used in these bioequivalence studies, it has been shown that this can be considered as identical qualitatively and quantitatively to the UK originator product.

Assessor’s Comment
Bioequivalence has been satisfactorily demonstrated for the 40mg product, in accordance with CPMP criteria. These products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98). Hence, the results and conclusions of the bioequivalence study on the 40mg strength can be extrapolated to the other strength tablets.

5. EFFICACY
No new data on the efficacy of simvastatin are submitted and none are required for this type of application.

6. SAFETY
No new data on the safety of simvastatin are submitted and none are required for this type of application.
7. **EXPERT REPORTS**
A clinical expert report is provided, written by an appropriately qualified Doctor. It includes a suitable review of the bioequivalence study.

8. **SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**
The SPCs are consistent with the approved SPCs for the originator products Zocor 10mg, 20mg and 40mg Tablets and are satisfactory.

9. **PATIENT INFORMATION LEAFLET (PIL)**
The PIL has been provided and is consistent the SPC.

10. **LABELLING**
Labelling text for all strengths are satisfactory. Mock-ups of labelling intended for marketing are satisfactory and comply with current regulations.

The applicant has stated that not all proposed pack sizes will be marketed initially, but has provided assurances that mock-ups will be submitted for assessment before any further pack sizes are marketed.

11. **APPLICATION FORM (MAA)**
The MAA form is satisfactory.

12. **DISCUSSION**
Bioequivalence has been satisfactorily demonstrated for the 40mg product in accordance with CPMP criteria. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 40mg strength can be extrapolated to the other strength tablets.

The SPC and PIL are consistent with those approved in the UK for the originator product Zocor 10mg, 20mg and 40mg Tablets and are satisfactory.

13. **MEDICAL CONCLUSION**
Marketing authorisations may be granted for these products.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Simvastatin 10mg, 20mg and 40mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Simvastatin 40mg Tablets and Zocor 40mg Tablets (Merck, Sharp and Dohme). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 40mg strength can be extrapolated to the other strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Zocor Tablets.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with simvastatin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
SIMVASTATIN 10MG TABLETS (PL 17907/0125)
SIMVASTATIN 20MG TABLETS (PL 17907/0126)
SIMVASTATIN 40MG TABLETS (PL 17907/0127)

STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 2\textsuperscript{nd} July 2004</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 4\textsuperscript{th} August 2004</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 19\textsuperscript{th} May 2005, and further information relating to the quality dossiers on 6\textsuperscript{th} April 2005, 5\textsuperscript{th} October 2005, 17\textsuperscript{th} July 2006 and 9\textsuperscript{th} February 2007.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 9\textsuperscript{th} June 2005 for the clinical dossiers, and again on 19\textsuperscript{th} August 2005, 31\textsuperscript{st} October 2005, 21\textsuperscript{st} October 2006 and 23\textsuperscript{rd} March 2007 for the quality dossiers.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 13\textsuperscript{th} September 2007</td>
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SIMVASTATIN 10MG TABLETS (PL 17907/0125)
SIMVASTATIN 20MG TABLETS (PL 17907/0126)
SIMVASTATIN 40MG TABLETS (PL 17907/0127)

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10mg of simvastatin
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Film-coated tablets

White, oblong, biconvex tablets, scored on one side, embossed with “10” on the scored side and with “SVT” on the opposite side.

OR
White oblong, biconvex tablets, scored on both sides, embossed with “SVT” and “10” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see section 5.1).

4.2 Posology and method of administration
The dosage range is 5-80 mg/day given orally as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.

Hypercholesterolaemia
The patient should be placed on a standard cholesterol-lowering diet, and should continue on this diet during treatment with Simvastatin tablets. The usual starting dose is 10-20mg/day given as a single dose in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 20-40 mg/day given as a single dose in the evening. Adjustments of dosage, if required, should be made as specified above.

Homozygous familial hypercholesterolaemia
Based on the results of a controlled clinical study, the recommended dosage is Simvastatin tablets 40mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. Simvastatin tablets should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Cardiovascular prevention
The usual dose of Simvastatin tablets is 20 to 40 mg/day given as a single dose in the evening in patients at high risk of coronary heart disease (CHD, with or without hyperlipidaemia). Drug therapy can be initiated simultaneously with diet and exercise. Adjustments of dosage, if required, should be made as specified above.
Concomitant therapy
Simvastatin is effective alone or in combination with bile acid sequestrants. Dosing should occur either > 2 hours before or > 4 hours after administration of a bile acid sequestrant.

In patients taking cyclosporine, danazol, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses (≥ 1g/day) of niacin concomitantly with ‘Simvastatin tablets’, the dose of ‘Simvastatin tablets’ should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with Simvastatin tablets, the dose of Simvastatin tablets should not exceed 20mg/day. (See sections 4.4 and 4.5)

Dosage in renal insufficiency
No modification of dosage should be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance <30ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

Use in the elderly
No dosage adjustment is necessary

Use in children and adolescents
Efficacy and safety of use in children have not been established. Therefore Simvastatin is not recommended for paediatric use.

4.3 Contraindications
- Hypersensitivity to simvastatin or to any of the excipients
- Active liver disease or unexplained persistent elevations of serum transaminases
- Pregnancy and lactation (see section 4.6)
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) (see section 4.5).

4.4 Special warnings and precautions for use

Myopathy/Rhabdomyolysis
Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,050 patients were treated with Simvastatin with 24,747 (approximately 60 %) treated for at least 4 years, the incidence of myopathy was approximately 0.02 %, 0.08 % and 0.53 % at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

Creatine Kinase measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (>5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment
All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.
Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:

- Elderly (age > 70 years)
- Renal impairment
- Uncontrolled hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with a different member of the class should only be initiated with caution. If CK levels are significantly elevated at baseline (>5 x ULN), treatment should not be started.

**Whilst on treatment**

If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (>5 x ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are <5 x ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

**Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)**

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone), as well as gemfibrozil, ciclosporine and danazol (see section 4.2)

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of other fibrates, lipid-lowering doses (≥ 1 g/day) of niacin or by concomitant use of amiodarone or verapamil with higher doses of simvastatin (see sections 4.2 and 4.5). There is also a slight increase in risk when diltiazem is used with simvastatin 80 mg.

Consequently, regarding CYP3A4 inhibitors, the use of simvastatin concomitantly with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated (see sections 4.3 and 4.5). If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Moreover, caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: ciclosporine, verapamil, diltiazem (see sections 4.2 and 4.5). Concomitant intake of grapefruit juice and simvastatin should be avoided.

The dose of simvastatin should not exceed 10mg daily in patients receiving concomitant medication with ciclosporine, danazol, gemfibrozil, or lipid-lowering doses (≥ 1 g/day) of niacin. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. The benefits of the combined use of simvastatin 10 mg daily with other fibrates (except fenofibrate), niacin or ciclosporine should be carefully weighed against the potential risks of these combinations. (See sections 4.2 and 4.5).
Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.

The combined use of simvastatin at doses higher than 20mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

Hepatic effects
In clinical studies, persistent increases (to > 3 x ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When simvastatin was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels.

It is recommended that liver function tests be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80-mg dose should receive an additional test prior to titration, 3 months after titration to the 80-mg dose, and periodically thereafter (e.g. semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 x ULN and are persistent, simvastatin should be discontinued.

The product should be used with caution in patients who consume substantial quantities of alcohol.

As with other lipid-lowering agents, moderate (<3 x ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Patients with rare hereditary problems of fructose or galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Interactions with lipid-lowering medicinal products that can cause myopathy when given alone
The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates and niacin (nicotinic acid) (≥ 1 g/day). Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see Pharmacokinetic interactions and sections 4.2 and 4.4). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.

Pharmacokinetic interactions
Prescribing recommendations for interacting agents are summarized in the table below (further details are provided in the text; see also sections 4.2, 4.3, and 4.4).
**Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis**

<table>
<thead>
<tr>
<th>Interacting agents</th>
<th>Prescribing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Potent CYP3A4 inhibitors:</em></td>
<td>Contraindicated with simvastatin</td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
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<tr>
<td>Clarithromycin</td>
<td></td>
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<tr>
<td>Telithromycin</td>
<td></td>
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<tr>
<td>HIV protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Avoid but if necessary, do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Danazol</td>
<td>Do not exceed 20 mg simvastatin daily</td>
</tr>
<tr>
<td>Other fibrates (except fenofibrate)</td>
<td></td>
</tr>
<tr>
<td>Niacin (≥1 g/day)</td>
<td>Do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Do not exceed 40 mg simvastatin daily</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Avoid grapefruit juice when taking simvastatin</td>
</tr>
</tbody>
</table>

**Effects of other medicinal products on simvastatin**

*Interactions involving CYP3A4*

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11-fold increase in exposure to simvastatin acid.

Therefore, combination with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: ciclosporine, verapamil, diltiazem (see sections 4.2 and 4.4).

*Ciclosporine*

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporine particularly with higher doses of simvastatin (see sections 4.2 and 4.4). Therefore, the dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with ciclosporine. Although the mechanism is not fully understood, ciclosporine has been shown to increase the AUC HMG-CoA reductase inhibitors. The increase in AUC of simvastatin acid presumably due, in part, to inhibition of CYP3A4.

*Danazol*

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with higher doses of simvastatin (see sections 4.2 and 4.4).

*Gemfibrozil*

Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway (see sections 4.2 and 4.4).

*Amiodarone and verapamil*

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see section 4.4). In an ongoing
clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

An analysis of the available clinical trials showed an approximately 1% incidence of myopathy in patients receiving simvastatin 40mg or 80 mg and verapamil. In a pharmacokinetic study, concomitant administration with verapamil resulted in a 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20mg daily in patients receiving concomitant medication with amiodarone or verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Diltiazem
An analysis of the available clinical trials showed a 1% incidence of myopathy in patients receiving simvastatin 80mg and diltiazem. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant diltiazem (see section 4.4). In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with diltiazem, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Grapefruit juice
Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 litre daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 ml of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

Effects of simvastatin on the pharmacokinetics of other medicinal products
Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is not expected to affect plasma concentrations of substances metabolised via cytochrome P450 3A4.

Oral anticoagulants
In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. Very rare cases of elevated INR have been reported. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

4.6 Pregnancy and lactation
Pregnancy
Simvastatin is contraindicated during pregnancy (see section 4.3).

Safety in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.
Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See section 4.3).

**Lactation**

It is not known whether simvastatin or its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions, women taking simvastatin should not breast-feed their infants (see section 4.3).

### 4.7 Effects on ability to drive and use machines

Simvastatin has no or negligible influence on the ability to drive and use machines.

However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported rarely in post-marketing experiences.

### 4.8 Undesirable effects

The frequencies of the following adverse events, which have been reported during clinical studies and/or post-marketing use, are categorized based on an assessment of their incidence rates in large, long-term, placebo-controlled, clinical trials including HPS and 4S with 20,536 and 4,444 patients, respectively (see section 5.1). For HPS, only serious adverse events were recorded as well as myalgia, increases in serum transaminases and CK. For 4S, all the adverse events listed below were recorded. If the incidence rates on simvastatin were less than or similar to that of placebo in these trials, and there were similar reasonably causally related spontaneous report events, these adverse events are categorized as ‘rare’.

In HPS (see section 5.1) involving 20,536 patients treated with 40mg/day of simvastatin (n=10,269) or placebo (n=10,267), the safety profiles were comparable between patients treated with simvastatin 40 mg and patients treated with placebo over the mean 5 years of the study. Discontinuation rates due to side effects were comparable (4.8 % in patients treated with simvastatin 40mg compared with 5.1% in patients treated with placebo). The incidence of myopathy was <0.1% in patients treated with simvastatin 40 mg. Elevated transaminases (>3 x ULN confirmed by repeat test) occurred in 0.21 % (n=21) of patients treated with simvastatin 40mg compared with 0.09% (n = 9) of patients treated with placebo.

The frequencies of adverse events are ranked according to the following: Very common (> 1/10), Common (≥ 1/100, <1/10), Uncommon (≥ 1/1000, <1/100), Rare (≥ 1/10,000, <1/1000), Very Rare (<1/10,000) including isolated reports.

**Blood and lymphatic system disorders:**

Rare: anaemia

**Nervous system disorders:**

Rare: headache, paresthesia, dizziness, peripheral neuropathy

**Gastrointestinal disorders:**

Rare: constipation, abdominal pain, flatulence, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis

**Hepato-biliary disorders:**

Rare: hepatitis/jaundice
Skin and subcutaneous tissue disorders:
Rare: rash, pruritus, alopecia

Musculoskeletal, connective tissue and bone disorders:
Rare: myopathy, rhabdomyolysis (see section 4.4), myalgia, muscle cramps

General disorders and administration site conditions:
Rare: asthenia

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

Investigations:
Rare: increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase) (see section 4.4 Hepatic effects), elevated alkaline phosphatase; increase in serum CK levels (see section 4.4).

4.9 Overdose
To date, a few cases of overdosage have been reported; the maximum dose was 3.6 g. All patients recovered without sequelae. There is no specific treatment in the event of overdose. In this case, symptomatic and supportive measures should be adopted.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitor
ATC-Code: C10A A01

After oral ingestion, simvastatin, which is an active lactone, is hydrolyzed in the liver to the corresponding active beta-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy – 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-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 tablets’ 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 tablets’. In addition, ‘Simvastatin tablets’ 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.

High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease
In the Heart Protection Study (HPS), the effects of therapy with Simvastatin tablets were assessed in 20,536 patients (age 40-48 years), with or without hyperlipidaemia, and with coronary heart disease, other occlusive arterial disease or diabetes mellitus. In this study, 10,269 patients were treated with simvastatin tablets 40mg/day and 10,267 patients were treated with placebo for a mean duration of 5 years. At baseline, 6,793 patients (33 %) had LDL-C levels below 116 mg/dL; 5,063 patients (25 %) had levels between 116 mg/dL and 135mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

Treatment with Simvastatin tablets 40 mg/day compared with placebo significantly reduced the risk of all cause mortality (1328 [12.9%] for simvastatin-treated patients versus 1507 [14.7 %] for patients given placebo; p=0.0003), due to an 18% reduction in coronary death rate (587 [5.7 %] versus 707 [6.9 %]; p=0.0005; absolute risk reduction of 1.2 %). The reduction in non-vascular deaths did not reach statistical significance. ‘Simvastatin tablets’ also decreased the risk of major coronary events (a composite endpoint comprised of non-fatal MI or CHD death) by 27 % (p<0.0001). Simvastatin tablets reduced the need for undergoing coronary revascularization procedures (including coronary artery bypass grafting or percutaneous...
In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with simvastatin on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomised, double-blind, placebo controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet, standard care, and either simvastatin 20-40 mg/day (n = 2,221) or placebo (n=2,223) for a median duration of 5.4 years. Simvastatin tablets reduced the risk of death by 30 % (absolute risk reduction of 3.3 %). The risk of CHD death was reduced by 42 % (absolute risk reduction of 3.5 %). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent nonfatal MI) by 34 %. Furthermore, simvastatin significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischemic attacks) by 28 %. There was no statistically significant difference between groups in non-cardiovascular mortality.

Primary Hypercholesterolaemia and Combined Hyperlipidaemia
In studies comparing the efficacy and safety of simvastatin 10, 20, 40 and 80 mg daily in patients with hypercholesterolaemia, the mean reductions of LDL-C were 30, 38, 41 and 47%, respectively. In studies of patients with combined (mixed) hyperlipidaemia on simvastatin 40 mg and 80 mg, the median reductions in triglycerides were 28 and 33 % (placebo: 2 %), respectively, and mean increases in HDL-C were 13 and 16 % (placebo: 3 %), respectively.

5.2 Pharmacokinetic properties
Simvastatin is an inactive lactone which is readily hydrolyzed in vivo to the corresponding beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

Absorption
In man simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependant on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systematic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicinal product occurred after multiple dosing.

Distribution
The protein binding of simvastatin and its active metabolite is >95 %.

Elimination
Simvastatin is a substrate of CYP3A4 (see sections 4.3 and 4.5). The major metabolites of simvastatin present in human plasma are the beta-hydroxyacid and four additional active metabolites. Following an oral dose of radioactive simvastatin to man, 13 % of the radioactivity was excreted in the urine and 60 % in the faeces within 96 hours. The amount recovered in the faeces represents absorbed medicinal product equivalents excreted in bile as well as unabsorbed medicinal product. Following an intravenous injection of the beta-hydroxyacid metabolite, its half-life averaged 1.9 hours. An average of only 0.3 % of the IV dose was excreted in urine as inhibitors.
5.3  **Preclinical safety data**
Based on conventional animal studies regarding pharmacodynamics, repeated dose toxicity, genotoxicity and carcinogenicity, there are no other risks for the patient than may be expected on account of the pharmacological mechanism. At maximally tolerated doses in both the rat and the rabbit, simvastatin produced no foetal malformations, and had no effects on fertility, reproductive function or neonatal development.

6  **PHARMACEUTICAL PARTICULARS**
6.1  **List of excipients**
Lactose, anhydrous  
Cellulose, microcrystalline  
Maize starch, pregelatinised  
Butyl-hydroxyanisole (E320)  
Magnesium stearate  
Talc  
Hyprolose  
Hypromellose  
Titanium dioxide (E 171)

6.2  **Incompatibilities**
None.

6.3  **Shelf life**
3 years

6.4  **Special precautions for storage**
Do not store above 25°C. Store in the original package.

6.5  **Nature and contents of container**
PVC/PE/PVDC/aluminium blisters- Each blister contains either 10 or 14 tablets to give pack sizes of 14, 28, 30, 56, 60 or 100 tablets,

PVC/PE/PVDC/aluminium blisters in polyester/aluminium/PE sachets, - Each blister contains either 10 or 14 tablets. The blisters will be enclosed in a sachet to give pack sizes of 14, 28, 30, 56, 60 or 100 tablets. These sachets will then be placed in an outer carton.

HDPE container with child-proof PP closure and aluminium original seal. The containers are available in pack sizes of 100’s and 500’s.

Not all pack sizes may be marketed.

6.6  **Special precautions for disposal**
Not applicable

7  **MARKETING AUTHORISATION HOLDER**
Bristol Laboratories Ltd.  
Unit 3  
Canalside  
Northbridge Road  
Berkhamsted  
Hertfordshire  
HP4 1EG  
UK

8  **MARKETING AUTHORISATION NUMBER(S)**
PL 17907/0125

9  **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
13/09/2007
DATE OF REVISION OF THE TEXT
13/09/2007
1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 20mg of simvastatin
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Film-coated tablets

White, oblong, biconvex tablets, scored on one side, embossed with “20” on the scored side and with “SVT” on the opposite side.
OR
White oblong, biconvex tablets, scored on both sides, embossed with “SVT” and “20” on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

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 (see section 5.1).

4.2 Posology and method of administration
The dosage range is 5-80 mg/day given orally as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.

Hypercholesterolaemia
The patient should be placed on a standard cholesterol-lowering diet, and should continue on this diet during treatment with Simvastatin tablets. The usual starting dose is 10-20mg/day given as a single dose in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 20-40 mg/day given as a single dose in the evening. Adjustments of dosage, if required, should be made as specified above.

Homozygous familial hypercholesterolaemia
Based on the results of a controlled clinical study, the recommended dosage is Simvastatin tablets 40mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. Simvastatin tablets should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Cardiovascular prevention
The usual dose of Simvastatin tablets is 20 to 40 mg/day given as a single dose in the evening in patients at high risk of coronary heart disease (CHD, with or without hyperlipidaemia). Drug therapy can be initiated simultaneously with diet and exercise. Adjustments of dosage, if required, should be made as specified above.
Concomitant therapy

Simvastatin is effective alone or in combination with bile acid sequestrants. Dosing should occur either > 2 hours before or > 4 hours after administration of a bile acid sequestrant.

In patients taking cyclosporine, danazol, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses (≥ 1g/day) of niacin concomitantly with ‘Simvastatin tablets’, the dose of ‘Simvastatin tablets’ should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with Simvastatin tablets, the dose of Simvastatin tablets should not exceed 20mg/day. (See sections 4.4 and 4.5)

Dosage in renal insufficiency

No modification of dosage should be necessary in patients with moderate renal insufficiency.

In patients with severe renal insufficiency (creatinine clearance <30ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

Use in the elderly

No dosage adjustment is necessary

Use in children and adolescents

Efficacy and safety of use in children have not been established. Therefore Simvastatin is not recommended for paediatric use.

4.3 Contraindications

- Hypersensitivity to simvastatin or to any of the excipients
- Active liver disease or unexplained persistent elevations of serum transaminases
- Pregnancy and lactation (see section 4.6)
- Concomitant administration of potent CYP3A4 inhibitors (e.g itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) (see section 4.5).

4.4 Special warnings and precautions for use

Myopathy/Rhabdomyolysis

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,050 patients were treated with Simvastatin with 24,747 (approximately 60 %) treated for at least 4 years, the incidence of myopathy was approximately 0.02 %, 0.08 % and 0.53 % at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

Creatine Kinase measurement

Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (>5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment

All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.
Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:

- Elderly (age > 70 years)
- Renal impairment
- Uncontrolled hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with a different member of the class should only be initiated with caution. If CK levels are significantly elevated at baseline (>5 x ULN), treatment should not be started.

Whilst on treatment

If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (>5 x ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are <5 x ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone), as well as gemfibrozil, ciclosporine and danazol (see section 4.2)

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of other fibrates, lipid-lowering doses (≥1 g/day) of niacin or by concomitant use of amiodarone or verapamil with higher doses of simvastatin (see sections 4.2 and 4.5). There is also a slight increase in risk when diltiazem is used with simvastatin 80 mg.

Consequently, regarding CYP3A4 inhibitors, the use of simvastatin concomitantly with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated (see sections 4.3 and 4.5). If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Moreover, caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: ciclosporine, verapamil, diltiazem (see sections 4.2 and 4.5). Concomitant intake of grapefruit juice and simvastatin should be avoided.

The dose of simvastatin should not exceed 10mg daily in patients receiving concomitant medication with ciclosporine, danazol, gemfibrozil, or lipid-lowering doses (≥1 g/day) of niacin. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. The benefits of the combined use of simvastatin 10 mg daily with other fibrates (except fenofibrate), niacin or ciclosporine should be carefully weighed against the potential risks of these combinations. (See sections 4.2 and 4.5).
Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.

The combined use of simvastatin at doses higher than 20mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

**Hepatic effects**

In clinical studies, persistent increases (to > 3 x ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When simvastatin was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels.

It is recommended that liver function tests be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80-mg dose should receive an additional test prior to titration, 3 months after titration to the 80-mg dose, and periodically thereafter (e.g. semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 x ULN and are persistent, simvastatin should be discontinued.

The product should be used with caution in patients who consume substantial quantities of alcohol.

As with other lipid-lowering agents, moderate (<3 x ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Patients with rare hereditary problems of fructose or galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### 4.5 Interaction with other medicinal products and other forms of interaction

**Pharmacodynamic interactions**

*Interactions with lipid-lowering medicinal products that can cause myopathy when given alone*

The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates and niacin (nicotinic acid) (≥ 1 g/day). Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see Pharmacokinetic interactions and sections 4.2 and 4.4). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.

**Pharmacokinetic interactions**

Prescribing recommendations for interacting agents are summarized in the table below (further details are provided in the text; see also sections 4.2, 4.3, and 4.4).
Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

<table>
<thead>
<tr>
<th>Interacting agents</th>
<th>Prescribing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Potent CYP3A4 inhibitors:</em></td>
<td>Contraindicated with simvastatin</td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
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<td>Clarithromycin</td>
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<tr>
<td>Telithromycin</td>
<td></td>
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<tr>
<td>HIV protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Avoid but if necessary, do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Danazol</td>
<td>Do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Other fibrates (except fenofibrate)</td>
<td>Do not exceed 20 mg simvastatin daily</td>
</tr>
<tr>
<td>Niacin (≥1 g/day)</td>
<td>Do not exceed 40 mg simvastatin daily</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Avoid grapefruit juice when taking simvastatin</td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td></td>
</tr>
</tbody>
</table>

Effects of other medicinal products on simvastatin

*Interactions involving CYP3A4*

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11-fold increase in exposure to simvastatin acid.

Therefore, combination with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: ciclosporine, verapamil, diltiazem (see sections 4.2 and 4.4).

*Ciclosporine*

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporine particularly with higher doses of simvastatin (see sections 4.2 and 4.4). Therefore, the dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with ciclosporine. Although the mechanism is not fully understood, ciclosporine has been shown to increase the AUC HMG-CoA reductase inhibitors. The increase in AUC of simvastatin acid presumably due, in part, to inhibition of CYP3A4.

*Danazol*

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with higher doses of simvastatin (see sections 4.2 and 4.4).

*Gemfibrozil*

Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway (see sections 4.2 and 4.4).

*Amiodarone and verapamil*

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see section 4.4). In an ongoing
clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

An analysis of the available clinical trials showed an approximately 1% incidence of myopathy in patients receiving simvastatin 40 mg or 80 mg and verapamil. In a pharmacokinetic study, concomitant administration with verapamil resulted in a 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

**Diltiazem**

An analysis of the available clinical trials showed a 1% incidence of myopathy in patients receiving simvastatin 80 mg and diltiazem. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant diltiazem (see section 4.4). In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with diltiazem, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

**Grapefruit juice**

Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 litre daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 ml of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

**Effects of simvastatin on the pharmacokinetics of other medicinal products**

Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is not expected to affect plasma concentrations of substances metabolised via cytochrome P450 3A4.

**Oral anticoagulants**

In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. Very rare cases of elevated INR have been reported. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

**4.6 Pregnancy and lactation**

**Pregnancy**

Simvastatin is contraindicated during pregnancy (see section 4.3).

Safety in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.
Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See section 4.3).

**Lactation**

It is not known whether simvastatin or its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions, women taking simvastatin should not breast-feed their infants (see section 4.3).

4.7 **Effects on ability to drive and use machines**

Simvastatin has no or negligible influence on the ability to drive and use machines.

However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported rarely in post-marketing experiences.

4.8 **Undesirable effects**

The frequencies of the following adverse events, which have been reported during clinical studies and/or post-marketing use, are categorized based on an assessment of their incidence rates in large, long-term, placebo-controlled, clinical trials including HPS and 4S with 20,536 and 4,444 patients, respectively (see section 5.1). For HPS, only serious adverse events were recorded as well as myalgia, increases in serum transaminases and CK. For 4S, all the adverse events listed below were recorded. If the incidence rates on simvastatin were less than or similar to that of placebo in these trials, and there were similar reasonably causally related spontaneous report events, these adverse events are categorized as ‘rare’.

In HPS (see section 5.1) involving 20,536 patients treated with 40mg/day of simvastatin (n=10,269) or placebo (n=10,267), the safety profiles were comparable between patients treated with simvastatin 40 mg and patients treated with placebo over the mean 5 years of the study. Discontinuation rates due to side effects were comparable (4.8 % in patients treated with simvastatin 40mg compared with 5.1% in patients treated with placebo). The incidence of myopathy was <0.1% in patients treated with simvastatin 40 mg. Elevated transaminases (>3 x ULN confirmed by repeat test) occurred in 0.21 % (n=21) of patients treated with simvastatin 40mg compared with 0.09% (n = 9) of patients treated with placebo.

The frequencies of adverse events are ranked according to the following: Very common (> 1/10), Common (≥ 1/100, <1/10), Uncommon (≥ 1/1000, <1/100), Rare (≥ 1/10,000, <1/1000), Very Rare (<1/10,000) including isolated reports.

**Blood and lymphatic system disorders:**

Rare: anaemia

**Nervous system disorders:**

Rare: headache, paresthesia, dizziness, peripheral neuropathy

**Gastrointestinal disorders:**

Rare: constipation, abdominal pain, flatulence, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis

**Hepato-biliary disorders:**

Rare: hepatitis/jaundice
Skin and subcutaneous tissue disorders:
Rare: rash, pruritus, alopecia

Musculoskeletal, connective tissue and bone disorders:
Rare: myopathy, rhabdomyolysis (see section 4.4), myalgia, muscle cramps

General disorders and administration site conditions:
Rare: asthenia

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

Investigations:
Rare: increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase, \(\gamma\)-glutamyl transpeptidase) (see section 4.4 Hepatic effects), elevated alkaline phosphatase; increase in serum CK levels (see section 4.4).

4.9 Overdose
To date, a few cases of overdosage have been reported; the maximum dose was 3.6 g. All patients recovered without sequelae. There is no specific treatment in the event of overdose. In this case, symptomatic and supportive measures should be adopted.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitor
ATC-Code: C10A A01

After oral ingestion, simvastatin, which is an active lactone, is hydrolyzed in the liver to the corresponding active beta-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy-3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-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 tablets’ 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 tablets’. In addition, ‘Simvastatin tablets’ 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.

High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease
In the Heart Protection Study (HPS), the effects of therapy with Simvastatin tablets were assessed in 20,536 patients (age 40-48 years), with or without hyperlipidaemia, and with coronary heart disease, other occlusive arterial disease or diabetes mellitus. In this study, 10,269 patients were treated with simvastatin tablets 40mg/day and 10,267 patients were treated with placebo for a mean duration of 5 years. At baseline, 6,793 patients (33 %) had LDL-C levels below 116 mg/dL; 5,063 patients (25 %) had levels between 116 mg/dL and 135mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

Treatment with Simvastatin tablets 40 mg/day compared with placebo significantly reduced the risk of all cause mortality (1328 [12.9%] for simvastatin-treated patients versus 1507 [14.7 %] for patients given placebo; p=0.0003), due to an 18% reduction in coronary death rate (587 [5.7 %] versus 707 [6.9 %]; p=0.0005; absolute risk reduction of 1.2 %). The reduction in non-vascular deaths did not reach statistical significance. ‘Simvastatin tablets’ also decreased the risk of major coronary events (a composite endpoint comprised of non-fatal MI or CHD death) by 27 % (p<0.0001). Simvastatin tablets reduced the need for undergoing coronary revascularization procedures (including coronary artery bypass grafting or percutaneous
transluminal coronary angioplasty) and peripheral and other non-coronary revascularization procedures by 30 % (p<0.0001) and 16 % (p = 0.006), respectively. Simvastatin tablets reduced the risk of stroke by 25 % (p<0.0001), attributable to a 30 % reduction in ischemic stroke (p<0.0001). In addition, within the subgroup of patients with diabetes, simvastatin tablets reduced the risk of developing macrovascular complications, including peripheral revascularization procedures (surgery or angioplasty), lower limb amputations, or leg ulcers by 21 % (p = 0.0293). The proportional reduction in event rate was similar in each subgroup of patients studied, including those without coronary disease but who had cerebrovascular or peripheral artery disease, men and women, those aged either under or over 70 years at entry into study, presence or absence of hypertension, and notably those with LDL cholesterol below 3.0 mmol/l at inclusion.

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with simvastatin on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomised, double-blind, placebo controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet, standard care, and either simvastatin 20-40 mg/day (n = 2,221) or placebo (n=2,223) for a median duration of 5.4 years. Simvastatin tablets reduced the risk of death by 30 % (absolute risk reduction of 3.3 %). The risk of CHD death was reduced by 42 % (absolute risk reduction of 3.5 %). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent nonfatal MI) by 34 %. Furthermore, simvastatin significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischemic attacks) by 28 %. There was no statistically significant difference between groups in non-cardiovascular mortality.

**Primary Hypercholesterolaemia and Combined Hyperlipidaemia**

In studies comparing the efficacy and safety of simvastatin 10, 20, 40 and 80 mg daily in patients with hypercholesterolaemia, the mean reductions of LDL-C were 30, 38, 41 and 47%, respectively. In studies of patients with combined (mixed) hyperlipidaemia on simvastatin 40 mg and 80 mg, the median reductions in triglycerides were 28 and 33 % (placebo: 2 %), respectively, and mean increases in HDL-C were 13 and 16 % (placebo: 3 %), respectively.

**5.2 Pharmacokinetic properties**

Simvastatin is an inactive lactone which is readily hydrolyzed in vivo to the corresponding beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

**Absorption**

In man simvastatin is well absorbed and undergoes extensive hepatic first–pass extraction. The extraction in the liver is dependant on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systematic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicinal product occurred after multiple dosing.

**Distribution**

The protein binding of simvastatin and its active metabolite is >95 %.

**Elimination**

Simvastatin is a substrate of CYP3A4 (see sections 4.3 and 4.5). The major metabolites of simvastatin present in human plasma are the beta-hydroxyacid and four additional active metabolites. Following an oral dose of radioactive simvastatin to man, 13 % of the radioactivity was excreted in the urine and 60 % in the faeces within 96 hours. The amount recovered in the faeces represents absorbed medicinal product equivalents excreted in bile as well as unabsorbed medicinal product. Following an intravenous injection of the beta-hydroxyacid metabolite, its half-life averaged 1.9 hours. An average of only 0.3 % of the IV dose was excreted in urine as inhibitors.
5.3 **Preclinical safety data**

Based on conventional animal studies regarding pharmacodynamics, repeated dose toxicity, genotoxicity and carcinogenicity, there are no other risks for the patient than may be expected on account of the pharmacological mechanism. At maximally tolerated doses in both the rat and the rabbit, simvastatin produced no foetal malformations, and had no effects on fertility, reproductive function or neonatal development.

### 6 PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

- Lactose, anhydrous
- Cellulose, microcrystalline
- Maize starch, pregelatinised
- Butyl-hydroxyanisole (E320)
- Magnesium stearate
- Talc
- Hyprolose
- Hypermellose
- Titanium dioxide (E 171)

**6.2 Incompatibilities**

None.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Do not store above 25°C. Store in the original package.

**6.5 Nature and contents of container**

- PVC/PE/PVDC/aluminium blisters- Each blister contains either 10 or 14 tablets to give pack sizes of 14, 28, 30, 56, 60 or 100 tablets,

- PVC/PE/PVDC/aluminium blisters in polyester/aluminium/PE sachets, - Each blister contains either 10 or 14 tablets. The blisters will be enclosed in a sachet to give pack sizes of 14, 28, 30, 56, 60 or 100 tablets. These sachets will then be placed in an outer carton.

HDPE container with child-proof PP closure and aluminium original seal. The containers are available in pack sizes of 100’s and 500’s.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

Not applicable

### 7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd.

Unit 3

Canalside

Northbridge Road

Berkhamsted

Hertfordshire

HP4 1EG

UK

### 8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0126

### 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/09/2007
10 DATE OF REVISION OF THE TEXT
13/09/2007
1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 40 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 40mg of simvastatin
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Film-coated tablets

White, oblong, biconvex tablets, scored on one side, embossed with “40” on the scored side and with “SVT” on the opposite side.

OR

White oblong, biconvex tablets, scored on both sides, embossed with “SVT” and “40” on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

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 (see section 5.1).

4.2 Posology and method of administration

The dosage range is 5-80 mg/day given orally as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.

Hypercholesterolaemia
The patient should be placed on a standard cholesterol-lowering diet, and should continue on this diet during treatment with Simvastatin tablets. The usual starting dose is 10-20mg/day given as a single dose in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 20-40 mg/day given as a single dose in the evening. Adjustments of dosage, if required, should be made as specified above.

Homozgyous familial hypercholesterolaemia
Based on the results of a controlled clinical study, the recommended dosage is Simvastatin tablets 40mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. Simvastatin tablets should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Cardiovascular prevention
The usual dose of Simvastatin tablets is 20 to 40 mg/day given as a single dose in the evening in patients at high risk of coronary heart disease (CHD, with or without hyperlipidaemia). Drug therapy can be initiated simultaneously with diet and exercise. Adjustments of dosage, if required, should be made as specified above.
Concomitant therapy
Simvastatin is effective alone or in combination with bile acid sequestrants. Dosing should occur either > 2 hours before or > 4 hours after administration of a bile acid sequestrant.

In patients taking cyclosporine, danazol, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses (≥ 1g/day) of niacin concomitantly with ‘Simvastatin tablets’, the dose of ‘Simvastatin tablets’ should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with Simvastatin tablets, the dose of Simvastatin tablets should not exceed 20 mg/day. (See sections 4.4 and 4.5)

Dosage in renal insufficiency
No modification of dosage should be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance <30ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

Use in the elderly
No dosage adjustment is necessary

Use in children and adolescents
Efficacy and safety of use in children have not been established. Therefore Simvastatin is not recommended for paediatric use.

4.3 Contraindications
- Hypersensitivity to simvastatin or to any of the excipients
- Active liver disease or unexplained persistent elevations of serum transaminases
- Pregnancy and lactation (see section 4.6)
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) (see section 4.5).

4.4 Special warnings and precautions for use

Myopathy/Rhabdomyolysis
Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,050 patients were treated with Simvastatin with 24,747 (approximately 60%) treated for at least 4 years, the incidence of myopathy was approximately 0.02 %, 0.08 % and 0.53 % at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

Creatine Kinase measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment
All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:
- Elderly (age > 70 years)
- Renal impairment
- Uncontrolled hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with a different member of the class should only be initiated with caution. If CK levels are significantly elevated at baseline (>5 x ULN), treatment should not be started.

**Whilst on treatment**

If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (>5 x ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are <5 x ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

**Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)**

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone), as well as gemfibrozil, ciclosporine and danazol (see section 4.2).

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of other fibrates, lipid-lowering doses (≥1 g/day) of niacin or by concomitant use of amiodarone or verapamil with higher doses of simvastatin (see sections 4.2 and 4.5). There is also a slight increase in risk when diltiazem is used with simvastatin 80 mg.

Consequently, regarding CYP3A4 inhibitors, the use of simvastatin concomitantly with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated (see sections 4.3 and 4.5). If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Moreover, caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: ciclosporine, verapamil, diltiazem (see sections 4.2 and 4.5). Concomitant intake of grapefruit juice and simvastatin should be avoided.

The dose of simvastatin should not exceed 10mg daily in patients receiving concomitant medication with ciclosporine, danazol, gemfibrozil, or lipid-lowering doses (≥1 g/day) of niacin. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. The benefits of the combined use of simvastatin 10 mg daily with other fibrates (except fenofibrate), niacin or ciclosporine should be carefully weighed against the potential risks of these combinations. (See sections 4.2 and 4.5).

Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.
The combined use of simvastatin at doses higher than 20mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

**Hepatic effects**

In clinical studies, persistent increases (to > 3 x ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When simvastatin was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels.

It is recommended that liver function tests be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80-mg dose should receive an additional test prior to titration, 3 months after titration to the 80-mg dose, and periodically thereafter (e.g. semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 x ULN and are persistent, simvastatin should be discontinued.

The product should be used with caution in patients who consume substantial quantities of alcohol.

As with other lipid-lowering agents, moderate (<3 x ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Patients with rare hereditary problems of fructose or galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### 4.5 Interaction with other medicinal products and other forms of interaction

**Pharmacodynamic interactions**

*Interactions with lipid-lowering medicinal products that can cause myopathy when given alone*

The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates and niacin (nicotinic acid) (≥ 1 g/day). Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see Pharmacokinetic interactions and sections 4.2 and 4.4). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.

**Pharmacokinetic interactions**

Prescribing recommendations for interacting agents are summarized in the table below (further details are provided in the text; see also sections 4.2, 4.3, and 4.4).
Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

<table>
<thead>
<tr>
<th>Interacting agents</th>
<th>Prescribing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potent CYP3A4 inhibitors:</strong></td>
<td>Contraindicated with simvastatin</td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
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<tr>
<td>Clarithromycin</td>
<td></td>
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<tr>
<td>Telithromycin</td>
<td></td>
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<tr>
<td>HIV protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Avoid but if necessary, do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Danazol</td>
<td>Do not exceed 20 mg simvastatin daily</td>
</tr>
<tr>
<td>Other fibrates (except fenofibrate)</td>
<td>Do not exceed 40 mg simvastatin daily</td>
</tr>
<tr>
<td>Niacin (≥1 g/day)</td>
<td>Avoid grapefruit juice when taking simvastatin</td>
</tr>
</tbody>
</table>

Effects of other medicinal products on simvastatin

**Interactions involving CYP3A4**

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11-fold increase in exposure to simvastatin acid.

Therefore, combination with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: ciclosporine, verapamil, dilitiazem (see sections 4.2 and 4.4).

**Ciclosporine**

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporine particularly with higher doses of simvastatin (see sections 4.2 and 4.4). Therefore, the dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with ciclosporine. Although the mechanism is not fully understood, ciclosporine has been shown to increase the AUC HMG-CoA reductase inhibitors. The increase in AUC of simvastatin acid presumably due, in part, to inhibition of CYP3A4.

**Danazol**

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with higher doses of simvastatin (see sections 4.2 and 4.4).

**Gemfibrozil**

Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway (see sections 4.2 and 4.4).

**Amiodarone and verapamil**

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see section 4.4). In an ongoing
clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

An analysis of the available clinical trials showed an approximately 1% incidence of myopathy in patients receiving simvastatin 40 mg or 80 mg and verapamil. In a pharmacokinetic study, concomitant administration with verapamil resulted in a 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

**Diltiazem**

An analysis of the available clinical trials showed a 1% incidence of myopathy in patients receiving simvastatin 80 mg and diltiazem. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant diltiazem (see section 4.4). In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with diltiazem, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

**Grapefruit juice**

Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 litre daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 ml of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

**Effects of simvastatin on the pharmacokinetics of other medicinal products**

Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is not expected to affect plasma concentrations of substances metabolised via cytochrome P450 3A4.

**Oral anticoagulants**

In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. Very rare cases of elevated INR have been reported. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

### 4.6 Pregnancy and lactation

**Pregnancy**

Simvastatin is contraindicated during pregnancy (see section 4.3).

Safety in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.
Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See section 4.3).

Lactation
It is not known whether simvastatin or its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions, women taking simvastatin should not breast-feed their infants (see section 4.3).

4.7 Effects on ability to drive and use machines
Simvastatin has no or negligible influence on the ability to drive and use machines.

However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported rarely in post-marketing experiences.

4.8 Undesirable effects
The frequencies of the following adverse events, which have been reported during clinical studies and/or post-marketing use, are categorized based on an assessment of their incidence rates in large, long-term, placebo-controlled, clinical trials including HPS and 4S with 20,536 and 4,444 patients, respectively (see section 5.1). For HPS, only serious adverse events were recorded as well as myalgia, increases in serum transaminases and CK. For 4S, all the adverse events listed below were recorded. If the incidence rates on simvastatin were less than or similar to that of placebo in these trials, and there were similar reasonably causally related spontaneous report events, these adverse events are categorized as ‘rare’.

In HPS (see section 5.1) involving 20,536 patients treated with 40mg/day of simvastatin (n=10,269) or placebo (n=10,267), the safety profiles were comparable between patients treated with simvastatin 40 mg and patients treated with placebo over the mean 5 years of the study. Discontinuation rates due to side effects were comparable (4.8 % in patients treated with simvastatin 40mg compared with 5.1% in patients treated with placebo). The incidence of myopathy was <0.1% in patients treated with simvastatin 40 mg. Elevated transaminases (>3 x ULN confirmed by repeat test) occurred in 0.21 % (n=21) of patients treated with simvastatin 40mg compared with 0.09% (n = 9) of patients treated with placebo.

The frequencies of adverse events are ranked according to the following: Very common (>1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1000), Very Rare (<1/10,000) including isolated reports.

**Blood and lymphatic system disorders:**
Rare: anaemia

**Nervous system disorders:**
Rare: headache, paresthesia, dizziness, peripheral neuropathy

**Gastrointestinal disorders:**
Rare: constipation, abdominal pain, flatulence, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis

**Hepato-biliary disorders:**
Rare: hepatitis/jaundice
Skin and subcutaneous tissue disorders:
Rare: rash, pruritus, alopecia

Musculoskeletal, connective tissue and bone disorders:
Rare: myopathy, rhabdomyolysis (see section 4.4), myalgia, muscle cramps

General disorders and administration site conditions:
Rare: asthenia

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

Investigations:
Rare: increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase, \( \gamma \)-glutamyl transpeptidase) (see section 4.4 Hepatic effects), elevated alkaline phosphatase; increase in serum CK levels (see section 4.4).

4.9 Overdose
To date, a few cases of overdosage have been reported; the maximum dose was 3.6 g. All patients recovered without sequelae. There is no specific treatment in the event of overdose. In this case, symptomatic and supportive measures should be adopted.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitor
ATC-Code: C10A A01

After oral ingestion, simvastatin, which is an active lactone, is hydrolyzed in the liver to the corresponding active beta-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy – 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-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 tablets’ 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 tablets’. In addition, ‘Simvastatin tablets’ 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.

High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease
In the Heart Protection Study (HPS), the effects of therapy with Simvastatin tablets were assessed in 20,536 patients (age 40-48 years), with or without hyperlipidaemia, and with coronary heart disease, other occlusive arterial disease or diabetes mellitus. In this study, 10,269 patients were treated with simvastatin tablets 40mg/day and 10,267 patients were treated with placebo for a mean duration of 5 years. At baseline, 6,793 patients (33 %) had LDL-C levels below 116 mg/dL; 5,063 patients (25 %) had levels between 116 mg/dL and 135mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

Treatment with Simvastatin tablets 40 mg/day compared with placebo significantly reduced the risk of all cause mortality (1328 [12.9%] for simvastatin-treated patients versus 1507 [14.7 %] for patients given placebo; p=0.0003), due to an 18% reduction in coronary death rate (587 [5.7 %] versus 707 [6.9 %]; p=0.0005; absolute risk reduction of 1.2 %). The reduction in non-vascular deaths did not reach statistical significance. ‘Simvastatin tablets’ also decreased the risk of major coronary events (a composite endpoint comprised of non-fatal MI or CHD death) by 27 % (p<0.0001). Simvastatin tablets reduced the need for undergoing coronary revascularization procedures (including coronary artery bypass grafting or percutaneous
transluminal coronary angioplasty) and peripheral and other non-coronary revascularization procedures by 30 % (p<0.0001) and 16 % (p = 0.006), respectively. Simvastatin tablets reduced the risk of stroke by 25 % (p<0.0001), attributable to a 30 % reduction in ischemic stroke (p<0.0001). In addition, within the subgroup of patients with diabetes, simvastatin tablets reduced the risk of developing macrovascular complications, including peripheral revascularization procedures (surgery or angioplasty), lower limb amputations, or leg ulcers by 21 % (p = 0.0293). The proportional reduction in event rate was similar in each subgroup of patients studied, including those without coronary disease but who had cerebrovascular or peripheral artery disease, men and women, those aged either under or over 70 years at entry into study, presence or absence of hypertension, and notably those with LDL cholesterol below 3.0 mmol/l at inclusion.

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with simvastatin on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomised, double-blind, placebo controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet, standard care, and either simvastatin 20-40 mg/day (n = 2,221) or placebo (n=2,223) for a median duration of 5.4 years. Simvastatin tablets reduced the risk of death by 30 % (absolute risk reduction of 3.3 %). The risk of CHD death was reduced by 42 % (absolute risk reduction of 3.5 %). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent nonfatal MI) by 34 %. Furthermore, simvastatin significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischemic attacks) by 28 %. There was no statistically significant difference between groups in non-cardiovascular mortality.

Primary Hypercholesterolaemia and Combined Hyperlipidaemia
In studies comparing the efficacy and safety of simvastatin 10, 20, 40 and 80 mg daily in patients with hypercholesterolaemia, the mean reductions of LDL-C were 30, 38, 41 and 47%, respectively. In studies of patients with combined (mixed) hyperlipidaemia on simvastatin 40 mg and 80 mg, the median reductions in triglycerides were 28 and 33 % (placebo: 2 %), respectively, and mean increases in HDL-C were 13 and 16 % (placebo: 3 %), respectively.

5.2 Pharmacokinetic properties
Simvastatin is an inactive lactone which is readily hydrolyzed in vivo to the corresponding beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

Absorption
In man simvastatin is well absorbed and undergoes extensive hepatic first –pass extraction. The extraction in the liver is dependant on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systematic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicinal product occurred after multiple dosing.

Distribution
The protein binding of simvastatin and its active metabolite is >95 %.

Elimination
Simvastatin is a substrate of CYP3A4 (see sections 4.3 and 4.5). The major metabolites of simvastatin present in human plasma are the beta-hydroxyacid and four additional active metabolites. Following an oral dose of radioactive simvastatin to man, 13 % of the radioactivity was excreted in the urine and 60 % in the faeces within 96 hours. The amount recovered in the faeces represents absorbed medicinal product equivalents excreted in bile as well as unabsorbed medicinal product. Following an intravenous injection of the beta-hydroxyacid metabolite, its half-life averaged 1.9 hours. An average of only 0.3 % of the IV dose was excreted in urine as inhibitors.
5.3 Preclinical safety data
Based on conventional animal studies regarding pharmacodynamics, repeated dose toxicity, genotoxicity and carcinogenicity, there are no other risks for the patient than may be expected on account of the pharmacological mechanism. At maximally tolerated doses in both the rat and the rabbit, simvastatin produced no foetal malformations, and had no effects on fertility, reproductive function or neonatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose, anhydrous
Cellulose, microcrystalline
Maize starch, pregelatinised
Butyl-hydroxyanisole (E320)
Magnesium stearate
Talc
Hyprolose
Hypermellose
Titanium dioxide (E 171)

6.2 Incompatibilities
None.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
PVC/PE/PVDC/aluminium blisters- Each blister contains either 10 or 14 tablets to give pack sizes of 14, 28, 30, 56, 60 or 100 tablets,
PVC/PE/PVDC/aluminium blisters in polyester/aluminium/PE sachets, - Each blister contains either 10 or 14 tablets. The blisters will be enclosed in a sachet to give pack sizes of 14, 28, 30, 56, 60 or 100 tablets. These sachets will then be placed in an outer carton.

HDPE container with child-proof PP closure and aluminium original seal. The containers are available in pack sizes of 100’s and 500’s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Ltd.
Unit 3
Canalside
Northbridge Road
Berkhamsted
Hertfordshire
HP4 1EG
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0127

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/09/2007
UKPAR Simvastatin 10mg, 20mg and 40mg Tablets

PL 17907/0125-7

10 DATE OF REVISION OF THE TEXT
13/09/2007
PATIENT INFORMATION LEAFLET

Read this entire leaflet carefully before you start taking this medicine. If you have further questions, please ask your doctor or pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Simvastatin tablets are and what are they used for?
2. Before you take Simvastatin tablets.
3. How to take Simvastatin tablets?
4. Possible side effects.
5. Storing Simvastatin tablets.

The name of this medicine is Simvastatin 10 mg Tablets or Simvastatin 20 mg Tablets or Simvastatin 40 mg Tablets

The tablets marketed by Bristol Laboratories Ltd are available in three strengths and contain either 10 mg, 20 mg or 40 mg of the active ingredient simvastatin.

The tablets also contain lactose (anhydrous), cellulose (microcrystalline), maize starch (pregelatinised), butylhydroxyanisole (E320), magnesium stearate, talc, hypromellose, hypromellose, titanium dioxide (E171).

Marketing Authorisation Holder and Manufacturer: Bristol Laboratories Ltd., Unit 3, Canalside, Northbridge Road, Berkhamsted, Hertfordshire, HP4 1EQ.

Product Licence Number: 17907/0125 Simvastatin 10 mg Tablets
17907/0125 Simvastatin 20 mg Tablets
17907/0127 Simvastatin 40 mg Tablets

1. WHAT SIMVASTATIN TABLETS ARE AND WHAT ARE THEY USED FOR?

Simvastatin Tablets are: white oblong, biconvex tablets, scored on one side, embossed with “10”, “20” or “40” on the scored side and with “SVT” on the opposite side.

The tablets are supplied to your pharmacist in packs containing 14, 28 or 56 tablets who will then provide you with the required number of tablets as prescribed by your doctor.

The Simvastatin contained in your tablets belongs to a group of medicines known as 'statins' or 'HMG-CoA reductase inhibitors'. These work by reducing the amount of cholesterol and fatty substances called triglycerides in your blood. Cholesterol is vital to the normal functioning of the body but if levels of cholesterol in the bloodstream are too high it can be deposited on the walls of the arteries.

Nearly all the cholesterol in our body is made by our own liver. The body produces most cholesterol at night, which is why it is recommended that Simvastatin tablets are taken in the evening or at night.

Your doctor may have done some blood tests which show that, even though you may be taking a low-fat diet, you still have too much fat (of which cholesterol is a type) in your blood.

You have been prescribed Simvastatin tablets for the following reason, which your doctor will explain to you:

- You have high cholesterol in your blood; the level of triglycerides may also be high. Simvastatin should lower these levels. It is generally accepted that a high cholesterol level in your blood adds to the risk of heart disease. The higher the level, the greater the risk,
- Your doctor may also have prescribed Simvastatin tablets to reduce the health risks associated with coronary heart disease (CHD). If you have CHD or are at risk of developing CHD (because you have diabetes, have had a stroke, or other blood vessel disease), Simvastatin may prolong your life by reducing the risk of heart disease by helping to keep your arteries clear, even if your cholesterol levels are normal.

2. BEFORE YOU TAKE SIMVASTATIN TABLETS

Do not take the tablets if:
- you are pregnant or breast feeding
- you have liver problems
- you have had a bad reaction to this or similar medicines or to any of the ingredients in the past.
- you are taking an antifungal drug called itraconazole or ketoconazole
- you are taking the antibiotics erythromycin or clarithromycin, or telithromycin
- you are taking the antidepressant nefazodone
- you are taking a medicine for the treatment of HIV infections (HIV protease inhibitor) such as indinavir, nelfinavir, ritonavir or saquinavir

If you think any of these apply to you, do not take the tablets, go and talk to your doctor first and follow the advice given.

Tell your doctor...
- about all your medical conditions, including allergies
- if you consume substantial quantities of alcohol or if you have a past history of liver disease. Your doctor may conduct some blood tests to check your liver before and after starting treatment,
- if you have any kidney problems
- quickly, if you experience unexplained muscle pain, tenderness or weakness. This is because on rare occasions, there is a risk of muscle problems which may be serious, including muscle breakdown, which can result in kidney damage. The doctor may perform a blood test to check the condition of your muscles before and after starting treatment.

Things to note regarding muscle effects
- the risk of muscle breakdown is greater at higher doses of Simvastatin
- the risk of muscle breakdown is greater in certain patients. Tell your doctor if any of the following applies to you:
  - kidney problems
  - thyroid problems
  - you are more than 70 years old
  - you have ever had muscle problems during treatment with cholesterol lowering medicines called 'statins' (such as simvastatin, atorvastatin, pravastatin), or fibrates (such as gemfibrozil, bezafibrate)
  - the risk of muscle problems can be greater if Simvastatin is taken with certain medicines (see below, and tell your doctor if you are taking any of these):
    - antifungal agents, such as itraconazole or ketoconazole (see section headed 'Before you take Simvastatin tablets')
    - the antibiotics erythromycin, clarithromycin or telithromycin (see section headed 'Before you take Simvastatin tablets')
    - nefazodone, an antidepressant (see section headed 'Before you take Simvastatin tablets').
    - HIV protease inhibitors such as indinavir, nelfinavir, ritonavir and saquinavir (see section headed 'Before you take Simvastatin tablets')
    - ciclosporin, a drug used to suppress the immune system
• fibrates (other cholesterol-lowering medicines), such as gemfibrozil and bezafibrate
• amiodarone, a medicine used for irregular heart beat
• verapamil or diltiazem- drugs used to treat high blood pressure, chest pain associated with heart disease, or other heart conditions.
• niacin or nicotinic acid (other cholesterol-lowering medicines) in large doses (i.e. greater than or equal to 1g per day)

It is also important to tell your doctor if you are taking anticoagulants (drugs that prevent blood clots), such as warfarin or fenofibrate, another fibric acid derivative.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Use in pregnancy and breastfeeding

Pregnancy: Do not take Simvastatin tablets if you are pregnant, trying to become pregnant or suspect you may be pregnant. If you become pregnant while taking Simvastatin, stop taking it immediately and contact your doctor.

Breast-feeding: Do not take Simvastatin tablets if you are breast-feeding. Consult your doctor before taking the tablets if you are breast-feeding or planning to breast-feed.

Use in children

Simvastatin is not recommended for use in children

Taking Simvastatin with grapefruit juice

Grapefruit juice contains one or more components that alter the metabolism of some medications, including Simvastatin. Therefore, consuming grapefruit juice should be avoided as it could increase your risk of muscle damage.

It is unlikely that these tablets will affect your ability to drive or operate machinery. If you experience any dizziness make sure that you are fit to drive or operate machinery before attempting to do so.

# HOW TO TAKE SIMVASTATIN TABLETS?

You should take your tablets exactly as advised by your doctor or pharmacist. The usual starting dose is 20 or 40 mg, given as a single dose in the evening. Your doctor may adjust your dose to a maximum of 80 mg per day. The 80 mg dose is only recommended in patients with very high blood cholesterol levels and high risk of other complications related to heart disease. Your doctor may prescribe lower doses, particularly if you are taking certain medicines listed above or you have certain kidney conditions. Your doctor may need to change this dose in order to have the best effect.

Do not take more or less than your doctor has prescribed.

Keep taking your tablets for as long as your doctor has asked you to. If you stop taking Simvastatin, your cholesterol may rise again.
If you forget to take Simvastatin tablets:
If you miss a dose, do not worry. Simply take your normal dose when it is next due. Do not take a double dose to make up for forgotten individual doses.

If you take more Simvastatin than you should
If you have taken more Simvastatin than you should, or if someone accidentally swallows some, contact your doctor or pharmacist, or go to your nearest hospital casualty department immediately. If possible take the tablets or the box with you to show the doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Simvastatin may occasionally cause side-effects in some patients.
For the most part, side effects have been mild and short-lived.
The following side effects were reported rarely: stomach upsets (such as sickness, constipation, diarrhoea, flatulence, indigestion, and abdominal pain), weakness, headache, dizziness, numbness or loss of sensation in the arms and legs, hair loss, rash, itchiness, liver disease (possibly presenting as yellowing of the eyes and/or skin, itchiness of the skin, dark coloured urine, pale coloured stool(s)), muscle disease (presenting as pains and aches, tenderness, weakness or cramps), or an allergic reaction to Simvastatin tablets. The allergic reaction may include some of the following: swelling of the face, tongue or throat (in which case you should contact your doctor immediately), joint pains, joint and blood vessel inflammation, unusual bruising, skin eruptions, swelling, hives, skin sensitivity to the sun, a high temperature, flushing, difficulty in breathing or tiredness.

Contact your doctor promptly if you experience muscle pain, tenderness or weakness.
This is because on rare occasions, muscle problem can be serious, including muscle breakdown resulting in kidney damage (see section headed 'Before you take Simvastatin tablets')

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING SIMVASTATIN TABLETS

Keep all medicines out of reach and sight of children.
Do not store above 25°C. Store in the original package.
Do not take Simvastatin tablets after the expiry date, which is marked on both the outer carton and on each blister strip of tablets.

If you find that you have tablets that have passed their expiry date, return them to your local pharmacist (chemist) who will dispose of them properly.

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UKPAR Simvastatin 10mg, 20mg and 40mg Tablets

Packaging

Each tablet contains Simvastatin 10 mg. Also contains Lactose. For oral administration. Take as directed by the physician.

For further information please see the enclosed patient information leaflet. Keep out of the reach and sight of children. Do not store above 25°C. Store in the original package.
UKPAR Simvastatin 10mg, 20mg and 40mg Tablets

Each tablet contains Simvastatin 20 mg. Also contains Lactose.

For oral administration, take as directed by the physician.

For further information please see the enclosed patient information leaflet. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Do not store above 25°C, store in the original package.