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SIMVASTATIN 10, 20, 40 and 80 MG TABLETS

PL 17907/0060-2 & 0205

LAY SUMMARY

On 7th April 2010, the MHRA granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Simvastatin 10, 20, 40, and 80mg Tablets. These medicines are only available on prescription from your doctor.

Simvastatin belongs to a group of medicines called statins or lipid-lowering medicines.
Simvastatin is part of the treatment to lower levels of cholesterol in your blood. It can also be used to reduce the risk of heart problems caused by fats building up in your blood vessels.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Simvastatin 10, 20, 40 and 80mg Tablets outweigh the risks. Hence Marketing Authorisations have been granted.
SIMVASTATIN 10, 20, 40 and 80 MG TABLETS

PL 17907/0060-2 & 0205

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 10, 20, 40 and 80mg Tablets (PL 17907/0060-2 & 0205) on the 7th April 2010. These products are prescription-only medicines (POM).

These are National abridged complex and standard applications for Simvastatin 10, 20, 40 and 80mg Tablets submitted under article 10 (1) of Directive 2001/83/EC, as amended. The application claims the products to be generic medicinal products of Zocor tablets, PL 00025/0241-3 and PL 00025/0366 (10-40mg and 80mg tablets), marketing authorisations for which were granted to MSD on 28/04/89. The claim of essential similarity is being based upon the results of a bioavailability study.

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.

Simvastatin is indicated for the treatment of coronary heart disease, hyperlipidaemia and homozygous familial hypercholesterolaemia.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN: Simvastatin

Chemical names: [1S-[1α,3α,7β,8β(2S*,4S*),8αβ]]1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl-2,2-dimethylbutanoate

CAS Registry no.: 79902-63-9

Structure

![Structure Diagram]

Molecular formula: C_{25}H_{38}O_{5}

Molecular weight: 418.57

General properties

A white crystalline powder. Practically insoluble in water, very soluble in methylene chloride, freely soluble in alcohol.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely Lactose monohydrate, Maize Starch, Pregelatinised starch, Sodium starch glycollate, Colloidal anhydrous silica, Butylated hydroxytoluene (E321), Citric acid monohydrate (E330), Ascorbic acid (E300), Microcrystalline cellulose (E460), Magnesium stearate (E572), Hypromellose 5 cps (E464), Purified Talc (E553b), Titanium dioxide (E171), Macrogol 400, Iron oxide red (E172) and Iron oxide yellow (E172).

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of Iron oxide red (E172) and Iron oxide yellow (E172) which comply with US Pharmacopoeia. Satisfactory Certificates of Analysis have been provided for all excipients.
The lactose used to produce lactose monohydrate is sourced from healthy animals under the same conditions as milk for human consumption.

The magnesium stearate is from vegetable origin and a declaration from the manufacturer is provided.

**Pharmaceutical development**
Suitable pharmaceutical development data have been provided for these applications. Comparable dissolution and impurity profile are provided for these products versus the originator product.

**Manufacture**
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and 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**
Product is packaged in aluminium/PVC/PVDC blister. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years with storage conditions of ‘Store below 25 degree C’ and ‘Store in the original package’ are set and this is acceptable.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling**
The SPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA Form**
The MAA form is pharmaceutically satisfactory.

**Expert Report**
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.
Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of the product are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A preclinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of an environmental risk assessment.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

BIOEQUIVALENCE (STUDY)
A bioequivalence study comparing the 40mg strength with the same strength of the innovator product, Zocor, from the UK market was carried out. It was an open, two-period, single dose, crossover study under fasting conditions in 60 healthy volunteers (59 completed, one subject withdrew on medical grounds), with a 1 week washout between treatment periods.
In the 40mg biostudy, plasma samples were taken prior to dosing and, intermittently, for up to 24 hours after administration. These were analysed to determine the concentration of simvastatin and its active metabolite (simvastatin hydroxy acid), and to calculate primary pharmacokinetic parameters: $T_{\text{max}}$, $C_{\text{max}}$, AUC$_{0-4}$ and AUC$_{0-\infty}$, $T_{\frac{1}{2}}$, $\lambda_z$ and AUC %extrapolated were also determined.

Table 1 - Simvastatin Pharmacokinetics, 40 mg, mean data, n=59

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Agent, mean</th>
<th>Reference mean</th>
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<tbody>
<tr>
<td>$C_{\text{max}}$ ng/ml</td>
<td>16.2</td>
<td>19.0</td>
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<tr>
<td>$T_{\text{max}}$ h</td>
<td>2.3</td>
<td>1.8</td>
</tr>
<tr>
<td>AUC$_{\alpha}$ ng.h/ml</td>
<td>69.3</td>
<td>61.4</td>
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<tr>
<td>$T_{\frac{1}{2}}$ hours</td>
<td>4.9</td>
<td>3.8</td>
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Table 2 - Hydroxymetabolite Pharmacokinetics, 40 mg, mean data, n=59

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Agent, mean (SD)</th>
<th>Reference, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ ng/ml</td>
<td>22.7</td>
<td>20.6</td>
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<tr>
<td>$T_{\text{max}}$ h</td>
<td>5.4</td>
<td>5.0</td>
</tr>
<tr>
<td>AUC$_{\alpha}$ ng.h/ml</td>
<td>251</td>
<td>212</td>
</tr>
<tr>
<td>$T_{\frac{1}{2}}$ hours</td>
<td>7.5</td>
<td>5.6</td>
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</table>

The applicant’s claim of bioequivalence between test and reference products can be accepted.
The lower strength formulations are of proportional composition, have similar in vitro dissolution profiles, same manufacturer and method of manufacture. Simvastatin exhibits linear pharmacokinetics over this dose range and the extrapolation of the results of the study conducted with the highest strength preparation to lower strengths can be accepted.

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

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

**EXPERT REPORT**
A clinical expert report has been written by clinical consultant to the pharmaceutical industry. The report is satisfactory.

**SUMMARY OF PRODUCT CHARACTERISTICS**
Clinically satisfactory

**PATIENT INFORMATION LEAFLET**
This is satisfactory

**LABELLING**
These are satisfactory.

**MARKETING AUTHORISATION FORM**
These are satisfactory.

**DISCUSSION**
The applicant has conducted a bioequivalent study comparing the applicant’s product with the cross referred medicinal product. The study has confirmed that both products are bioequivalent and therefore would exhibit the same efficacy and safety profile. The multiple dose waiver criteria are met and hence this study is accepted as demonstrating bioequivalence for the other product strengths.

**CONCLUSIONS**
The Applicant appears to have demonstrated that the product and the reference compound are bioequivalent.

The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Simvastatin 10, 20, 40 and 80mg 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
No new data have been submitted and none are required for an application of this type.

Simvastatin 10, 20, 40 and 80mg Tablets are the generic versions of Zocor tablets (MSD). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredients, simvastatin and are the same pharmaceutical form.

Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

No new safety data are supplied or required for these generic applications. Simvastatin have well-established side-effect profiles and are generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

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 product and the innovator product are interchangeable. Extensive clinical experience with Simvastatin 10, 20, 40 and 80mg Tablets are considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
**SIMVASTATIN 10, 20, 40 and 80 MG TABLETS**

**PL 17907/0060-2 & 0205**

**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 23rd June 2003</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 21st August 2003</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossier on 24/09/2003</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information to the quality section on 30/11/2005</td>
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<tr>
<td>5</td>
<td>The applications were determined on 07 April 2010</td>
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SIMVASTATIN 10, 20, 40 and 80 MG TABLETS

PL 17907/0060-2 & 0205

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 10 mg, film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 10 mg of simvastatin.

For excipients, see 6.1

Each 10 mg tablet contains 75.5 mg of Lactose monohydrate

3 PHARMACEUTICAL FORM
Film-coated tablet.

Simvastatin 10mg film-coated tablets are Pinkish-brown coloured, oval, biconvex, film-coated tablets with ‘BL’ embossing on one side & ‘10’ embossing on the other 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 80 mg/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'. The usual starting dose is 10–20 mg/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' 40 mg/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' 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' 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 ciclosporin, danazol, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses (>1 g/day) of niacin concomitantly with 'Simvastatin', the dose of 'Simvastatin' should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with 'Simvastatin', the dose of 'Simvastatin' 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 < 30 ml/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**

The experience in children is limited. '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.

The risk of myopathy/rhabdomyolysis is dose related. The incidence in clinical trials, in which patients were carefully monitored and some interacting medicinal products were excluded, has been approximately 0.03% at 20mg, 0.08% at 40mg and 0.4% at 80mg.

**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 and ciclosporin 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: ciclosporin, 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 10 mg daily in patients receiving concomitant medication with ciclosporin, 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, ciclosporin, or danazol 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 20 mg 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.

Excipient

This product contains lactose. Patients with rare hereditary problems of 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 below 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

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: ciclosporin, verapamil, diltiazem (see sections 4.2 and 4.4).

Ciclosporin
The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporin 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 ciclosporin. Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is 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.

Fusidic acid

The risk of myopathy may be increased by concomitant administration of fusidic acid with statins, including simvastatin. Isolated cases of rhabdomyolysis have been reported with simvastatin. Temporary suspension of simvastatin treatment may be considered. If it proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.4).

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.
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.

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.

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 and 5.3.)

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 40 mg/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' 40 mg compared with 5.1 % in patients treated with placebo). The incidence of myopathy was < 0.1 % in patients treated with 'Simvastatin' 40 mg compared with 5.1 % in patients treated with placebo. The incidence of elevated transaminases (> 3 x ULN confirmed by repeat test) occurred in 0.21 % (n = 21) of patients treated with 'Simvastatin' 40 mg 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 taken 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 inactive 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' may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with 'Simvastatin'. In addition, 'Simvastatin' moderately increases HDL-C and reduces plasma TG. As a result of these changes the ratios of total-to HDL-C and LDL- to HDL-C are reduced.

High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease

In the Heart Protection Study (HPS), the effects of therapy with 'Simvastatin' were assessed in 20,536 patients (age 40–80 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' 40 mg/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 135 mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

Treatment with 'Simvastatin' 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' 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' 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' 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' 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 the 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
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' 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 hypercholesterolemia, 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 dependent 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 systemic 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
Tablet core
- Lactose monohydrate
- Maize Starch
- Pregelatinised starch
- Sodium starch glycollate
- Colloidal anhydrous silica
- Butylated hydroxytoluene (E321)
- Citric acid monohydrate (E330)
- Ascorbic acid (E300)
- Microcrystalline cellulose (E460)
- Magnesium stearate (E572)

Tablet coating
- Hesperine 5 cps (E464)
- Purified Talc (E553b)
- Titanium dioxide (E171)
- Macrogol 400
- Iron oxide red (E172)
- Iron oxide yellow (E172)

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Al / PVDC-PVC blisters of 14, 28 or 56 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
BRISTOL LABORATORIES LIMITED
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0060

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
07/04/2010

10 DATE OF REVISION OF THE TEXT
07/04/2010
1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 20 mg, film coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains 20 mg of simvastatin.

For excipients, see 6.1

Each 20 mg tablet contains 151 mg of Lactose monohydrate

3 PHARMACEUTICAL FORM
Film-coated tablet.

Simvastatin 20mg film-coated tablets are Peach coloured, oval, biconvex, film-coated tablets with 'BL' embossing on one side & '20' embossing on the other 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 80 mg/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'. The usual starting dose is 10 – 20 mg/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' 40 mg/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' 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' 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 ciclosporin, danazol, gemfibrozil, other fibrates (except fenofibrate) or lipido-lowering doses (≥ 1 g/day) of niacin concomitantly with 'Simvastatin', the dose of 'Simvastatin' should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with 'Simvastatin', the dose of 'Simvastatin' 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 < 30 ml/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

The experience in children is limited. '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. The risk of myopathy/rhabdomyolysis is dose related. The incidence in clinical trials, in which patients were carefully monitored and some interacting medicinal products were excluded, has been approximately 0.03% at 20mg, 0.08% at 40mg and 0.4% at 80mg.

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 and ciclosporin 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: ciclosporin, 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 10 mg daily in patients receiving concomitant medication with ciclosporin, 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, ciclosporin, or danazol 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 20 mg 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.

Excipient

This product contains lactose. Patients with rare hereditary problems of 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 below 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

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: ciclosporin, verapamil, diltiazem (see sections 4.2 and 4.4).

Ciclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin 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 ciclosporin. Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is 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.
**Fusidic acid**

The risk of myopathy may be increased by concomitant administration of fusidic acid with statins, including simvastatin. Isolated cases of rhabdomyolysis have been reported with simvastatin. Temporary suspension of simvastatin treatment may be considered. If it proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.4).

**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.

**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.

**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.

### 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 and 5.3.)

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 40 mg/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' 40 mg 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' 40 mg 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 transeptidase) (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 taken 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 inactive 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' may involve both reduction of VLDL-cholesterol (VLDL–C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL–C. Apolipoprotein B also falls substantially during treatment with 'Simvastatin'. In addition, 'Simvastatin' moderately increases HDL–C and reduces plasma TG. As a result of these changes the ratios of total- to HDL–C and LDL- to HDL–C are reduced.

High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease

In the Heart Protection Study (HPS), the effects of therapy with 'Simvastatin' were assessed in 20,536 patients (age 40–80 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' 40 mg/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 135 mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

Treatment with 'Simvastatin' 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' 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' 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' 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' 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 the 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' 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 hypercholesterolemia, 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 dependent 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 systemic 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

**Tablet core**
- Lactose monohydrate
- Maize Starch
- Pregelatinised starch
- Sodium starch glycollate
- Colloidal anhydrous silica
- Butylated hydroxytoluene (E321)
- Citric acid monohydrate (E330)
- Ascorbic acid (E300)
- Microcrystalline cellulose (E460)
- Magnesium stearate (E572)

**Tablet coating**
- Hypromellose 5 cps (E464)
- Purified Talc (E553b)
- Titanium dioxide (E171)
- Macrogol 400
- Iron oxide red (E172)
- Iron oxide yellow (E172)

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
3 Years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Al/PVDC-PVC blisters of 14, 28 or 56 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
BRISTOL LABORATORIES LIMITED
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
   PL 17907/ 0061

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   07/04/2010

10 DATE OF REVISION OF THE TEXT
    07/04/2010
1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 40 mg, film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 40 mg of simvastatin.

For excipients, see 6.1
Each 40 mg tablet contains 302 mg of Lactose monohydrate

3 PHARMACEUTICAL FORM
Film-coated tablet.
Simvastatin 40mg film-coated tablets are Dull pink coloured, oval, biconvex, film-coated tablets with ‘BL’ embossing on one side & ‘40’ embossing on the other 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 80 mg/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'. The usual starting dose is 10–20 mg/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' 40 mg/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' 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’ 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 ciclosporin, danazol, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses (> 1 g/day) of niacin concomitantly with ’Simvastatin’, the dose of ’Simvastatin’ should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with ’Simvastatin’, the dose of ’Simvastatin’ 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 < 30 ml/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

The experience in children is limited. ’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. The risk of myopathy/rhabdomyolysis is dose related. The incidence in clinical trials, in which patients were carefully monitored and some interacting medicinal products were excluded, has been approximately 0.03% at 20mg, 0.08% at 40mg and 0.4% at 80mg.

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 and ciclosporin 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: ciclosporin, 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 10 mg daily in patients receiving concomitant medication with ciclosporin, 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, ciclosporin, or danazol 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 20 mg 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.

**Excipient**

This product contains lactose. Patients with rare hereditary problems of 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 below 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

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: ciclosporin, verapamil, diltiazem (see sections 4.2 and 4.4).

Ciclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin 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 ciclosporin. Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is 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.

**Fusidic acid**

The risk of myopathy may be increased by concomitant administration of fusidic acid with statins, including simvastatin. Isolated cases of rhabdomyolysis have been reported with simvastatin. Temporary suspension of simvastatin treatment may be considered. If it proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.4).

**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.

**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.

**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.

### 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 and 5.3.)

*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 40 mg/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' 40 mg 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' 40 mg 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 taken 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 inactive 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' may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with 'Simvastatin'. In addition, 'Simvastatin' moderately increases HDL-C and reduces plasma TG. As a result of these changes the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease

In the Heart Protection Study (HPS), the effects of therapy with 'Simvastatin' were assessed in 20,536 patients (age 40–80 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' 40 mg/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 135 mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

Treatment with 'Simvastatin' 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 nonvascular deaths did not reach statistical significance. 'Simvastatin' 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' 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' 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' 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 the 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' 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 hypercholesterolemia, 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 dependent 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 systemic 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.
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**

**Tablet core**
- Lactose monohydrate
- Maize Starch
- Pregelatinised starch
- Sodium starch glycollate
- Colloidal anhydrous silica
- Butylated hydroxytoluene (E321)
- Citric acid monohydrate (E330)
- Ascorbic acid (E300)
- Microcrystalline cellulose (E460)
- Magnesium stearate (E572)

**Tablet coating**
- Hypromellose 5 cps (E464)
- Purified Talc (E553b)
- Titanium dioxide (E171)
- Macrogol 400
- Iron oxide red (E172)

6.2 **INCOMPATIBILITIES**

Not applicable

6.3 **SHELF LIFE**

3 years

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**

Store below 25°C. Store in the original package.

6.5 **NATURE AND CONTENTS OF CONTAINER**

Al / PVDC-PVC blisters of 14, 28 or 56 tablets

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**

Any unused product or waste material should be disposed of in accordance with local requirements.
7 MARKETING AUTHORIZATION HOLDER
BRISTOL LABORATORIES LIMITED
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom

8 MARKETING AUTHORIZATION NUMBER(S)
PL 17907/0062

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
07/04/2010

10 DATE OF REVISION OF THE TEXT
07/04/2010
UKPAR Simvastatin 10, 20, 40, and 80mg Tablets

1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 80 mg, film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 80 mg of simvastatin.

For excipients, see 6.1

Each 80 mg tablet contains 604 mg of Lactose monohydrate

3 PHARMACEUTICAL FORM
Film-coated tablet.

Simvastatin 80mg film-coated tablets are pink coloured, capsule shaped, biconvex, film-coated tablets with ‘BL’ embossing on one side & ‘80’ embossing on the other 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 80 mg/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'. The usual starting dose is 10–20 mg/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' 40 mg/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’ 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' 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 ciclosporin, danazol, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses (≥1 g/day) of niacin concomitantly with 'Simvastatin', the dose of 'Simvastatin' should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with 'Simvastatin', the dose of 'Simvastatin' 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 <30 ml/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

The experience in children is limited. '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. The risk of myopathy/rhabdomyolysis is dose related. The incidence in clinical trials, in which patients were carefully monitored and some interacting medicinal products were excluded, has been approximately 0.03% at 20mg, 0.08% at 40mg and 0.4% at 80mg.

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 and ciclosporin 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: ciclosporin, 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 10 mg daily in patients receiving concomitant medication with ciclosporin, 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, ciclosporin, or danazol 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 20 mg 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.

**Excipient**

This product contains lactose. Patients with rare hereditary problems of 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 below 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*

*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: ciclosporin, verapamil, diltiazem (see sections 4.2 and 4.4).

Ciclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin 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 ciclosporin. Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is 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.

*Fusidic acid*

The risk of myopathy may be increased by concomitant administration of fusidic acid with statins, including simvastatin. Isolated cases of rhabdomyolysis have been reported with simvastatin. Temporary suspension of simvastatin treatment may be considered. If it proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.4).

*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.

*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.

*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.

### 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 and 5.3.)

**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 40 mg/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' 40 mg 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' 40 mg 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 transeptidase) (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 taken 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 inactive 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' may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with 'Simvastatin'. In addition, 'Simvastatin' moderately increases HDL-C and reduces plasma TG. As a result of these changes the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease

In the Heart Protection Study (HPS), the effects of therapy with 'Simvastatin' were assessed in 20,536 patients (age 40–80 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' 40 mg/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 135 mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

Treatment with 'Simvastatin' 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 nonvascular deaths did not reach statistical significance. 'Simvastatin' 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' 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' 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' 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 the 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' 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 hypercholesterolemia, 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 dependent 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 systemic 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
Tablet core
Lactose monohydrate
Maize Starch
Pregelatinised starch
Sodium starch glycinate
Colloidal anhydrous silica
Butylated hydroxytoluene (E321)
Citric acid monohydrate (E330)
Ascorbic acid (E300)
Microcrystalline cellulose (E460)
Magnesium stearate (E572)

Tablet coating
Hypromellose 5 cps (E464)
Purified Talc (E553b)
Titanium dioxide (E171)
Macrogol 400
Iron oxide red (E172)

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Al / PVDC-PVC blisters of 14, 28 or 56 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
BRISTOL LABORATORIES LIMITED
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom
MARKETING AUTHORISATION NUMBER(S)
17907/0205

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
07/04/2010

DATE OF REVISION OF THE TEXT
07/04/2010
UKPAR Simvastatin 10, 20, 40, and 80mg Tablets

PL 17907/0060-2&0205

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

SIMVASTATIN 10 MG, 20 MG, 40 MG and 80 MG
FILM-COATED TABLETS

Read all of this leaflet carefully before you start taking this medicine. Even if you have used this medicine or a similar product before, you should read this text carefully as the information may have changed.

- Keep the leaflet. You may need to read it again.
- If you have further queries, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

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. How to store Simvastatin Tablets
6. Further Information

1. What Simvastatin Tablets are and what they are used for

Simvastatin belongs to a group of medicines called statins or lipid-lowering medicines. Simvastatin is part of the treatment to lower levels of cholesterol in your blood. It can also be used to reduce the risk of heart problems caused by fats building up in your blood vessels.

2. Before you take Simvastatin Tablets

Do not take Simvastatin Tablets if you:
- have ever been told you are allergic to simvastatin or to any other ingredients (these are listed in Section 6, Further Information)
- have liver problems
- if you are pregnant or breastfeeding
- if you are taking any of the following medicines: anti-fungal drugs (such as itraconazole and ketoconazole), antiviral medicines (such as ritonavir, indinavir), antibiotics (such as erythromycin, clarithromycin and telithromycin) or nefazodone (an antidepressant)

Take special care whilst taking this medicine if you:
- have any other medical conditions, including allergies
- consume substantial amount of alcohol or have a past history of liver disease. Your doctor may conduct some blood tests to check your liver before and after starting treatment.
- have kidney problems
- if you have muscle aches or pains or have a family history of muscle problems

Taking other medicines

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed, for example, herbal remedies and health food shops. As this medicine may interact with other drugs.
- cholesterol lowering medicines called 'statins' (such as atorvastatin, pravastatin, niacin, nicotinic acid)
- fibrates (other cholesterol lowering medicines such as gemfibrozil, bezafibrate, fenofibrate)
Stop taking Simvastatin and tell your doctor immediately if you suddenly develop muscle pain, muscle tenderness or muscle 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. Your 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

If you forget to take Simvastatin Tablets
If you forget to take a dose, take it as soon as you remember.

DO NOT TAKE A DOUBLE DOSE TO MAKE UP FOR A FORGOTTEN DOSE.

If you take more Simvastatin Tablets than you should
If you accidentally take too many tablets, tell your doctor immediately or contact your nearest Hospital Casualty/Accident and Emergency Department even if there are no signs of discomfort. Take your medicine in its original packaging with you in order to identify your medication easily.

If you stop taking Simvastatin Tablets
Do not stop taking these tablets without talking to your doctor. Keep taking your tablets for as long as your doctor has asked you to. If you stop taking Simvastatin tablets, your cholesterol may rise again.

4. Possible Side Effects
Like all medicines, Simvastatin Tablets can cause side effects, although not everybody gets them.

The following rare serious side effects were reported.

If any of these serious side effects happen, STOP taking the medicine and tell your doctor immediately or go to the emergency room at your nearest hospital.
- muscle pain, tenderness, weakness or cramps. On rare occasions, these muscle problems can be serious, including muscle breakdown resulting in kidney damage (see section 2)
- hypersensitivity (allergic) reactions including:
  - swelling of the face, tongue and throat which may cause difficulty in breathing
  - severe muscle pain usually in the shoulders and hips
  - rash with weakness of limbs and neck muscles
  - pain or inflammation of the joints
  - inflammation of the blood vessels
  - unusual bruising, skin eruptions and swelling, hives, skin sensitivity to the sun, fever, flushing
  - shortness of breath and feeling unwell
- lupus-like disease picture (including rash, joint disorders, and effects on blood cells)
- inflammation of the liver with yellowing of the skin and eyes, itching, dark-coloured urine or pale-coloured stool, liver failure (very rare)

The following side effects have also been reported rarely:
- low red blood cell count (anaemia)
- numbness or weakness of the arms and legs
• drugs used to suppress the immune system (e.g. ciclosporin)
• medicine used for irregular heart beat (e.g. amiodarone)
• medicine used for the treatment of endometriosis and breast cysts in women (e.g. danazol)
• drugs used to treat high blood pressure, chest pain associated with heart disease, or other heart conditions (e.g. verapamil, diltiazem)
• anticoagulants (such as warfarin)

Taking food or drink with Simvastatin Tablets
• 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.

Pregnancy and Breast-feeding
Pregnancy
• Do NOT take this medicine if you are pregnant, think you have become pregnant or intend to become pregnant whilst taking these tablets.
• Always ask your doctor or pharmacist for advice before taking any medicine.

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.

Driving and using Machines
• 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.

Important Information about some of the ingredients of these tablets
This medicine contains lactose. If you have been previously told by your doctor that you have intolerance to some sugars (such as lactose), contact your doctor before taking this medicine.

3. How to take Simvastatin Tablets
• Always take these tablets exactly as advised by your doctor. You should check with your doctor or pharmacist if you are not sure.
• You should check the label to see how often you should take your tablets. Check with your doctor or pharmacist if you are not sure.
• Ensure that you do not run out of your tablets.
• The number of tablets you need will depend on your condition. The tablets should be swallowed whole with a glass of water.

The usual dosages are as follows:
Adults
• 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.

Children
• Simvastatin Tablets are not recommended for use in children.
5. How to Store Simvastatin Tablets

- Keep the medicine in a safe place where children cannot see or reach it.
- Do not store above 25°C. Store in the original package.
- Do not take your tablets after the expiry date shown on the pack.
- If you have any left over tablets then take them back to your pharmacist for safe disposal.

6. Further Information

What Simvastatin Tablets contain

- The active substance is simvastatin.
- Simvastatin Tablets come in four strengths 10 mg, 20 mg, 40 mg and 80 mg. Each tablet contains either 10 mg, 20mg, 40 mg or 80 mg of the active ingredient.
- The other ingredients are lactose monohydrate, maize starch, pregelatinised maize starch, sodium starch glycollate, colloidal anhydrous silica, microcrystalline cellulose, magnesium stearate, hypromellose, purified talc, titanium dioxide, ferric oxide yellow, ferric oxide red, macrogol 400.

What Simvastatin Tablets look like and contents of the pack

- Simvastatin 10mg Film-coated Tablets are pinkish-brown coloured, oval, biconvex, tablets with 'BL' embossing on one side and '10' embossing on the other side.
- Simvastatin 20mg Film-coated Tablets are peach coloured, oval, biconvex, tablets with 'BL' embossing on one side and '20' embossing on the other side.
- Simvastatin 40mg Film-coated Tablets are dull pink coloured, oval, biconvex, tablets with 'BL' embossing on one side and '40' embossing on the other side.
- Simvastatin 80mg Film-coated Tablets are pink coloured, capsule shaped, biconvex, tablets with 'BL' embossing on one side and '80' embossing on the other side.
- Simvastatin Tablets come in blister packs containing 14, 28 or 56 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Name and address: Bristol Laboratories Ltd,
Unit 3, Canalside, Northbridge Road, Berkhamsted, Hertfordshire,
HP4 1EG, United Kingdom
Telephone: 0044 (0)1442 200922
Fax: 0044 (0)1442 873717
Email: info@bristol-habs.co.uk

Simvastatin 10mg Film-coated Tablets: PL 17907/0060
Simvastatin 20mg Film-coated Tablets: PL 17907/0061
Simvastatin 40mg Film-coated Tablets: PL 17907/0062
Simvastatin 80mg Film-coated Tablets: PL 17907/0205

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