SIMVASTATIN 10 MG, 20 MG AND 40 MG FILM-COATED TABLETS

PL 04077/0221-3

UKPAR

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SIMVASTATIN 10 MG, 20 MG AND 40 MG FILM-COATED TABLETS

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LAY SUMMARY

On 20th January 2011, the MHRA granted M & A Pharmachem Limited Marketing Authorisations (licences) for Simvastatin 10 mg, 20 mg and 40 mg film-coated tablets.

Simvastatin 10 mg, 20 mg and 40 mg film-coated tablets contain the active ingredient, simvastatin. Simvastatin belongs to a group of medicines called statins. Simvastatin lowers the levels of cholesterol and fatty substances known as triglycerides in your blood.

Simvastatin tablets are used, together with diet to treat:
• Raised cholesterol levels (primary hypercholesterolaemia) or elevated fat levels (mixed hypercholesterolaemia) in your blood.

• Homozygous familial hypercholesterolaemia (an inherited disease that causes raised levels of cholesterol.)

• Coronary heart disease (CHD) or are at high risk of CHD (because you have diabetes, history of stroke, or other blood vessel disease.)

Simvastatin tablets may reduce the risk of heart disease by keeping your arteries clear, even if your cholesterol levels are normal.

These tablets have been proven to be similar to tablets of Zocor based on the data provided. No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Simvastatin 10 mg, 20 mg and 40 mg film-coated tablets outweigh the risks; hence Marketing Authorisations have been granted.
SIMVASTATIN 10 MG, 20 MG AND 40 MG FILM-COATED TABLETS

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SCIENTIFIC DISCUSSION

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**INTRODUCTION**

The UK granted M & A Pharmachem Limited Marketing Authorisations for the medicinal products Simvastatin 10 mg, 20 mg and 40 mg film-coated tablets (PL 04077/0221-3) on 20th January 2011. Simvastatin 10 mg, 20 mg and 40 mg film-coated tablets are prescription only medicines (POM).

Simvastatin 10 mg, 20 mg and 40 mg film-coated tablets are indicated for the 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.
- Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Simvastatin 10 mg, 20 mg and 40 mg film-coated tablets can also be used to reduce cardiovascular mortality and morbidity in patients with manifest artherosclerotic 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.

These applications for Simvastatin 10 mg, 20 mg and 40 mg film-coated tablets are submitted under Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Zocor 10 mg, 20 mg and 40 mg tablets (PL 00025/0241-3), first authorised in the UK to Merck Sharp & Dohme Limited in 28th April 1989.

Simvastatin, an inactive lactone is a potent inhibitor of HMG Co-A reductase, an enzyme that catalyses the conversion of HMG Co-A to mevalonate. This is a rate limiting early step in the biosynthetic pathway of cholesterol. The role of high plasma lipids (LDL cholesterol) in atherogenesis with attendant complications (cardiovascular mortality and stroke) is well established, as is the role of statins in reduction of such clinical events and improvement in survival.

The pharmacovigilance system as described by the applicant fulfils the requirements. It also provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Simvastatin
INN: Simvastatin
Chemical name: (1S, 3R, 7S, 8S, 8aR)-8-[2-[(2R, 4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl]-3, 7-dimethyl-1, 2, 3, 7, 8, 8a-hexahydronaphthalen-1-yl-2, 2-dimethylbutanoate.

Structure:

Physical form: White or almost white crystalline powder.

Molecular formula: \( \text{C}_{25}\text{H}_{38}\text{O}_{5} \)
Molecular weight: 418.6

Simvastatin complies with its European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof of molecular structure has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Suitable Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Adequate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.
DRUG PRODUCT

Other ingredients
Other ingredients in the tablet core consist of pharmaceutical excipients including lactose monohydrate, microcrystalline cellulose, pregelatinised starch, butylated hydroxyanisole (E320), ascorbic acid, anhydrous citric acid, colloidal anhydrous silica, talc and magnesium stearate.
Ingredients in the film-coating are hypromellose, red iron oxide (E172), yellow iron oxide (E172), triethyl citrate, titanium dioxide (E171), talc, povidone K-30.

All the ingredients with the exception of yellow iron oxide (E172) and red iron oxide (E172) comply with their relevant European Pharmacopoeia monographs. Yellow iron oxide and red iron oxide comply with the National Formulary and the United States Pharmacopoeia.

None of the excipients with the exception of magnesium stearate contain material of human or animal origin. The supplier has provided a valid TSE Certificate of Suitability.

The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

Product development
The objective of the development programme was to produce products that could be considered generic medicinal products of Zocor 10 mg, 20 mg and 40 mg tablets (Merck Sharp & Dohme Limited).

The reference product used in the bioequivalence study is Zocor 40 mg tablets, authorised in Spain to Merck Sharp & Dohme Limited. The Spanish product is considered qualitatively and quantitatively similar to the reference product marketed in the UK.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacture
A description and flow-chart of the manufacturing method has been provided. Satisfactory batch formulae have been provided for the manufacture of the products. The manufacturing process has been validated and has shown satisfactory results. In-process controls are satisfactory based on batch data and controls on the finished product. Process validation data on pilot batches of each strength have been provided. The applicant has committed to perform process validation on commercial-scale batches of each strength.
Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis for all working standards used have been provided and are satisfactory.

Container-Closure System
The products are packaged in blisters composed of aluminium, polyvinyl chloride (PVC) and polyvinylidene chloride.

Pack sizes are:
PL 04077/0221: 10, 14, 20, 28, 30, 40, 50, 56, 60, 84, 98 or 100 tablets.
PL 04077/0222 and 3: 10, 14, 20, 28, 30, 40, 50, 56, 60, 84, 98 or 100 tablets.
PL 04077/0223: 10, 14, 20, 28, 30, 40, 50, 56, 60, 84, 98 or 100 tablets.

Specifications and Certificates of Analysis have been provided. 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 has been set, with special storage instructions ‘Do not store above 25°C’ and ‘Store in the original package.’ This is satisfactory.

Administrative
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SmPC)
These are pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

MAA Form
These are pharmaceutically satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, the Marketing Authorisation Holder has included a single bioequivalence study:

A single-dose, two-period, crossover, open-label, randomised bioequivalence study comparing the pharmacokinetics of Simvastatin 40 mg tablets (Test) versus Zocor (simvastatin) 40 mg tablets (Reference) in healthy volunteers.

Blood sampling was performed pre-dose and up to 24 hours post dose in each treatment period. There was a washout period of one week. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-last} (pg.h/mL)</th>
<th>AUC_{0-15} (pg.h/mL)</th>
<th>C_{max} (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>21795±19288</td>
<td>-</td>
<td>2858±2593</td>
</tr>
<tr>
<td>Reference</td>
<td>19957±15955</td>
<td>-</td>
<td>3011±2683</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>109.21</td>
<td>100.85</td>
<td>94.92</td>
</tr>
<tr>
<td></td>
<td>96.11 – 124.09</td>
<td>89.18 – 114.04</td>
<td>83.02 – 108.53</td>
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</tbody>
</table>

Standard parameters for assessing bioequivalence are presented (AUC_{last}, C_{max}) for the principal active metabolite, beta-hydroxy-acid.

The following justification for the measurement of the metabolite, beta-hydroxy-acid only is given below:

‘The metabolite is the active form, and given the suprabioavailability of the parent compound, the AUC of the metabolite (t or infinity) assumes greater significance.’ In this context, bioequivalence between formulations has been acceptable.

The use of AUC_{0-last} rather than AUC_{0-inf} was pre-specified by the applicant and should be regarded as being of primary interest. This is satisfactory. Following the CHMP guidance, the use of AUC_{last} is considered acceptable providing that the derived measure has sufficient coverage.

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{last} and C_{max} for beta-hydroxy-acid, the simvastatin metabolite, lie within the normal 80-125% limits. The metabolite data shows bioequivalence as per CPMP guidance note provisions. There no major safety implications as the metabolite is bioequivalent. Thus, bioequivalence has been shown between the test and reference products.

As the 40 mg strength product meets all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 40 mg strength can be extrapolated to Simvastatin 10 mg and 20 mg film-coated tablets.
EFFICACY
These are generic applications based on demonstration of bioequivalence and new data relating to efficacy are not required as per EU legislation once bioequivalence has been demonstrated.

SAFETY
These are generic applications based on demonstration of bioequivalence and new data relating to safety are not required as per EU legislation once bioequivalence has been demonstrated.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
These are consistent with those for the reference products and are satisfactory.

DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that Simvastatin 10 mg, 20 mg and 40 mg film-coated tablets can be considered as generic medicinal products to the reference products Zocor 10 mg, 20 mg and 40 mg tablets.

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

QUALITY
The important quality characteristics of Simvastatin 10 mg, 20 mg and 40 mg film-coated 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Simvastatin 40 mg film-coated tablets and the reference product.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with simvastatin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
**SIMVASTATIN 10 MG, 20 MG AND 40 MG FILM-COATED TABLETS**

**PL 04077/0221-3**

**STEPS TAKEN FOR ASSESSMENT**

<table>
<thead>
<tr>
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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation Applications on 12\textsuperscript{th} May 2004.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 21\textsuperscript{st} June 2006.</td>
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<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the dossier on 21\textsuperscript{st} June 2006 and 3\textsuperscript{rd} August 2007.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 3\textsuperscript{rd} December 2006 and 14\textsuperscript{th} January 2008.</td>
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<tr>
<td>5</td>
<td>The applications were determined on 20\textsuperscript{th} January 2011.</td>
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SIMVASTATIN 10 MG, 20 MG AND 40 MG FILM-COATED TABLETS

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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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 simvastatin 10 mg
Excipients: lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Peach-coloured, oval, biconvex, film-coated tablet, scored on one side.
The tablet can be divided into equal halves.

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, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks (see section 4.4 and 5.1).

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, or other fibrates (except fenofibrate) 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. In patients taking diltiazem or amlopidine concomitantly with Simvastatin, the
dose of Simvastatin should not exceed 40 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 (10-17 years of age)**

For children and adolescents (boys Tanner Stage II and above and girls who are at least one year
post-menarche, 10-17 years of age) with heterozygous familial hypercholesterolaemia, the
recommended usual starting dose is 10 mg once a day in the evening. Children and adolescents
should be placed on a standard cholesterol-lowering diet before simvastatin treatment initiation; this
diet should be continued during simvastatin treatment.

The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day.
Doses should be individualized according to the recommended goal of therapy as recommended by
the paediatric treatment recommendations (see sections 4.4 and 5.1). Adjustments should be made at
intervals of 4 weeks or more.

The experience of simvastatin in pre-pubertal children is limited.

### 4.3 CONTRAINDICATIONS

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

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Myopathy/Rhabdomolysis**

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

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related.
In a clinical trial database in which 41,413 patients were treated with Zocor 24,747 (approximately
60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of
myopathy was approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In
these trials, patients were carefully monitored and some interacting medicinal products were
excluded.

In a clinical trial in which patients with a history of myocardial infarction were treated with Zocor 80
mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared
with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occurred during
the first year of treatment. The incidence of myopathy during each subsequent year of treatment was
approximately 0.1%. (See sections 4.8 and 5.1).

**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 ≥ 65 years)
- Female gender
- 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.

A higher rate of myopathy has been observed in patients titrated to the 80 mg dose (see section 5.1). Periodic CK measurements are recommended as they may be useful to identify subclinical cases of myopathy. However, there is no assurance that such monitoring will prevent myopathy. 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, ciclosporin and dananzol (see section 4.2)

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of other fibrates or by concomitant use of amiodarone or verapamil with higher doses of simvastatin (see sections 4.2 and 4.5). The risk is increased by concomitant use of diltiazem or amlopidine with simvastatin 80 mg (see sections 4.2 and 4.5).

The risk of myopathy including rhabdomyolysis may be increased by concomitant administration of fusidic acid with statins (see section 4.5).

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 or gemfibrozil. 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), 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).

The combined use of simvastatin at doses higher then 40 mg daily with diltiazem or amlopidine should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of HMG-CoA reductase inhibitors and lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid), either of which can cause myopathy when given alone.

Physicians contemplating combined therapy with simvastatin and lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when the dose of either medicinal product is increased.

In an interim analysis of an ongoing clinical outcomes study, an independent safety monitoring committee identified a higher than expected incidence of myopathy in Chinese patients taking simvastatin 40 mg and nicotinic acid/laropiprant 2000 mg/40 mg. Therefore, caution should be used when treating Chinese patients with simvastatin (particularly doses of 40 mg or higher) co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin. Because the risk of myopathy with statins is dose-related, the use of simvastatin 80 mg with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin is not recommended in Chinese patients. It is unknown whether there is an increased risk of myopathy in other Asian patients treated with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin.

If the combination proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.5). Temporary suspension of simvastain treatment may be considered.

**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.
Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long-term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Use in children and adolescents (10-17 years of age)
Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys Tanner Stage II and above and in girls who were at least one year postmenarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. (See sections 4.2, 4.8, and 5.1.) Adolescent females should be counselled on appropriate contraceptive methods while on simvastatin therapy (see sections 4.3 and 4.6). In patients aged <18 years, efficacy and safety have not been studied for treatment periods >48 weeks' duration and long-term effects on physical, intellectual, and sexual maturation are unknown. Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-pubertal children and pre-menarchal girls.

**Warning on excipients**
This product contains lactose monohydrate. 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**
Interaction studies have only been performed in adults.

**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. 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. Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥1g/day) of niacin (see section 4.4).

**Pharmacokinetic interactions**
Prescribing recommendations for interacting agents are summarized in the table below (further details are provided in the text; see also sections 4.2, 4.3, and 4.4).

<table>
<thead>
<tr>
<th>Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interacting agents</strong></td>
</tr>
<tr>
<td><strong>Potent CYP3A4 inhibitors:</strong></td>
</tr>
<tr>
<td>Itraconazole</td>
</tr>
<tr>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Erythromycin</td>
</tr>
<tr>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Telithromycin</td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
</tr>
<tr>
<td>Nefazodone</td>
</tr>
<tr>
<td>Gemfibrozil</td>
</tr>
<tr>
<td>Ciclosporin</td>
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<tr>
<td>Danazol</td>
</tr>
<tr>
<td>Other fibrates (except fenofibrate)</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
</tbody>
</table>
Verapamil

Diltiazem
Amlodipine

Do not exceed 40 mg simvastatin daily

Fusidic acid

Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.

Grapefruit juice

Avoid grapefruit juice when taking simvastatin

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 or 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 increases the AUC of simvastatin acid presumably due, in part, to inhibition of CYP3A4.

Danazol

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

Gemfibrozil

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

Amiodarone

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with higher doses of simvastatin (see section 4.4). In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. Therefore the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Calcium Channel Blockers

Verapamil

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of verapamil with simvastatin 40 mg or 80 mg (see section 4.4). 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 verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Diltiazem

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg (see section 4.4). 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.

**Amlodipine**
Patients on amlodipine treated concomitantly with simvastatin 80 mg have a slightly increased risk of myopathy. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant amlodipine. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

**Niacin (nicotinic acid)**
Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid). In a pharmacokinetic study, the co-administration of a single dose of nicotinic acid prolonged-release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin and simvastatin acid and in the Cmax of simvastatin acid plasma concentrations.

**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.

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

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

### 4.6 PREGNANCY AND LACTATION

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

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

### 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Simvastatin has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported rarely in post-marketing experiences.

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

In HPS (see section 5.1) involving 20,536 patients treated with 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, **Not known** (cannot be estimated from the available data).

**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).

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

**Nervous system disorders:**
*Rare*: headache, paresthesia, dizziness, peripheral neuropathy
**Very rare**: memory impairment

**Gastrointestinal disorders:**
*Rare*: constipation, abdominal pain, flatulence, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis
Hepato-biliary disorders:
Rare: hepatitis/jaundice
Very rare: hepatic failure

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.

Psychiatric disorders:
Very rare: insomnia

The following adverse events have been reported with some statins:
- sleep disturbances, including insomnia and nightmares
- sexual dysfunction
- depression
- exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

Children and adolescents (10-17 years of age)
In a 48-week study involving children and adolescents (boys Tanner Stage II and above and girls who were at least one year post-menarche) 10-17 years of age with heterozygous familial hypercholesterolaemia (n=175), the safety and tolerability profile of the group treated with simvastatin was generally similar to that of the group treated with placebo. The long-term effects on physical, intellectual, and sexual maturation are unknown. No sufficient data are currently available after one year of treatment. (See sections 4.2, 4.4, and 5.1.)

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 inhibitors.
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.

In a double-blind, placebo-controlled study, 175 patients (99 boys Tanner Stage II and above and 76 girls who were at least one year post-menarche) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (heFH) were randomized to simvastatin or placebo for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg
thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

Simvastatin significantly decreased plasma levels of LDL-C, TG, and Apo B. Results from the extension at 48 weeks were comparable to those observed in the base study. After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the simvastatin 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

After 24 weeks of simvastatin treatment (with dosages increasing from 10, 20 and up to 40 mg daily at 8-week intervals), simvastatin decreased the mean LDL-C by 36.8% (placebo: 1.1% increase from baseline), Apo B by 32.4% (placebo: 0.5%), and median TG levels by 7.9% (placebo: 3.2%) and increased mean HDL-C levels by 8.3% (placebo: 3.6%). The long-term benefits of simvastatin on cardiovascular events in children with heFH are unknown.

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolaemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

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.

The pharmacokinetic properties have been evaluated in adults. Pharmacokinetic data in children and adolescents are not available.

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,
Microcrystalline cellulose,
Pregelatinised starch,
Butylated hydroxyanisole (E320),
Ascorbic acid,
Anhydrous Citric acid,
Colloidal anhydrous silica,
Talc,
Magnesium stearate

Coating:
Hypromellose,
Red iron oxide (E172),
Yellow iron oxide (E172),
Triethyl citrate,
Titanium dioxide (E171),
Talc,
Povidone K-30

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C.
Store in original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Simvastatin 10 mg film-coated tablets are supplied in blister foils (PVC/ PVDC/Aluminium), in packs of 10, 14, 20, 28, 30, 40, 50, 56, 60, 84, 98 or 100 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable

7 MARKETING AUTHORISATION HOLDER
M & A Pharmachem Limited
Allenby Laboratories
Wigan Road
Westhoughton
Bolton
Lancashire, BL5 2AL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 04077/0221

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/01/2011

10 DATE OF REVISION OF THE TEXT
20/01/2011
1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains simvastatin 20 mg
Excipients: lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Tan-coloured, oval, biconvex, film-coated tablet.

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 artherosclerotic 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 who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks (see section 4.4 and 5.1).

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, or other fibrates (except fenofibrate) 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. In patients taking diltiazem or amlopidine concomitantly with Simvastatin, the dose of Simvastatin should not exceed 40 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 (10-17 years of age)
For children and adolescents (boys Tanner Stage II and above and girls who are at least one year post-menarche, 10-17 years of age) with heterozygous familial hypercholesterolaemia, the recommended usual starting dose is 10 mg once a day in the evening. Children and adolescents should be placed on a standard cholesterol-lowering diet before simvastatin treatment initiation; this diet should be continued during simvastatin treatment.

The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy as recommended by the paediatric treatment recommendations (see sections 4.4 and 5.1). Adjustments should be made at intervals of 4 weeks or more.

The experience of simvastatin in pre-pubertal children is limited.

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

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

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,413 patients were treated with Zocor 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which patients with a history of myocardial infarction were treated with Zocor 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%. (See sections 4.8 and 5.1).

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 ≥ 65 years)
- Female gender
- Renal impairment
- Uncontrolled hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Personal or familial history of hereditary muscular disorders
- Personal or familial history of hereditary muscular disorders
- Personal or familial history of hereditary muscular disorders
- 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.

A higher rate of myopathy has been observed in patients titrated to the 80 mg dose (see section 5.1). Periodic CK measurements are recommended as they may be useful to identify subclinical cases of myopathy. However, there is no assurance that such monitoring will prevent myopathy. 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, ciclosporin and danazol (see section 4.2)

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of other fibrates or by concomitant use of amiodarone or verapamil with higher doses of simvastatin (see sections 4.2 and 4.5). The risk is increased by concomitant use of diltiazem or amlopidine with simvastatin 80 mg (see sections 4.2 and 4.5). The risk of myopathy including rhabdomyolysis may be increased by concomitant administration of fusidic acid with statins (see section 4.5).

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 or gemfibrozil. 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),
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).

The combined use of simvastatin at doses higher then 40 mg daily with diltiazem or amlopidine should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of HMG-CoA reductase inhibitors and lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid), either of which can cause myopathy when given alone.

Physicians contemplating combined therapy with simvastatin and lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when the dose of either medicinal product is increased.

In an interim analysis of an ongoing clinical outcomes study, an independent safety monitoring committee identified a higher than expected incidence of myopathy in Chinese patients taking simvastatin 40 mg and nicotinic acid/laropiprant 2000 mg/40 mg. Therefore, caution should be used when treating Chinese patients with simvastatin (particularly doses of 40 mg or higher) co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin. Because the risk of myopathy with statins is dose-related, the use of simvastatin 80 mg with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin is not recommended in Chinese patients. It is unknown whether there is an increased risk of myopathy in other Asian patients treated with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin.

If the combination proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.5). Temporary suspension of simvastain treatment may be considered.

**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.

**Interstitial lung disease**

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough
and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Use in children and adolescents (10-17 years of age)
Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys Tanner Stage II and above and in girls who were at least one year postmenarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. (See sections 4.2, 4.8, and 5.1.) Adolescent females should be counselled on appropriate contraceptive methods while on simvastatin therapy (see sections 4.3 and 4.6). In patients aged <18 years, efficacy and safety have not been studied for treatment periods >48 weeks' duration and long-term effects on physical, intellectual, and sexual maturation are unknown. Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-pubertal children and pre-menarchal girls.

**Warning on excipients**
This product contains lactose monohydrate. 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

Interaction studies have only been performed in adults.

**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. 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. Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (see section 4.4).

**Pharmacokinetic interactions**
Prescribing recommendations for interacting agents are summarized in the table below (further details are provided in the text; see also sections 4.2, 4.3, and 4.4).

**Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis**

<table>
<thead>
<tr>
<th>Interacting agents</th>
<th>Prescribing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potent CYP3A4 inhibitors:</strong></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Contraindicated with simvastatin</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
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<tr>
<td>Erythromycin</td>
<td></td>
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<tr>
<td>Clarithromycin</td>
<td></td>
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<tr>
<td>Telithromycin</td>
<td></td>
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<tr>
<td>HIV protease inhibitors</td>
<td></td>
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<tr>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Avoid but if necessary, do not exceed 10mg simvastatin daily</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Danazol</td>
<td>Do not exceed 20 mg simvastatin daily</td>
</tr>
<tr>
<td>Other fibrates (except fenofibrate)</td>
<td>Do not exceed 40 mg simvastatin daily</td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
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<tr>
<td>Diltiazem</td>
<td></td>
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<tr>
<td>Amlodipine</td>
<td></td>
</tr>
</tbody>
</table>
Fusidic acid  Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.

Grapefruit juice  Avoid grapefruit juice when taking simvastatin

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 increases the AUC of simvastatin acid presumably due, in part, to inhibition of CYP3A4.

Danazol

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

Gemfibrozil

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

Amiodarone

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with higher doses of simvastatin (see section 4.4). In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. Therefore the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Calcium Channel Blockers

Verapamil

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of verapamil with simvastatin 40 mg or 80 mg (see section 4.4). 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 verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Diltiazem

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg (see section 4.4). 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.
Amlodipine
Patients on amlodipine treated concomitantly with simvastatin 80 mg have a slightly increased risk of myopathy. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant amlodipine. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Niacin (nicotinic acid)
Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (>1 g/day) of niacin (nicotinic acid). In a pharmacokinetic study, the co-administration of a single dose of nicotinic acid prolonged-release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin and simvastatin acid and in the Cmax of simvastatin acid plasma concentrations.

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.

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

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

4.6 PREGNANCY AND LACTATION

Pregnancy
Simvastatin is contraindicated during pregnancy (see section 4.3). Safety in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels
of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, Simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See section 4.3.)

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

**4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**
Simvastatin has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported rarely in post-marketing experiences.

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

In HPS (see section 5.1) involving 20,536 patients treated with 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, Not known (cannot be estimated from the available data).

**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).

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

**Nervous system disorders:**
*Rare:* headache, paresthesia, dizziness, peripheral neuropathy
*Very rare:* memory impairment

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

**Hepato-biliary disorders:**
*Rare:* hepatitis/jaundice
*Very rare:* hepatic failure

**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.

Psychiatric disorders:  
Very rare: insomnia

The following adverse events have been reported with some statins:  
• sleep disturbances, including insomnia and nightmares  
• sexual dysfunction  
• depression  
• exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

Children and adolescents (10-17 years of age)  
In a 48-week study involving children and adolescents (boys Tanner Stage II and above and girls who were at least one year post-menarche) 10-17 years of age with heterozygous familial hypercholesterolaemia (n=175), the safety and tolerability profile of the group treated with simvastatin was generally similar to that of the group treated with placebo. The long-term effects on physical, intellectual, and sexual maturation are unknown. No sufficient data are currently available after one year of treatment. (See sections 4.2, 4.4, and 5.1.)

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 inhibitors.  
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.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) evaluated the effect of treatment with Zocor 80 mg versus 20 mg (median followup 6.7 yrs) on major vascular events (MVEs; defined as fatal CHD, non-fatal MI, coronary revascularization procedure, non-fatal or fatal stroke, or peripheral revascularization procedure) in 12,064 patients with a history of myocardial infarction. There was no significant difference in the incidence of MVEs between the 2 groups; Zocor 20 mg (n = 1553; 25.7 %) vs. Zocor 80 mg (n = 1477; 24.5 %); RR 0.94, 95 % CI: 0.88 to 1.01. The absolute difference in LDL-C between the two groups over the course of the study was 0.35 ± 0.01 mmol/L. The safety profiles were similar between the two treatment groups except that the incidence of myopathy was approximately 1.0 % for patients on Zocor 80 mg compared with 0.02 % for patients on 20 mg. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1 %.

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.

Clinical Studies in Children and Adolescents (10-17 years of age)

In a double-blind, placebo-controlled study, 175 patients (99 boys Tanner Stage II and above and 76 girls who were at least one year post-menarche) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (heFH) were randomized to simvastatin or placebo for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

Simvastatin significantly decreased plasma levels of LDL-C, TG, and Apo B. Results from the extension at 48 weeks were comparable to those observed in the base study. After 24 weeks of
treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the simvastatin 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

After 24 weeks of simvastatin treatment (with dosages increasing from 10, 20 and up to 40 mg daily at 8-week intervals), simvastatin decreased the mean LDL-C by 36.8% (placebo: 1.1% increase from baseline), Apo B by 32.4% (placebo: 0.5%), and median TG levels by 7.9% (placebo: 3.2%) and increased mean HDL-C levels by 8.3% (placebo: 3.6%). The long-term benefits of simvastatin on cardiovascular events in children with heFH are unknown.

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolaemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 PHARMACOKINETIC PROPERTIES
Simvastatin is an inactive lactone which is readily hydrolyzed \textit{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.

The pharmacokinetic properties have been evaluated in adults. Pharmacokinetic data in children and adolescents are not available.

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,
Microcrystalline cellulose,
Pregelatinised starch,
Butylated hydroxyanisole (E320),
Ascorbic acid,
Anhydrous Citric acid,
Colloidal anhydrous silica,
Talc,
Magnesium stearate

Coating:
Hypermellose,
Red iron oxide (E172),
Yellow iron oxide (E172),
Triethyl citrate,
Titanium dioxide (E171),
Talc,
Povidone K-30

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C.
Store in original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Simvastatin 20 mg film-coated tablets are supplied in blister foils (PVC/ PVDC/Aluminium), in packs of 10, 14, 20, 28, 30, 40, 50, 56, 60, 84, 98 or 100 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable

7 MARKETING AUTHORISATION HOLDER
M & A Pharmachem Limited,
Allenby Laboratories,
Wigan Road,
Westhoughton,
Bolton,
Lancashire, BL5 2AL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 04077/0222

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/01/2011

10 DATE OF REVISION OF THE TEXT
20/01/2011
1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 40 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains simvastatin 40 mg
Excipients: lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Brick red-coloured, oval, biconvex, film-coated tablet.

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, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks (see section 4.4 and 5.1).

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, or other fibrates (except fenofibrate) 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. In patients taking diltiazem or amlopidine concomitantly with Simvastatin, the dose of Simvastatin should not exceed 40 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 (10-17 years of age)
For children and adolescents (boys Tanner Stage II and above and girls who are at least one year post-menarche, 10-17 years of age) with heterozygous familial hypercholesterolaemia, the recommended usual starting dose is 10 mg once a day in the evening. Children and adolescents should be placed on a standard cholesterol-lowering diet before simvastatin treatment initiation; this diet should be continued during simvastatin treatment.

The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy as recommended by the paediatric treatment recommendations (see sections 4.4 and 5.1). Adjustments should be made at intervals of 4 weeks or more.

The experience of simvastatin in pre-pubertal children is limited.

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

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

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,413 patients were treated with Zocor 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which patients with a history of myocardial infarction were treated with Zocor 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%. (See sections 4.8 and 5.1).

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 ≥ 65 years)
- Female gender
- 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.

A higher rate of myopathy has been observed in patients titrated to the 80 mg dose (see section 5.1). Periodic CK measurements are recommended as they may be useful to identify subclinical cases of myopathy. However, there is no assurance that such monitoring will prevent myopathy. 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, ciclosporin and danazol (see section 4.2).

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of other fibrates or by concomitant use of amiodarone or verapamil with higher doses of simvastatin (see sections 4.2 and 4.5). The risk is increased by concomitant use of diltiazem or amlopine with simvastatin 80 mg (see sections 4.2 and 4.5).

The risk of myopathy including rhabdomyolysis may be increased by concomitant administration of fusidic acid with statins (see section 4.5).

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 or gemfibrozil. 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),
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).

The combined use of simvastatin at doses higher then 40 mg daily with diltiazem or amlopidine should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of HMG-CoA reductase inhibitors and lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid), either of which can cause myopathy when given alone.

Physicians contemplating combined therapy with simvastatin and lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when the dose of either medicinal product is increased.

In an interim analysis of an ongoing clinical outcomes study, an independent safety monitoring committee identified a higher than expected incidence of myopathy in Chinese patients taking simvastatin 40 mg and nicotinic acid/laropiprant 2000 mg/40 mg. Therefore, caution should be used when treating Chinese patients with simvastatin (particularly doses of 40 mg or higher) co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin. Because the risk of myopathy with statins is dose-related, the use of simvastatin 80 mg with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin is not recommended in Chinese patients. It is unknown whether there is an increased risk of myopathy in other Asian patients treated with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin.

If the combination proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.5). Temporary suspension of simvastain treatment may be considered.

**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.

**Interstitial lung disease**

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough
and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Use in children and adolescents (10-17 years of age)
Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys Tanner Stage II and above and in girls who were at least one year postmenarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. (See sections 4.2, 4.8, and 5.1.) Adolescent females should be counselled on appropriate contraceptive methods while on simvastatin therapy (see sections 4.3 and 4.6). In patients aged <18 years, efficacy and safety have not been studied for treatment periods >48 weeks' duration and long-term effects on physical, intellectual, and sexual maturation are unknown. Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-pubertal children and pre-menarchal girls.

**Adolescent females should be counselled on appropriate contraceptive methods while on simvastatin therapy (see sections 4.3 and 4.6).**

**Warning on excipients**
This product contains lactose monohydrate. 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

Interaction studies have only been performed in adults.

**Pharmacodynamic interactions**

_Her 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. 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. Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥1g/day) of niacin (see section 4.4).

**Pharmacokinetic interactions**

Prescribing recommendations for interacting agents are summarized in the table below (further details are provided in the text; see also sections 4.2, 4.3, and 4.4).

**Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis**

<table>
<thead>
<tr>
<th>Interacting agents</th>
<th>Prescribing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potent CYP3A4 inhibitors:</strong> Itraconazole, Ketoconazole, Erythromycin, Clarithromycin, Telithromycin, HIV protease inhibitors, Nefazodone</td>
<td>Contraindicated with simvastatin</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Avoid but if necessary, do not exceed 10mg simvastatin daily</td>
</tr>
<tr>
<td>Ciclosporin, Danazol, Other fibrates (except fenofibrate)</td>
<td>Do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Amiodarone, Verapamil, Diltiazem, Amlodipine</td>
<td>Do not exceed 20 mg simvastatin daily, Do not exceed 40 mg simvastatin daily</td>
</tr>
</tbody>
</table>
### Effects of other medicinal products on simvastatin

#### Interactions involving CYP3A4

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

Therefore, combination with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: 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 increases the AUC of simvastatin acid presumably due, in part, to inhibition of CYP3A4.

#### Danazol

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

#### Gemfibrozil

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

#### Amiodarone

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with higher doses of simvastatin (see section 4.4). In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. Therefore the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

#### Calcium Channel Blockers

**Verapamil**

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of verapamil with simvastatin 40 mg or 80 mg (see section 4.4). 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 verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

**Diltiazem**

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg (see section 4.4). 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.
Amlodipine
Patients on amlodipine treated concomitantly with simvastatin 80 mg have a slightly increased risk of myopathy. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant amlodipine. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Niacin (nicotinic acid)
Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid). In a pharmacokinetic study, the co-administration of a single dose of nicotinic acid prolonged-release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin and simvastatin acid and in the Cmax of simvastatin acid plasma concentrations.

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.

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

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

4.6 PREGNANCY AND LACTATION

Pregnancy
Simvastatin is contraindicated during pregnancy (see section 4.3). Safety in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that
observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, Simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See section 4.3.)

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Simvastatin has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported rarely in post-marketing experiences.

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

In HPS (see section 5.1) involving 20,536 patients treated with 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, Not known (cannot be estimated from the available data).

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).

Blood and lymphatic system disorders:
Rare: anaemia

Nervous system disorders:
Rare: headache, paresthesia, dizziness, peripheral neuropathy
Very rare: memory impairment

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

Hepato-biliary disorders:
Rare: hepatitis/jaundice
Very rare: hepatic failure
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 maleste.

Psychiatric disorders:
Very rare: insomnia

The following adverse events have been reported with some statins:
• sleep disturbances, including insomnia and nightmares
• sexual dysfunction
• depression
• exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

Children and adolescents (10-17 years of age)
In a 48-week study involving children and adolescents (boys Tanner Stage II and above and girls who were at least one year post-menarche) 10-17 years of age with heterozygous familial hypercholesterolaemia (n=175), the safety and tolerability profile of the group treated with simvastatin was generally similar to that of the group treated with placebo. The long-term effects on physical, intellectual, and sexual maturation are unknown. No sufficient data are currently available after one year of treatment. (See sections 4.2, 4.4, and 5.1.)

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 inhibitors.
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.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) evaluated the effect of treatment with Zocor 80 mg versus 20 mg (median followup 6.7 yrs) on major vascular events (MVEs; defined as fatal CHD, non-fatal MI, coronary revascularization procedure, non-fatal or fatal stroke, or peripheral revascularization procedure) in 12,064 patients with a history of myocardial infarction. There was no significant difference in the incidence of MVEs between the 2 groups; Zocor 20 mg (n = 1553; 25.7 %) vs. Zocor 80 mg (n = 1477; 24.5 %); RR 0.94, 95 % CI: 0.88 to 1.01. The absolute difference in LDL-C between the two groups over the course of the study was 0.35 ± 0.01 mmol/L. The safety profiles were similar between the two treatment groups except that the incidence of myopathy was approximately 1.0 % for patients on Zocor 80 mg compared with 0.02 % for patients on 20 mg. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1 %.

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.

Clinical Studies in Children and Adolescents (10-17 years of age)

In a double-blind, placebo-controlled study, 175 patients (99 boys Tanner Stage II and above and 76 girls who were at least one year post-menarche) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (heFH) were randomized to simvastatin or placebo for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

Simvastatin significantly decreased plasma levels of LDL-C, TG, and Apo B. Results from the extension at 48 weeks were comparable to those observed in the base study. After 24 weeks of
treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the simvastatin 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

After 24 weeks of simvastatin treatment (with dosages increasing from 10, 20 and up to 40 mg daily at 8-week intervals), simvastatin decreased the mean LDL-C by 36.8% (placebo: 1.1% increase from baseline), Apo B by 32.4% (placebo: 0.5%), and median TG levels by 7.9% (placebo: 3.2%) and increased mean HDL-C levels by 8.3% (placebo: 3.6%). The long-term benefits of simvastatin on cardiovascular events in children with heFH are unknown.

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolaemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

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.

The pharmacokinetic properties have been evaluated in adults. Pharmacokinetic data in children and adolescents are not available.

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, Microcrystalline cellulose, Pregelatinised starch, Butylated hydroxyanisole (E320), Ascorbic acid, Anhydrous Citric acid, Colloidal anhydrous silica, Talc,
Magnesium stearate

Coating:
- Hypromellose,
- Red iron oxide (E172),
- Yellow iron oxide (E172),
- Triethyl citrate,
- Titanium dioxide (E171),
- Talc,
- Povidone K-30

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C.
Store in original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Simvastatin 40 mg film-coated tablets are supplied in blister foils (PVC/ PVDC/Aluminium), in packs of 10, 14, 20, 28, 30, 40, 50, 56, 60, 84, 98 or 100 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable

7 MARKETING AUTHORISATION HOLDER
M & A Pharmachem Limited,
Allenby Laboratories,
Wigan Road,
Westhoughton,
Bolton,
Lancashire, BL5 2AL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 04077/0223

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/01/2011

10 DATE OF REVISION OF THE TEXT
20/01/2011
Simvastatin 10mg, 20mg, 40mg
Film-coated Tablets

Read all of this leaflet carefully before you start taking this medicine

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

In this leaflet:
1. What Simvastatin tablets are and what they are 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, which are lipid-lowering medicines.

Simvastatin lowers the levels of cholesterol and fatty substances known as triglycerides in your blood.

Most cholesterol is produced in the body by the liver. This happens mainly at night, which is why it is recommended that Simvastatin tablets are taken in the evening or at night.

Simvastatin tablets are used, together with diet if you have:
- Raised cholesterol levels (primary hypercholesterolaemia) or elevated fat levels (mixed hypercholesterolaemia) in your blood.
- Homozygous familial hypercholesterolaemia (an inherited disease that causes raised levels of cholesterol.)
- Coronary heart disease (CHD) or other high risk of CHD (because you have diabetes, history of stroke, or other blood vessel disease.)

Simvastatin tablets may reduce the risk of heart disease by keeping your arteries clear, even if your cholesterol levels are normal.

It is generally accepted that a high cholesterol level in your blood increases the risk of heart disease. The higher the level, the greater the risk. The presence of other factors, such as existing heart disease, high blood pressure, high blood sugar (diabetes), increased weight, lack of exercise and smoking adds to the risk of getting or worsening of heart disease with high cholesterol.

In most people there are no obvious signs of high cholesterol. Your doctor will measure the levels of cholesterol with a blood test.

2. BEFORE YOU TAKE SIMVASTATIN TABLETS

DO NOT TAKE Simvastatin tablets if:
- you are hypersensitive (allergic) to simvastatin or any of the other ingredients of the tablets (listed in section 6)
- you have liver problems
- you are pregnant or breast-feeding
- you are taking:
  - antifungal drugs such as itaconazole or ketoconazole
  - antibiotics erythromycin, tetracyclines or clindamycin
  - the antidepressant nefazodone
  - a medicine for the treatment of HIV infections (HIV protease inhibitor) such as indinavir, nelfinavir, ritonavir or saquinavir

If you think any of these apply to you talk to your doctor before taking the tablets.

Before taking Simvastatin tablets, it is important to tell your doctor:
- if you are taking anticoagulants (drugs that prevent blood clots such as warfarin)
- if you have an intolerance to some sugars
- about your present and past health problems, especially muscle problems, diabetes and kidney problems, as well as any allergies.
- if you consume large quantities of alcohol
- if you have a history of liver disease
- if you are due to have major surgery. You may need to stop taking Simvastatin tablets for a while.
- if you have severe respiratory failure

Muscle problems with Simvastatin
In rare occasions there is a risk of muscle problems, which may be serious. The doctor may perform a blood test to check the condition of your muscles before and after starting treatment.

Contact your doctor immediately if you experience unexplained muscle pain, tenderness or weakness

The risk of developing muscle problems is greater with high doses of Simvastatin and in certain patients.

Tell your doctor before you take Simvastatin if any of the following apply to you:
- you are female
- you are more than 65 years old
- you have kidney problems
- you have thyroid problems
- you or close family members have a hereditary muscle disease
- you have ever had muscle problems during treatment with cholesterol lowering medicines called statins (e.g. simvastatin, atorvastatin, pravastatin) or fibrates (e.g. gemfibrozil)
- you have a history of alcohol abuse
- you are taking certain other medicines (see 'Taking other medicines' below): Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

It is particularly important that your doctor knows if you are taking any of the following medicines as they may cause an increased risk of muscle problems:
- ciclosporin, a medicine used to suppress the immune system
- antifungal agents (such as itaconazole or ketoconazole)
- medicines for the treatment of HIV infections (such as indinavir, nelfinavir, ritonavir and saquinavir)
- other cholesterol lowering medicines such as fibric acid derivatives e.g. gemfibrozil, bezafibrate, fenofibrate
- antibiotic medicines containing erythromycin, tetracyclines, fusidic acid or clindamycin
- nefazodone (an antidepressant)
- amiodarone (used to treat irregular heart beat)
- verapamil, diltiazem or amiodipine (used to treat high blood pressure, angina or other heart conditions)
- danazol (used to treat endometriosis)

Also tell your doctor or pharmacist if you are taking:
- oral anticoagulants (drugs that prevent blood clots), such as warfarin, phenprocoumon or acenocoumarol, as simvastatin may increase the risk of bleeding
- niacin or nicotinic acid (cholesterol lowering medicines) containing products, especially if you are Chinese.

Taking Simvastatin tablets with food and drink

Grapefruit juice contains substances that change how the body uses some medicines, including Simvastatin tablets. You should not drink grapefruit juice when taking Simvastatin tablets.

Children

Safety and effectiveness have been studied in 10-17 year old boys and in girls who have started their menstrual period at least one year before (see HOW TO TAKE SIMVASTATIN TABLETS). Simvastatin has not been studied in children under the age of 10 years. For more information, talk to your doctor.
Pregnancy and Breastfeeding
Do not take Simvastatin tablets if you are pregnant, trying to become pregnant or think you might be pregnant. If you become pregnant while taking Simvastatin tablets, stop taking it immediately and contact your doctor.
If you are breastfeeding your baby you should not take Simvastatin tablets. Consult your doctor before taking the tablets if you are breastfeeding or planning to breastfeed.

Driving and using machines
At the recommended doses, Simvastatin tablets are not expected to affect your ability to drive or use machines. However, when driving or operating machinery, it should be taken into account that dizziness has been reported rarely.

Important information about one of the ingredients of Simvastatin:
Simvastatin tablets contain lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE SIMVASTATIN TABLETS
Always take Simvastatin tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Remember to take your medicine.

Your doctor will tell you how long you have to take Simvastatin tablets. Do not stop treatment early or your cholesterol will rise to pre-treatment levels.

Your doctor will have explained the importance of staying on a cholesterol lowering diet as well as taking the Simvastatin tablets.

Dosage:
- Your doctor will determine the appropriate tablet strength for you, depending on your condition, current treatment and personal risk status.
- Take the tablets in the evening with or without food.
- The usual starting dose is 10, 20 or, in some cases, 40mg a day, by mouth. Your doctor may adjust your dose after at least 4 weeks to a maximum of 80mg a day.
- The 80mg dose is only recommended for adults with very high cholesterol levels and at high risk of heart disease problems, who have not reached their cholesterol goal on lower doses.

If your doctor has prescribed Simvastatin along with any bile acid sequestrant (medicines for lowering cholesterol), you should take Simvastatin at least 2 hours before or 4 hours after taking the bile acid sequestrant.

Your doctor may prescribe lower doses, especially if you are taking certain medicines (see above), or suffer from kidney disorders.

If the required dose is 5mg, break the scored 10mg tablet in two.

Do not take more or less than has been prescribed for you by your doctor.

Use in children (10-17 years old)
The recommended usual starting dose is 10mg a day in the evening. The maximum recommended dose is 40mg a day.

If you take more Simvastatin tablets than you should talk to a doctor or pharmacist immediately. If you forget to take Simvastatin tablets
Do not take a double dose to make up for forgotten individual doses. Continue with the next tablet as usual.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Simvastatin tablets can have side effects in some patients. In most cases the side effects are mild and of short duration.

Rare, serious side effects (occurring in less than 1 in 1000 people)
Stop taking the tablets and tell your doctor immediately, or go to the nearest hospital casualty department if you have any of the following:
- muscle pain, tenderness, weakness or cramps. On rare occasions these muscle problems can be serious such as muscle breakdown, resulting in kidney damage, and very rarely deaths have occurred.
- hypersensitivity (allergic) syndrome which may include:
  - swelling of the face, tongue or throat
  - muscle pain and wasting
  - joint pain and inflammation
- stiffness in the morning with pain in the shoulders and hips
- inflammation of the blood vessels
- unusual bruising, skin eruptions, swelling
- skin sensitivity to the sun, raised itchy rash
- fever, flushing
- feeling unwell
- shortness of breath
- liver problems and jaundice (yellowing of the skin and/or eyes, dark coloured urine, pale coloured stools)
- inflammation of the pancreas giving severe abdominal pain.

Other rare side effects (occurring in less than 1 in 1000 people)
Tell your doctor or pharmacist if any of the following side effects gets serious:
- dizziness, headache
- hair loss
- rash and itchiness
- stomach upsets (such as sickness, diarrhoea, stomach pain, indigestion, constipation and flatulence)
- abnormal sensations in the arms and legs
- numbness and tingling
- weakness
- anaemia
- trouble sleeping (very rare)
- poor memory (very rare).

Possible side effects reported with some statins:
- sleep disturbances, including insomnia and nightmares
- sexual difficulties
- depression
- breathing problems including persistent cough and/or shortness of breath or fever.

Laboratory Values
Increases in some blood tests of liver function and a muscle enzyme (creatine kinase) have been observed.

If you notice any side effect not mentioned in this leaflet tell your doctor or pharmacist.

5. HOW TO STORE SIMVASTATIN TABLETS
Keep out of reach and sight of children.
Do not store above 25°C.
Store in the original package in order to protect from moisture.
Do not use Simvastatin tablets after the expiry date marked on the pack.

6. FURTHER INFORMATION
What Simvastatin tablets contain
Each tablet contains the active ingredient simvastatin 10mg, 20mg or 40mg.
The other ingredients are: lactose monohydrate, microcrystalline cellulose, pregelatinised starch, butylated hydroxyanisole (E320), ascorbic acid, citric acid anhydrous, colloidal anhydrous silica, talc, magnesium stearate, hypromellose, red iron oxide (E172), yellow iron oxide (E172), triethyl citrate, titanium dioxide (E171), povidone.

What this medicine looks like and contents of the pack
Simvastatin 10mg Tablets are peach-coloured, film-coated, oval shaped tablets scored on one side.
Simvastatin 20mg Tablets are tan-coloured, film-coated, oval shaped tablets.
Simvastatin 40mg Tablets are brick red-coloured, film-coated, oval shaped tablets.
They are available in packs of 10, 14, 28, 26, 30, 40, 50, 56, 60, 84, 98 or 100 tablets contained in an outer carton. Not all pack sizes may be marketed.
Marketing authorisation holder and manufacturer:
M & A Pharmacem Ltd, Wigan Road, Westhoughton, Bolton, Lancs, BL5 2AL
Date of approval of the leaflet: MM/YYYY

PP2202
Simvastatin 40mg film-coated tablets.
Please read the enclosed leaflet, it contains important information for the correct use of Simvastatin 40mg film-coated tablets.
Each tablet contains 40mg simvastatin. It also contains lactose monohydrate.
Take the tablets by mouth as directed by your doctor.
Keep out of reach and sight of children.
Do not store above 25°C.
Store in the original package to protect from moisture.
Do not use after the expiry date shown on the package and on the blister pack.
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M&A Pharmachem Ltd Bolton, Lancashire BL5 2AL.
PL 04077/0223
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