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

PL 21880/0064-7

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

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LAY SUMMARY

On 4th August 2010, the MHRA granted Marketing Authorisations (licences) for the medicinal products Simvastatin 10, 20, 40 and 80mg Tablets. These medicines are only available on prescription from your doctor.

The licences were granted to the company Medreich plc. This company is the marketing authorisation holder.

Simvastatin is a medicine used to lower levels of cholesterol, “bad” cholesterol (LDL cholesterol) and fatty substances called triglycerides in the blood. In addition simvastatin raises levels of “good” cholesterol (HDL cholesterol).

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

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SCIENTIFIC DISCUSSION

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INTRODUCTION

MHRA granted marketing authorisations for medicinal products Simvastatin 10, 20, 40 and 80mg Film-coated Tablets (PL 21880/0064-7) to Medreich PLC on the 4th August 2010. These are prescription only medicines (POM) used in the treatment of:

- primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (such as 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.
- 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

These applications were submitted as simple abridged applications according to Article 10c of Directive 2001/83/EC, cross-referring to Simvastatin 10, 20, 40 and 80mg Film-coated Tablets (PL 20532/0176-9), held by Aurobindo Pharma Limited, which was granted marketing authorisations on 26th September 2008.

No new data were submitted nor were they necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products.

A pharmacovigilance system has been provided with these applications and is satisfactory. A suitable justification for non-submission of the Risk Management Plan has been provided for the reference products.

No environmental risk assessment (ERA) has been undertaken, as this is not considered necessary. Simvastatin is essentially similar and the therapeutic indications and posology of the finished product are the same as those already licensed products. The applicant’s justification for absence of ERA is satisfactory.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 21880/0064-7
PROPRIETARY NAME: Simvastatin 10, 20, 40 and 80mg Film-coated Tablets
COMPANY NAME: Medreich PLC
E.C. ARTICLE: Article 10c of Directive 2001/83/EC
LEGAL STATUS: POM

1 INTRODUCTION
These are simple, informed consent applications for Simvastatin 10, 20, 40 and 80mg Film-coated Tablets, submitted under Article 10c of Directive 2001/83/EC. The applications cross-refer to Simvastatin 10, 20, 40 and 80mg Film-coated Tablets (PL 20532/0176-9), approved on 26th September 2008 to the marketing authorisation holder Aurobindo Pharma Limited. The current application is considered valid.

2 MARKETING AUTHORISATION APPLICATION (MAA)

2.1 Name(s)
The proposed names of the products are Simvastatin 10, 20, 40 and 80mg Film-coated Tablets. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The product contains the active ingredient simvastatin.

The tablets are packed in polyvinylchloride/polyethylene/polyvinylidene chloride/aluminium blisters. The pack sizes are 10, 14, 28, 30, 50, 56, 84, 98 and 100 tablets. Specification and Certificate of Analysis for all packaging components used have been provided and are satisfactory. The packaging and pack sizes are the same as those for the reference products.

The proposed shelf life is 3 years, with no special storage conditions. The shelf-life and storage condition are identical to those for the reference products and are satisfactory.

2.3 Legal status
These products are prescription only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
The proposed Marketing Authorisation holder is Medreich Plc, 9 Royal Parade, Kew Gardens, Surrey, TW9 3QD, United Kingdom.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.
2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specifications
The proposed finished product and shelf-life specifications are in line with the details registered for the reference products.

2.9 Drug substance specification
The proposed drug substance specifications conform to the current European Pharmacopoeia monograph for simvastatin, and are in-line with those for the reference products.

European Directorate for the Quality of Medicines (EDQM) certificates of suitability for the manufacturer of simvastatin has been provided. The active substance manufacturer is in line with those for the reference products.

2.10 TSE Compliance
No materials of human or animal origin have been used in the manufacture of these products. This is consistent with the reference products.

2.11 Bioequivalence
No bioequivalence data are required to support these informed consent applications, as the proposed products are manufactured to the same formula utilising the same process as the reference products Simvastatin 10, 20, 40 and 80mg Film-coated Tablets (PL 20532/0176-9).

3 EXPERT REPORT
The applicant has included detailed expert reports of the application. Signed declarations and copies of the experts’ CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4 PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearance of the product is identical to those of the reference products.

5 SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The proposed SmPCs are consistent with the details registered for the reference products.
6. **PATIENT INFORMATION LEAFLET (PIL)/LABELLING**
No user testing has been conducted as these are informed consent applications which use the content of the cross-reference product’s package leaflet. A declaration has been made that the applicant’s PIL is identical in content and layout, and therefore an additional user test should not be required.

The applicant has provided a declaration that they will commit to make the package leaflet available in a format that is appropriate for the blind and partially sighted.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. **CONCLUSIONS**
The data submitted with the applications are acceptable. The grant of marketing authorisations is recommended.
PRECLINICAL ASSESSMENT

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

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the reference products and, as such, have been judged to be satisfactory.

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

EFFICACY
These applications are identical to the previously granted applications for Simvastatin 10, 20, 40 and 80mg Film-coated Tablets (PL 20532/0176-9), granted to Aurobindo Pharma Limited on the 26th September 2008.

Pharmaceutical preclinical and clinical expert statements have been provided, together with CVs showing the experts are appropriately qualified. The experts confirm that the products are identical in composition, manufacture and pharmaceutical characteristics to the respective reference products and that there are no toxicological or clinical issues.

No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the reference products. Extensive clinical experience with simvastatin is considered to have demonstrated the therapeutic values of the compounds. The risk benefit is, therefore, considered to be positive.
SIMVASTATIN 10MG, 20MG, 40MG and 80MG FILM-COATED TABLETS

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STEPS TAKEN FOR ASSESSMENT

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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 5th March 2010</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications are valid on 8th March (Simvastatin 10 and 20mg Film-coated Tablets) and 10th March 2010 (Simvastatin 40 and 80mg Film-coated Tablets)</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information on 28th May 2010</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s request, providing further information on 8th June 2010</td>
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<tr>
<td>5</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 10 mg simvastatin.
Excipient: Lactose monohydrate
One film-coated tablet contains 70 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Light pink, round and biconvex film-coated tablets with “A” debossed on one side and “01” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia
Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (such as exercise, weight reduction) is inadequate.
Treatmnt of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL-apheresis) or if such treatments are not appropriate.
Cardiovascular prevention
Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy (see section 5.1).

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

Hypercholesterolaemia
The patient should be placed on a standard cholesterol-lowering diet, and should continue with 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 simvastatin dose is 40mg/day in the evening or 80mg/day in 3 divided doses of 20mg, 20mg, and an evening dose of 40mg. 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 treatment
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 cyclosporin, 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. (See sections 4.4 and 4.5).

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

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

Use in the elderly
No dosage adjustment is necessary.

Use in children and adolescents
The experience in children is limited. Therefore Simvastatin is not recommended for paediatric use.

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

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

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

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

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

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

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

**Whilst on treatment**

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

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

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

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

The risk of myopathy or 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, cyclosporin 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). There is also a slight increase in risk when diltiazem is used with simvastatin 80 mg. The risk of myopathy 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: cyclosporin, 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 cyclosporin, 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), cyclosporin 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 or niacin (≥ 1g/day) 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).

If the combination proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.5). Temporary suspension of simvastatin 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 medicinal product should be used with caution in patients who consume substantial quantities of alcohol.

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

Excipient
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 and niacin (nicotinic acid) (≥ 1 g/day). Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see below Pharmacokinetic interactions and sections 4.2 and 4.4). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.
Pharmacokinetic interactions
Prescribing recommendations for interacting agents are summarised 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>
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<tr>
<td><strong>Interacting agents</strong></td>
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<tr>
<td>Hotent CYP3A4 inhibitors:</td>
</tr>
<tr>
<td>Itraconazole</td>
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<tr>
<td>Ketoconazole</td>
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<tr>
<td>Erythromycin</td>
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<td>Clarithromycin</td>
</tr>
<tr>
<td>Telithromycin</td>
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<tr>
<td>HIV protease inhibitors</td>
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<tr>
<td>Nefazodone</td>
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<tr>
<td>Gemfibrozil</td>
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<tr>
<td>Cyclosporin</td>
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<tr>
<td>Danazol</td>
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<tr>
<td>Other fibrates (except fenofibrate)</td>
</tr>
<tr>
<td>Amiodarone</td>
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<td>Verapamil</td>
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<tr>
<td>Diltiazem</td>
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<tr>
<td>Fusidic acid</td>
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<tr>
<td>Grapefruit juice</td>
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</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,
erthythromycin, 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 experienced when combining simvastatin with certain other less potent
CYP3A4 inhibitors: cyclosporin, verapamil and diltiazem (see sections 4.2 and 4.4).

Cyclosporin

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

Danazol

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

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

**Amiodarone and verapamil**

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

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

**Diltiazem**

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

**Fusidic acid**

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

**Grapefruit juice**

Grapefruit juice inhibits cytochrome P4503A4. 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 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

**Oral anticoagulants**

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

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

4.6 Pregnancy and lactation

Pregnancy

Simvastatin is contraindicated during pregnancy (see section 4.3). Safety in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence. Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, Simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (see section 4.3 and 5.3).

Lactation

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

4.7 Effects on ability to drive and use machines

Simvastatin has no or negligible influence on 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 Heart Protection Study (HPS) and Scandinavian Simvastatin Survival Study (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 frequency of the undesirable effects is indicated as follows:

Very common (≥ 1/10),
Common (≥ 1/100 to <1/10),
Uncommon (≥ 1/1,000 to <1/100),
Rare (≥ 1/10,000 to <1/1,000),
Very rare (<1/10,000), not known (cannot be estimated from the available data)

Blood and lymphatic system disorders:
*Rare*: anaemia

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

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.

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

### 4.9 Overdose

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

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA-reductase inhibitor
ATC code: C10A A01

After oral administration, 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
The Heart Protection Study (HPS), the effects of therapy with simvastatin were assessed in 20,536 patients (age 40-80 years), with or without hyperlipidaemia and with coronary heart disease, other occlusive arterial disease or diabetes mellitus. In this study, 10,269 patients were treated with simvastatin 40 mg/day and 10,267 patients were treated with placebo for a mean duration of 5 years. At baseline, 6,793 patients (33 %) had LDL-C levels below 116 mg/dL; 5,063 patients (25 %) had levels between 116 mg/dL and 135 mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

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

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with simvastatin on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomised, double-blind, placebo-controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet, standard care, and either simvastatin 20-40 mg/day (n = 2,221) or placebo (n = 2,223) for a median duration of 5.4 years. Simvastatin reduced the risk of death by 30 % (absolute risk reduction of 3.3 %). The risk of CHD death was reduced by 42 % (absolute risk reduction of 3.5 %). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent nonfatal MI) by 34 %. Furthermore, Simvastatin significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischemic attacks) by 28 %. There was no statistically significant difference between groups in non-cardiovascular mortality.
Primary hypercholesterolaemia and combined hyperlipidaemia
In studies comparing the efficacy and safety of simvastatin 10, 20, 40 and 80 mg daily in patients with hypercholesterolemia, the mean reductions of LDL-C were 30, 38, 41 and 47 %, respectively. In studies of patients with combined (mixed) hyperlipidaemia on simvastatin 40 mg and 80 mg, the median reductions in triglycerides were 28 and 33 % (placebo: 2 %), respectively, and mean increases in HDL-C were 13 and 16 % (placebo: 3 %), respectively.

5.2 Pharmacokinetic properties
Simvastatin is an inactive lactone readily hydrolysed \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.

\textit{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 the 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.

\textit{Distribution}
The protein binding of simvastatin and its active metabolite is > 95%.

\textit{Elimination}
Simvastatin is a substrate of CYP3A4 (see sections 4.3 and 4.5). The major metabolites of simvastatin 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 intravenous 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:
- Butylated hydroxyanisole (E 320)
- Ascorbic acid (E 300)
- Citric acid monohydrate (E 330)
- Cellulose, microcrystalline (E 460a)
- Pregelatinised maize starch
- Lactose monohydrate
- Magnesium stearate (E 470B)

Film coating:
- Hypromellose (E 464)
- Hydroxy propyl cellulose (E 463)
- Titanium dioxide (E 171)
- Talc (E 553b).
- Iron oxide yellow (E 172)
- Iron oxide red (E 172)
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
The tablets are packed in PVC/PE/PVdC/aluminium blisters with 10, 14, 28, 30, 50, 56, 84, 98 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed off in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Medrech Plc
9 Royal Parade
Kew Gardens
Surrey
TW9 3QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 21880/0064

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/08/2010

10 DATE OF REVISION OF THE TEXT
04/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 20 mg simvastatin.
Excipient: Lactose monohydrate
One film-coated tablet contains 140 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Light pink, round and biconvex film-coated tablets with the inscription “A” debossed on one side and “02” on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Hypercholesterolaemia
Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (such as exercise, weight reduction) is inadequate.

Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL-apheresis) or if such treatments are not appropriate.

Cardiovascular prevention
Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy (see section 5.1).

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

Hypercholesterolaemia
The patient should be placed on a standard cholesterol-lowering diet, and should continue with 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 LDC-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 simvastatin dose is 40mg/day in the evening or 80mg/day in 3 divided doses of 20mg, 20mg, and an evening dose of 40mg. 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 treatment
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 cyclosporin, 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. (See sections 4.4 and 4.5).

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

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

Use in the elderly
No dosage adjustment is necessary.

Use in children and adolescents
The experience in children is limited. Therefore Simvastatin is not recommended for paediatric use.

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

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

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

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

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

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

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

**Whilst on treatment**

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

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

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

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

The risk of myopathy or 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, cyclosporin 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). There is also a slight increase in risk when diltiazem is used with simvastatin 80 mg. The risk of myopathy 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: cyclosporin, 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 cyclosporin, 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), cyclosporin 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 or niacin (≥ 1g/day) 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).

If the combination proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.5). Temporary suspension of simvastatin 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 medicinal product should be used with caution in patients who consume substantial quantities of alcohol.

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

Excipient
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 and niacin (nicotinic acid) (≥ 1 g/day). Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see below Pharmacokinetic interactions and sections 4.2 and 4.4). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.
Pharmacokinetic interactions
Prescribing recommendations for interacting agents are summarised 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>Interacting agents</th>
<th>Prescribing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potent CYP3A4 inhibitors:</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Contraindicated with simvastatin</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
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<tr>
<td>Clarithromycin</td>
<td></td>
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<tr>
<td>Telithromycin</td>
<td></td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Avoid but if necessary, do not exceed 10 mg</td>
</tr>
<tr>
<td></td>
<td>simvastatin daily</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Danazol</td>
<td></td>
</tr>
<tr>
<td>Other fibrates (except fenofibrate)</td>
<td>Do not exceed 20 mg simvastatin daily</td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>Do not exceed 40 mg simvastatin daily</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td></td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Avoid grapefruit juice when taking simvastatin</td>
</tr>
</tbody>
</table>

Effects of other medicinal products on simvastatin

Interactions involving CYP3A4
Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors and nefazodone. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11-fold increase in exposure to simvastatin acid.

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

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

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

Gemfibrozil
Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway (see sections 4.2 and 4.4).
Amiodarone and verapamil
The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see section 4.4). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

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

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

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

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

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

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

Pregnancy
Simvastatin is contraindicated during pregnancy (see section 4.3). Safety in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence. Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, Simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (see section 4.3 and 5.3).

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

4.7 Effects on ability to drive and use machines
Simvastatin has no or negligible influence on 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 Heart Protection Study (HPS) and Scandinavian Simvastatin Survival Study (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 frequency of the undesirable effects is indicated as follows:
Very common (≥ 1/10),
Common (≥ 1/100 to <1/10),
Uncommon (≥ 1/1,000 to <1/100),
Rare (≥ 1/10,000 to <1/1,000),
Very rare (<1/10,000), not known (cannot be estimated from the available data)
Blood and lymphatic system disorders:
*Rare:* anaemia

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

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.

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

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

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

After oral administration, 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
The Heart Protection Study (HPS), the effects of therapy with simvastatin were assessed in 20,536 patients (age 40-80 years), with or without hyperlipidaemia and with coronary heart disease, other occlusive arterial disease or diabetes mellitus. In this study, 10,269 patients were treated with simvastatin 40 mg/day and 10,267 patients were treated with placebo for a mean duration of 5 years. At baseline, 6,793 patients (33 %) had LDL-C levels below 116 mg/dL; 5,063 patients (25 %) had levels between 116 mg/dL and 135 mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

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

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

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

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

Absorption
In man simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose. Maximum plasma concentration of the 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 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 intravenous 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:**

- Butylated hydroxyanisole (E 320)
- Ascorbic acid (E 300)
- Citric acid monohydrate (E 330)
- Cellulose, microcrystalline (E 460a)
- Pregelatinised maize starch
- Lactose monohydrate
- Magnesium stearate (E 470B)

**Film coating:**

- Hypromellose (E 464)
- Hydroxy propyl cellulose (E 463)
- Titanium dioxide (E 171)
- Talc (E 553b).
- Iron oxide yellow (E 172)
- Iron oxide red (E 172)

#### 6.2 Incompatibilities

Not applicable.

#### 6.3 Shelf life

3 years.

#### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

#### 6.5 Nature and contents of container

The tablets are packed in PVC/PE/PVdC/aluminium blisters with 10, 14, 28, 30, 50, 56, 84, 98 and 100 tablets. Not all pack sizes may be marketed.

#### 6.6 Special precautions for disposal

Any unused product or waste material should be disposed off in accordance with local requirements.
7 MARKETING AUTHORISATION HOLDER
Medreich Plc
9 Royal Parade
Kew Gardens
Surrey
TW9 3QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 21880/0065

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/08/2010

10 DATE OF REVISION OF THE TEXT
04/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 40mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 40mg simvastatin.
Excipient: Lactose monohydrate
One film-coated tablet contains 280 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Pink, round and biconvex film-coated tablets with “A” debossed on one side and “03” on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypercholesterolaemia
Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (such as exercise, weight reduction) is inadequate.

Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL-apheresis) or if such treatments are not appropriate.

Cardiovascular prevention
Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy (see section 5.1).

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

Hypercholesterolaemia
The patient should be placed on a standard cholesterol-lowering diet, and should continue with 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 simvastatin dose is 40mg/day in the evening or 80mg/day in 3 divided doses of 20mg, 20mg, and an evening dose of 40mg. 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 20to 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 treatment
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 cyclosporin, 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. (See sections 4.4 and 4.5).

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

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

Use in the elderly
No dosage adjustment is necessary.

Use in children and adolescents
The experience in children is limited. Therefore Simvastatin is not recommended for paediatric use.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

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

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

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

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

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

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

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

The risk of myopathy or 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, cyclosporin 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). There is also a slight increase in risk when diltiazem is used with simvastatin 80 mg. The risk of myopathy 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: cyclosporin, 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 cyclosporin, 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), cyclosporin 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 or niacin (≥ 1g/day) 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). If the combination proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.5). Temporary suspension of simvastatin 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 medicinal product should be used with caution in patients who consume substantial quantities of alcohol.

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

**Excipient**
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### 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 and niacin (nicotinic acid) (≥ 1 g/day). Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see below Pharmacokinetic interactions and sections 4.2 and 4.4). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.
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>Potent CYP3A4 inhibitors:</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>
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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 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Danazol</td>
<td>Do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Other fibrates (except fenofibrate)</td>
<td>Do not exceed 10 mg simvastatin daily</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Do not exceed 20 mg simvastatin daily</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Do not exceed 40 mg simvastatin daily</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Avoid grapefruit juice when taking simvastatin</td>
</tr>
</tbody>
</table>

Effects of other medicinal products on simvastatin

**Interactions involving CYP3A4**

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

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

**Cyclosporin**

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

**Danazol**

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

**Gemfibrozil**

Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway (see sections 4.2 and 4.4).
Amiodarone and verapamil
The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see section 4.4). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

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

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

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

Grapefruit juice
Grapefruit juice inhibits cytochrome P4503A4. 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 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

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

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

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

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

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, Simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (see section 4.3 and 5.3).

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

4.7 Effects on ability to drive and use machines
Simvastatin has no or negligible influence on 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 Heart Protection Study (HPS) and Scandinavian Simvastatin Survival Study (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 frequency of the undesirable effects is indicated as follows:

Very common (≥ 1/10),
Common (≥ 1/100 to <1/10),
Uncommon (≥ 1/1,000 to <1/100),
Rare (≥ 1/10,000 to <1/1,000),
Very rare (<1/10,000), not known (cannot be estimated from the available data)

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

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

**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.

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

### 4.9 Overdose

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

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA-reductase inhibitor  
**ATC code:** C10A A01

After oral administration, 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
The Heart Protection Study (HPS), the effects of therapy with simvastatin were assessed in 20,536 patients (age 40-80 years), with or without hyperlipidaemia and with coronary heart disease, other occlusive arterial disease or diabetes mellitus. In this study, 10,269 patients were treated with simvastatin 40 mg/day and 10,267 patients were treated with placebo for a mean duration of 5 years. At baseline, 6,793 patients (33 %) had LDL-C levels below 116 mg/dL; 5,063 patients (25 %) had levels between 116 mg/dL and 135 mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

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

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

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

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

Absorption
In man simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose. Maximum plasma concentration of the 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 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 intravenous 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:
- Butylated hydroxyanisole (E 320)
- Ascorbic acid (E 300)
- Citric acid monohydrate (E 330)
- Cellulose, microcrystalline (E 460a)
- Pregelatinised maize starch
- Lactose monohydrate
- Magnesium stearate (E 470B)

Film coating:
- Hypromellose (E 464)
- Hydroxy propyl cellulose (E 463)
- Titanium dioxide (E 171)
- Talc (E 553b).
- Iron oxide red (E 172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
The tablets are packed in PVC/PE/PVdC/aluminium blisters with 10, 14, 28, 30, 50, 56, 84, 98 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed off in accordance with local requirements.
MARKETING AUTHORISATION HOLDER
Medreich Plc
9 Royal Parade
Kew Gardens
Surrey
TW9 3QD
United Kingdom

MARKETING AUTHORISATION NUMBER(S)
PL 21880/0066

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/08/2010

DATE OF REVISION OF THE TEXT
04/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 80mg film-coated tablets

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

Excipient: Lactose monohydrate
One film-coated tablet contains 560 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Pink, capsule-shaped and biconvex film-coated tablets with “A” debossed on one side and “04” on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypercholesterolaemia
Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (such as exercise, weight reduction) is inadequate.

Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL-apheresis) or if such treatments are not appropriate.

Cardiovascular prevention
Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy (see section 5.1).

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

Hypercholesterolaemia
The patient should be placed on a standard cholesterol-lowering diet, and should continue with 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 LDC-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 simvastatin dose is 40mg/day in the evening or 80mg/day in 3 divided doses of 20mg, 20mg, and an evening dose of 40mg. 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 20to 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 treatment
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 cyclosporin, danazol, gemfibrozil or other fibrate (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. (See sections 4.4 and 4.5).

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

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

Use in the elderly
No dosage adjustment is necessary.

Use in children and adolescents
The experience in children is limited. Therefore Simvastatin is not recommended for paediatric use.

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

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

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

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

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

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

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

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

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

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

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

The risk of myopathy or 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, cyclosporin 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). There is also a slight increase in risk when diltiazem is used with simvastatin 80 mg. The risk of myopathy 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: cyclosporin, 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 cyclosporin, 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), cyclosporin 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 or niacin (≥ 1g/day) 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).

If the combination proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.5). Temporary suspension of simvastatin 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 medicinal product should be used with caution in patients who consume substantial quantities of alcohol.

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

Excipient
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 and niacin (nicotinic acid) (≥ 1 g/day). Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see below Pharmacokinetic interactions and sections 4.2 and 4.4). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.
Pharmacokinetic interactions
Prescribing recommendations for interacting agents are summarised 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 |
|-------------------------------------------------|------------------------------------------------------------------|
| Interacting agents                              | Prescribing recommendations                                     |
| *Potent CYP3A4 inhibitors:*                     |                                                                  |
| Itraconazole                                     | Contraindicated with simvastatin                                 |
| Ketoconazole                                     |                                                                  |
| Erythromycin                                     |                                                                  |
| Clarithromycin                                    |                                                                  |
| Telithromycin                                     |                                                                  |
| HIV protease inhibitors                          |                                                                  |
| Nefazodone                                        |                                                                  |
| Gemfibrozil                                       | Avoid but if necessary, do not exceed 10 mg simvastatin daily    |
| Cyclosporin                                       | Do not exceed 10 mg simvastatin daily                           |
| Danazol                                           | Do not exceed 20 mg simvastatin daily                           |
| Other fibrates (except fenofibrate)              | Do not exceed 40 mg simvastatin daily                           |
| Amiodarone                                       | Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered. |
| Verapamil                                         |                                                                  |
| Diltiazem                                         |                                                                  |
| Fusidic acid                                      | Avoid grapefruit juice when taking simvastatin                   |
| Grapefruit juice                                  |                                                                  |

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-hydroxy acid 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 experienced when combining simvastatin with certain other less potent CYP3A4 inhibitors: cyclosporin, verapamil and diltiazem (see sections 4.2 and 4.4).

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

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

**Gemfibrozil**
Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway (see sections 4.2 and 4.4).
Amiodarone and verapamil
The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see section 4.4). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

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

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

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

Grapefruit juice
Grapefruit juice inhibits cytochrome P4503A4. 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 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

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

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

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

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

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, Simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (see section 4.3 and 5.3).

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

4.7 Effects on ability to drive and use machines
Simvastatin has no or negligible influence on 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 Heart Protection Study (HPS) and Scandinavian Simvastatin Survival Study (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 frequency of the undesirable effects is indicated as follows:
Very common (≥ 1/10),
Common (≥ 1/100 to <1/10),
Uncommon (≥ 1/1,000 to <1/100),
Rare (≥ 1/10,000 to <1/1,000),
Very rare (<1/10,000), not known (cannot be estimated from the available data)

Blood and lymphatic system disorders:
Rare: anaemia

Nervous system disorders:
Rare: headache, paraesthesia, dizziness, peripheral neuropathy

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.

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

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

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

After oral administration, 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
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 multcenter, randomised, double-blind, placebo-controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet, standard care, and either simvastatin 20-40 mg/day (n = 2,221) or placebo (n = 2,223) for a median duration of 5.4 years. Simvastatin reduced the risk of death by 30 % (absolute risk reduction of 3.3 %). The risk of CHD death was reduced by 42 % (absolute risk reduction of 3.5 %). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent nonfatal MI) by 34 %. Furthermore, Simvastatin significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischemic attacks) by 28 %. There was no statistically significant difference between groups in non-cardiovascular mortality.

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

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

Absorption
In man simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose. Maximum plasma concentration of the 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 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 intravenous 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:
- Butylated hydroxyanisole (E 320)
- Ascorbic acid (E 300)
- Citric acid monohydrate (E 330)
- Cellulose, microcrystalline (E 460a)
- Pregelatinised maize starch
- Lactose monohydrate
- Magnesium stearate (E 470B)

Film coating:
- Hypromellose (E 464)
- Hydroxy propyl cellulose (E 463)
- Titanium dioxide (E 171)
- Talc (E 553b).
- Iron oxide red (E 172)

#### 6.2 Incompatibilities
Not applicable.

#### 6.3 Shelf life
3 years.

#### 6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

#### 6.5 Nature and contents of container
The tablets are packed in PVC/PE/PVdC/aluminium blisters with 10, 14, 28, 30, 50, 56, 84, 98 and 100 tablets.

Not all pack sizes may be marketed.

#### 6.6 Special precautions for disposal
Any unused product or waste material should be disposed off in accordance with local requirements.
7 MARKETING AUTHORISATION HOLDER
Medreich Plc
9 Royal Parade
Kew Gardens
Surrey
TW9 3QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 21880/0067

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/08/2010

10 DATE OF REVISION OF THE TEXT
04/08/2010
PATIENT INFORMATION LEAFLET
INFORMATION FOR PATIENTS
Simvastatin 10 mg film-coated tablets
Simvastatin 20 mg film-coated tablets
Simvastatin 40 mg film-coated tablets
Simvastatin 80 mg film-coated tablets
(Simvastatin)

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

In this leaflet:
1. What Simvastatin is and what it is used for
2. Before you take Simvastatin
3. How to take Simvastatin
4. Possible side effects
5. How to store Simvastatin
6. Further information

1. WHAT SIMVASTATIN IS AND WHAT IT IS USED FOR
Simvastatin is a medicine used to lower levels of cholesterol, “bad” cholesterol (LDL cholesterol) and fatty substances called triglycerides in the blood. In addition Simvastatin raises levels of “good” cholesterol (HDL cholesterol). You should stay on a cholesterol-lowering diet while taking this medicine.
Simvastatin is used along with diet if you have:
- a raised cholesterol level in your blood (primary hypercholesterolaemia)
- or elevated fat levels in your blood (mixed hyperlipidaemia)
- a hereditary illness (homozygous familial hypercholesterolaemia) that increases the cholesterol level in your blood. You may also receive other treatments.
- coronary heart disease (CHD) or are at high risk of CHD (because you have diabetes, history of stroke, or other blood vessel disease).
Simvastatin may prolong your life by reducing the risk of heart disease problems, regardless of the amount of cholesterol in your blood.
In most people, there are no immediate symptoms of high cholesterol. Your doctor can measure your cholesterol with a simple blood test. Visit your doctor regularly, keep track of your cholesterol, and discuss your goal with your doctor.

2. BEFORE YOU TAKE SIMVASTATIN
DO NOT use Simvastatin
- if you are allergic (hypersensitive) to simvastatin or any of the other ingredients of Simvastatin
- if you currently have a liver disorder
- if you are pregnant or breast-feeding
- if you are using at the same time one or more than one of the following drugs, which strongly inhibit a specific liver enzyme (CYP3A4):
  - the antifungal agents itraconazole and ketoconazole
  - the drugs erythromycin, dantrolene or telithromycin, which are used to prevent/flight against certain infections
  - HIV drugs (see Using other medicines)
  - the antidepressant drug, nafazadone.
Take special care with Simvastatin
- if you have kidney problems
- if you have uncontrolled thyroid problems (hypothyroidism)
- if you have or ever had muscle pain, tenderness or weakness when using a statin (a group of cholesterol-lowering drugs) or when using fibrates (drugs that lower the lipid content of the blood)
- if you or close family member have a hereditary muscle disorder or previous history of muscle problems
- if you drink or have drink large amounts of alcohol (alcohol abuse)
- tell your doctor if you are due to have an operation. You may need to stop taking Simvastatin tablets for a short time.
- if you ever had liver problems
- if you are over 70 years of age
Your doctor may want to do simple blood tests to check your liver function before and during your treatment with simvastatin.
The dose of 80 mg is only recommended for patients with a severely raised cholesterol level in the blood (hypercholesterolaemia) and a high risk of cardiovascular complications.
If you develop unexplained muscle pain, hypersensitive muscles, muscle weakness or muscle cramp, contact your doctor immediately.
The usual starting dose is 10 mg or 20 mg simvastatin once daily in the evening. If cholesterol has to be lowered by a large amount, your doctor may prescribe an initial dose of 20 mg or 40 mg once daily in the evening. If necessary, your doctor will adjust the dose as described under "Dosage".

**Dosage for homozygous familial hypercholesterolemia (hereditary high blood cholesterol):**
The recommended dose is 40 mg/day in the evening, or 80 mg/day (to be taken in three doses of 20 mg, 20 mg and 40 mg in the evening). Simvastatin tablets should be used in addition to other lipid-lowering treatments (e.g. LDL-apheresis) or if such supplementary treatments are not available.

**Dosage for prevention of cardiovascular disease:**
The usual dose is 20 mg or 40 mg once a day in the evening in patients at a high risk of coronary artery disease (with or without high blood lipids). Treatment can be started with diet and exercise. If necessary your doctor will adjust the dose as described in "Dosage".

**Dosage for concomitant therapy with other medicines:**
If Simvastatin is taken with other drugs (e.g. colestipol and colesteramine) to reduce cholesterol levels, it should be taken two hours before or four hours after taking those drugs.
If you are using cyclosporin (drug that suppresses the defence) or certain other cholesterol-lowering medicines (gemfibrozil, other fibrates (except fenofibrate)) or niacin (in doses of more than 1 g/day) with simvastatin, the simvastatin dose must not be higher than 10 mg/day. If you are using amiodarone or verapamil (medicines for heart disorders) together with simvastatin, the simvastatin dose should be no higher than 20 mg/day (see "Take special care with Simvastatin").

**Dosage for decreased renal function:**
If your kidney function is severely impaired, your doctor may prescribe a lower initial dose.

**Dosage for children under 18 years:**
The use of simvastatin is not recommended in children, because its safety and efficacy have not yet been established.

**Dosage for elderly patients:**
There is no need of dosage adjustment.

**Duration of treatment:**
You will have to take simvastatin for a fairly long-time. Your doctor will tell you how long to take simvastatin for.

If you take more Simvastatin than you should
If you take more Simvastatin tablets than you should, talk to your doctor or pharmacist or contact with the nearest hospital.

If you forget to take Simvastatin
If you forget to take Simvastatin, just continue with your normal dose. Do not take a double dose to make up for a forgotten dose. Simply continue the treatment as usual the next day.

If you stop taking Simvastatin
Keep taking Simvastatin unless your doctor tells you to stop. If you stop taking Simvastatin your cholesterol levels may increase again.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Simvastatin can cause side effects, although not everybody gets them.
The following term is used to describe how often side effects have been reported:
Rare: affecting more than 1 out of 10000 patients and less than 1 out of 1000 patients treated
Very rare: affecting less than 1 out of 10000 patients
The following rare serious side effects were reported.

- muscle pain, tenderness, weakness, or cramps. On rare occasions, these muscle problems can be serious, including muscle breakdown resulting in kidney damage; and very rare deaths have occurred.
- hypersensitivity (allergic) reactions including:
  - swelling of the face, tongue and throat which may cause difficulty in breathing
  - severe muscle pain usually in the shoulders and hips
  - rash with weakness of limbs and neck muscles
Rarely during the use of simvastatin, muscle tissue breakdown (rhabdomyolysis) occurs, accompanied by pain, sensitivity, weakness or cramp in the muscles, fever, and reddish brown urina (see “Possible side effects”). The risk of muscle problems can be increased by the simultaneous use of certain drugs (see “Using other medicines”).

Consult your doctor if any of the above warnings is applicable to you or has been applicable to you in the past.

Using other medicines
It is particularly important to tell your doctor if you are taking any of the following medicinal products. Taking Simvastatin with any of these medicinal products can increase the risk of muscle problems (some of these have already been listed in the above section “Do not take Simvastatin.”)

- cyclosporin (a medicine often used in organ transplant patients)
- danazol (an anti-hormonal medicine that is used in the treatment of the development of uterine mucous membrane outside the uterus (endometriosis) and the treatment of painful or sensitive breasts)
- medicines like itraconazole or ketoconazole (medicines for fungal infections)
- fibrates like gemfibrozil and bezafibrate (medicines for lowering cholesterol)
- erythromycin, Clarithromycin, telithromycin or fusidic acid (medicines for bacterial infections)
- HIV protease inhibitors such as indinavir, nelfinavir, ritonavir and saquinavir (medicines for AIDS).
- nefazodone (a medicine for depression)
- amiodarone (a medicine used for an irregular heart beat)
- verapamil or diltiazem (medicines for high blood pressure, chest pain associated with heart disease, or other heart conditions)

As well as medicines listed above, tell your doctor or pharmacist if you are taking or have recently taken any medicines, including those obtained without a prescription. In particular, tell your doctor if you are taking any of the following:

- medicines to prevent blood clots, such as warfarin phenprocoumon or acenocoumarol (anticoagulants).
- fenofibrate (another medicine for lowering cholesterol).
- large amounts (at least 1 g each day) of niacin or nicotinic acid (medicines for lowering cholesterol).

Using Simvastatin with food and drink
Grapefruit juice contains one or more components that alter the transformation of other medicines, such as Simvastatin. Consumption of grapefruit juice must therefore be avoided.

Pregnancy and breast-feeding
Do not take Simvastatin if you are pregnant, trying to become pregnant or think you may be pregnant. If you get pregnant while taking Simvastatin, stop taking it immediately and contact your doctor.

Do not take Simvastatin if you are breast-feeding, because it is not known if the medicine is passed into breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Simvastatin is not expected to affect your ability to drive and use machines. However, when driving vehicles or using machines, it should be borne in mind that dizziness has been rarely reported.

Important information about some of the ingredients of Simvastatin
Simvastatin contain lactose monohydrate (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO USE SIMVASTATIN

Always take Simvastatin exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Method of administration:
Simvastatin tablets should be taken with water. It can be taken with or without food.

Dosage
The dose is 5-80 mg simvastatin once daily in the evening. Your doctor may adjust your dose to a maximum of 80 mg per day, given as a single dose in the evening at least for 4 weeks. The 80 mg dose is only recommended in patients with severely raised cholesterol level (hypercholesterolaemia) and high risk cardiovascular complications.

Dosage for high cholesterol levels in blood (Hypercholesterolaemia):
You should follow a cholesterol-lowering standard diet before starting the treatment and continue this diet during treatment with simvastatin.
- pain or inflammation of the joints
- inflammation of the blood vessels
- unusual bruising, skin eruptions and swelling, hives, skin sensitivity to the sun, fever, flushing
- shortness of breath and feeling unwell
- lupus-like disease picture (including rash, joint disorders, and effects on blood cells)
- inflammation of the liver with yellowing of the skin and eyes, itching, dark-coloured urine or pale-coloured stool
- inflammation of the pancreas often with severe abdominal pain.

The following side effects have also been reported rarely:
- low red blood cell count (anaemia)
- numbness or weakness of the arms and legs
- headache, tingling sensation, dizziness
- digestive disturbances (abdominal pain, constipation,flatulence, indigestion, diarrhoea, nausea, vomiting)
- rash, itching, hair loss
- weakness.

Laboratory values
Elevations in some laboratory blood tests of liver function and a muscle enzyme (creatinine kinase) have been observed.
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.

6. HOW TO STORE SIMVASTATIN

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.
Do not use Simvastatin tablets after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.
Medicines should not be disposed off via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Simvastatin tablets contain
- The active substance is simvastatin.
  Each film-coated tablet contains 10 mg simvastatin.
  Each film-coated tablet contains 20 mg simvastatin.
  Each film-coated tablet contains 40 mg simvastatin.
  Each film-coated tablet contains 80 mg simvastatin.
- The other ingredients are:
  Tablet core: Butylated hydroxyanisole (E320), Ascorbic acid (E300), Citric acid monohydrate (E330), Microcrystalline cellulose (E460a), Pregelatinised maize starch, Lactose monohydrate, Magnesium stearate (E470b)
  Film coating: Hypromellose (E464), Hydroxy propyl cellulose (E 463), Titanium dioxide (E171), Talc (E553b), Iron oxide yellow (E172) - For 10 and 20 mg, Iron oxide red (E172) – For 10, 20, 40 and 80 mg

What Simvastatin tablets look like and contents of the pack
Film-coated tablets
Simvastatin 10 mg film-coated tablets: Light pink, round, and biconvex with the inscription “A” on one side and “01” on the other.
Simvastatin 20 mg film-coated tablets: Light pink, round, and biconvex with the inscription “A” on one side and “02” on the other.
Simvastatin 40 mg film-coated tablets: Pink, round, and biconvex with the inscription “A” on one side and “03” on the other.
Simvastatin 80 mg film-coated tablets: Pink, capsule-shaped and biconvex with the inscription “A” on one side and “04” on the other.

Simvastatin 10, 20, 40 and 80 mg film-coated tablets are available in blister packs containing 10, 14, 28, 30, 50, 56, 84, 98 and 100 tablets.
Not all pack sizes may be marketed.

This leaflet was last approved in 02/2010.

PL No.: 10 mg - 21880/0064
PL No.: 20 mg - 21880/0065
PL No.: 40 mg - 21880/0066
PL No.: 80 mg - 21880/0067

MA Holder:
MIDREICH PLC
9, Royal Parade, Kew Gardens,
Surrey TW9 3QD, England.
LABELLING

Simvastatin 10 mg
28 film-coated tablets
Each film-coated tablet contains:
10 mg simvastatin.
Also contains lactose
• Read the package leaflet before use.
• For oral administration.
• Use as directed by the physician,
• Store in the original package,
KEEP OUT OF THE REACH AND
SIGHT OF CHILDREN

Pharmacode
No.: 2763