Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

SIMVASTATIN 10MG TABLETS
SIMVASTATIN 20MG TABLETS
SIMVASTATIN 40MG TABLETS
SIMVASTATIN 80MG TABLETS

UK/H/0613/001-4/E01

UK licence no: PL 04569/0516-9

Generics (UK) Limited

SIMVASTATIN 10MG TABLETS
SIMVASTATIN 20MG TABLETS
SIMVASTATIN 40MG TABLETS
SIMVASTATIN 80MG TABLETS

LAY SUMMARY

On 16th October 2006, Czech Republic, Greece, France, Poland and Slovenia granted Generics (UK) Limited Marketing Authorisations (licences) for the medicinal products Simvastatin 10mg, 20mg, 40mg and 80mg Tablets.

These are prescription-only medicines to reduce excessive cholesterol levels in your blood (hypercholesterolaemia), or to reduce a combination of excessive cholesterol levels and excessive fat levels in your blood when the effect of other measures, such as diet, weight loss and physical exercise, is not satisfactory. Simvastatin is also prescribed to reduce the risks of coronary heart disease (CHD). If you have CHD or if you are at risk of CHD (because you have diabetes, or if you have had a stroke or any other disorder affecting your blood vessels), Simvastatin may prolong your life. Simvastatin reduces the risk of heart attack or other heart-related problems, regardless of the amount of cholesterol in your blood.

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

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

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Module 1

Product Name	Simvastatin 10mg Tablets Simvastatin 20mg Tablets Simvastatin 40mg Tablets Simvastatin 80mg Tablets
Type of Application	Generic, Article 10.1
Active Substance	Simvastatin
Form	Tablets
Strength	10mg, 20mg, 40mg and 80mg Tablets
MA Holder	Generics [UK] Ltd, Station Close, Potters Bar, Hertfordshire, EN6 1TL, UK
RMS	UK
CMS	UK/H/0613/001-3/E01: Czech Republic, France, Poland, Slovenia UK/H/0613/004/E01: France, Greece, Poland
Procedure Number	UK/H/0613/001-4/E01
Timetable	Day 90 – 16th October 2006

Module 2

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 of active ingredient Simvastatin.

Excipient(s):
Lactose monohydrate (tablet core and tablet coat)
72.03 mg per film-coated tablet

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Simvastatin 10 mg film-coated tablets are presented as “dark peach to pink” coloured, oval shaped, film-coated tablets with “G” on one side and “SM” scoreline “10” on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolemia

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

Treatment of homozygous familial hypercholesterolemia 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 hypercholesterolemia and high risk for cardiovascular complications.

Hypercholesterolaemia

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

Homozygous familial hypercholesterolemia

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

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

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

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

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

Use in the elderly
No dosage adjustment is necessary.

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

4.3 Contra-indications

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

4.4 Special warnings and precautions for use

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

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

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

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

Caution should be exercised in patients with pre-disposing factors of rhabdomyolysis.
In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:

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

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

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

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

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

Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)
The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone), as well as gemfibrozil, danazol, and ciclosporin (see section 4.2).

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

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

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

Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.

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

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

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

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

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

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 medicine.

The 40 mg film-coated tablets contain small amounts of glucose and sorbitol (E420) in the film-coating. Patients with rare hereditary problems of fructose intolerance or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates and niacin (nicotinic acid) (≥ 1g/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 and given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.

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

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

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

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

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

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

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 240ml of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

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

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

4.6 Pregnancy and lactation

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

Pregnancy
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 the 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 hypercholesterolemia. For these reasons simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant(see section 4.3).

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

4.7 Effects on ability to drive and to use machines

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

4.8 Undesirable effects

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

In HPS (see section 5.1) involving 20,536 patients treated with 40 mg/day of simvastatin (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with simvastatin

40 mg and patients treated with placebo over the mean 5 years of the study. Discontinuation rates due to side effects were comparable (4.8 % in patients treated with simvastatin 40 mg compared with 5.1 % in patients treated with placebo). The incidence of myopathy was < 0.1% in patients treated with simvastatin 40 mg. Elevated transaminases (> 3 x ULN confirmed by repeat test) occurred in 0.21 % (n = 21) of patients treated with simvastatin 40 mg compared with 0.09 % (n = 9) of patients treated with placebo.

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

Blood and lymphatic system disorders:
Rare: anaemia

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

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

Hepato-biliary disorders:
Rare: hepatitis/jaundice

Skin and subcutaneous tissue disorders:
Rare: rash, pruritus, alopecia

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

General disorders and administration site conditions:
Rare: asthenia

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

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

4.9 Overdosage

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitor
ATC-Code: C10A A01

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

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during

treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

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

Treatment with simvastatin 40 mg/day compared with placebo significantly reduced the risk of all cause mortality (1328 [12.9 %] for simvastatin-treated patients versus 1507 [14.7 %] for patients given placebo; $p = 0.0003$), due to an 18 % reduction in coronary death rate 587 [5.7 %] versus 707 [6.9 %]; $p = 0.0005$; absolute risk reduction of 1.2 %). The reduction in non-vascular deaths did not reach statistical significance. Simvastatin also decreased the risk of major coronary events (a composite endpoint comprised of non-fatal MI or CHD death) by 27 % ($p < 0.0001$). Simvastatin reduced the need for undergoing coronary revascularisation procedures (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) and peripheral and other non-coronary revascularisation 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 revascularisation 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/1 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 multicentre, 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 hypercholesterolaemia, the mean reductions of LDL-C were 30, 38, 41 and 47 %, respectively. In studies of patients with combined (mixed) hyperlipidaemia on simvastatin 40 mg and 80mg, the median reductions in triglycerides were 28 and 33 % (placebo: 2 %) respectively, and mean increases in HDL-C were 13 and 16 % (placebo: 3 %), respectively.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone which is readily 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 flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption.

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

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

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

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
ascorbic acid
butylated hydroxyanisole (E320)
butylated hydroxytoluene
citric acid monohydrate
lactose monohydrate
magnesium stearate
microcrystalline cellulose
pregelatinised maize starch
talc

Tablet Coat
hypromellose
lactose monohydrate
titanium dioxide
triacetin
iron oxide red (E172)

6.2 Incompatibilities
Not Applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 25 °C.

6.5 Nature and contents of the container
PP containers with PE caps (with optional PE ullage fillers)
Al/PVC/PVdC Blisters
Al/PVC/PVAC Blisters

Pack sizes for all pack types: 10, 20, 28, 30, 49, 50, 56, 60, 84, 90, 98, 100 and 250.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd
Station Close, Potters Bar,
Hertfordshire EN6 1TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04569/0516

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2007

10. DATE OF REVISION OF THE TEXT

19/09/2007

1. NAME OF THE MEDICINAL PRODUCT

Simvastatin 20mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg of active ingredient Simvastatin.

Excipient(s):
Lactose monohydrate (tablet core and tablet coat)
144.06 mg per film-coated tablet

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Simvastatin 20 mg film-coated tablets are presented as dark tan coloured, oval shaped, film-coated tablets with "G" on one side and "SM" scoreline "20" on the other side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolemia

To reduce increased plasma total and LDL cholesterol in patients with primary hypercholesterolaemia (type IIa) or combined hyperlipidaemia (type IIb) in combination with dietary measures when no adequate effect is obtained with dietary measures and other non-pharmacological measures alone (e.g. fitness training and weight loss).

Coronary heart disease

For secondary prevention of coronary heart disease in patients with elevated plasma cholesterol levels (>5.5 mmol/l).

Prophylaxis with simvastatin is indicated if total cholesterol-serum concentration is 5.5 mmol/l (212 mg/dl) or higher despite lipid-lowering diet and other non-pharmacological measures and should be carried out in conjunction with diet and other non-pharmacological measures (e.g. physical training and weight reduction).

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 hypercholesterolemia and high risk for cardiovascular complications.

Hypercholesterolaemia

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

Homozygous familial hypercholesterolemia

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

Cardiovascular prevention

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

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

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

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

Use in the elderly
No dosage adjustment is necessary.

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

4.3 Contra-indications

- Hypersensitivity to simvastatin or to any of the excipients
- Active liver disease or unexplained persistent elevations of serum transaminases
- Porphyria
- Myopathy (See Section 4.4)
- Concomitant administration of itraconazole, ketoconazole, itraconazole, HIV-protease inhibitors, delavirdine, mibefradil and amiodarone (see section 4.5).
- Pregnancy and lactation (see section 4.6)
- Women of child-bearing potential, unless adequate contraception is used.

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 of rhabdomyolysis.
In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:

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

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

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

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

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

Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)
The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone), as well as gemfibrozil, danazol, and ciclosporin (see section 4.2).

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

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

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

Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.

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

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

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

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

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

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 medicine.

The 40 mg film-coated tablets contain small amounts of glucose and sorbitol (E420) in the film-coating. Patients with rare hereditary problems of fructose intolerance or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates and niacin (nicotinic acid) (≥ 1g/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 and given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.

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

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

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

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

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

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

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 240ml of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

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

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

4.6 Pregnancy and lactation

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

Pregnancy
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 the 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 hypercholesterolemia. For these reasons simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant(see section 4.3).

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

In HPS (see section 5.1) involving 20,536 patients treated with 40 mg/day of simvastatin (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with simvastatin

40 mg and patients treated with placebo over the mean 5 years of the study. Discontinuation rates due to side effects were comparable (4.8 % in patients treated with simvastatin 40 mg compared with 5.1 % in patients treated with placebo). The incidence of myopathy was < 0.1% in patients treated with simvastatin 40 mg. Elevated transaminases (> 3 x ULN confirmed by repeat test) occurred in 0.21 % (n = 21) of patients treated with simvastatin 40 mg compared with 0.09 % (n = 9) of patients treated with placebo.

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

Blood and lymphatic system disorders:
Rare: anaemia

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

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

Hepato-biliary disorders:
Rare: hepatitis/jaundice

Skin and subcutaneous tissue disorders:
Rare: rash, pruritus, alopecia

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

General disorders and administration site conditions:
Rare: asthenia

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

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

4.9 Overdose

A few cases of overdose have been reported; no patient had any specific symptoms, and all patients recovered without sequelae. The highest dose taken was 450 mg.

In cases of overdose, general therapeutic measures should be adopted and liver function should be monitored

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitor
ATC-Code: C10A A01

Simvastatin is a synthetic blood lipid-lowering agent deriving from a fermentation product of *Aspergillus terreus.*

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed to the corresponding beta-hydroxyacid. This main metabolite of simvastatin inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase which catalyses an early step in the biosynthesis of cholesterol limiting the rate of the total reaction. In clinical studies, at daily doses of 10 to 80 mg, simvastatin reduced total plasma

cholesterol, LDL and VLDL cholesterol. Simvastatin also slightly increased HDL cholesterol thus reducing the LDL/HDL ratio and total cholesterol/HDL ratio.

In a study of patients with hypertriglyceridaemia (TG concentration exceeding 2.25 mmol/l), simvastatin reduced the plasma triglyceride concentration by up to 30%.
Treatment with simvastatin also results in a substantial reduction of Apo-B.

In a controlled clinical study performed in 12 patients aged 15-39 suffering from homozygous familial hypercholesterolaemia, simvastatin administered at the 40 mg daily dose or at the 20 mg + 20 mg + 40 mg daily dose was effective in reducing LDL-cholesterol levels.

The active form of simvastatin specifically inhibits HMG-CoA reductase which catalyses the conversion of HMG-CoA to mevalonate. As the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol, treatment with simvastatin is not expected to cause accumulation of potentially toxic sterols. In addition, HMG-CoA is easily converted back into acetyl-CoA which is a common precursor for many biosynthetic reactions.

Simvastatin has been studied in the treatment of primary hypercholesterolaemia when satisfactory results have not been obtained with diet alone. Simvastatin was very effective in reducing total and LDL cholesterol in plasma in heterozygous familial and non-familial hypercholesterolaemia and in mixed hyperlipidaemia where particularly the cholesterol level is elevated. A clear effect was seen within two weeks and the maximum therapeutic response was achieved within 4 to 6 weeks. The response was maintained on continued treatment. Total cholesterol has been found to return to pre-treatment levels when simvastatin treatment is discontinued.

Although cholesterol is the precursor of all steroid hormones, simvastatin has not been shown to have any clinical effect on steroidogenesis. Simvastatin has not been shown to cause increase in biliary lithogenicity and, therefore, would not be expected to increase the incidence of cholelithiasis.

In the Scandinavian Simvastatin Survival Study (4S), the effect of simvastatin on total mortality was assessed in 4,444 patients between 35 and 70 years of age with coronary heart disease (with or without a history of myocardial infarction) and a baseline total serum cholesterol of 5.5 to 8.0 mmol/l and serum triglycerides ≤ 2.5 mmol/l following a two-month diet. The dose used was 20 to 40 mg/day. The median duration of treatment was 5.4 years. In this randomised, double-blind, placebo-controlled (n = 2223) multicentre study, treatment with simvastatin (n = 2221) resulted in mean reductions in total cholesterol, LDL cholesterol and triglycerides of 25%, 35%, and 10%, respectively, and a mean increase in HDL cholesterol of 8%. Simvastatin reduced the risk of total mortality by 30%, p = 0.00003 (182 deaths in the simvastatin group vs. 256 deaths in the placebo group), and the risk of CHD mortality by 42%, p = 0.00001 (111 vs. 189). Simvastatin also reduced the risk of major coronary events (CHD mortality and hospital-verified and silent non-fatal myocardial infarctions) by 34%, p < 0.00001 (431 patients vs. 622 patients with one or more events), and the risk of having a hospital-verified non-fatal myocardial infarction by 37%.

Furthermore, simvastatin reduced the risk of coronary revascularization procedures (coronary bypass grafts or percutaneous transluminal coronary angioplasty) by 37%, p < 0.00001 (252 patients vs. 383 patients).

No statistically significant difference was seen between groups in non-cardiovascular mortality. Simvastatin reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels.

Because there were only 53 female deaths, the effect of simvastatin on mortality in women could not be adequately assessed. However, simvastatin reduced the risk of having major coronary events by 34% in women, (p=0.012 60 women vs. 91 women with one or more events).

In a post hoc analysis performed on non-fatal cerebrovascular events (stroke, TIA), 75 patients receiving simvastatin and 102 patients receiving placebo were found to have experienced these events, indicating that the risk of these events was reduced by 28%, p = 0.033. The safety and tolerability of simvastatin were comparable to placebo.

In a placebo-controlled multicentre study involving 404 patients assessed with quantitative coronary angiography, simvastatin slowed the progression of coronary arterosclerosis and reduced the

development of new lesions and new total occlusions. The clinical relevance of these data has not been established.

In controlled clinical studies in patients aged over 65 years receiving simvastatin, the efficacy expressed as lowering of total and LDL cholesterol levels seemed to be of the same order as in the general population on average. There was no increase in the frequency of clinical or laboratory adverse findings.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone which 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 flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption.

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

Distribution

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

Elimination

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

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential or toxicity to reproduction.

Administration of high dosage levels of simvastatin and related analogues to a variety of animal species has revealed a spectrum of changes in several tissues. Extensive data generated on several of these changes indicate that they represent an exaggeration of the biochemical effect of these drugs at the high end of the dose-response curve.

A battery of genetic toxicity studies (*in vitro* and *in vivo)* provided no evidence of a genotoxic potential.

In long-term studies conducted in rodents, high doses of simvastatin produced tumours in various organs (mouse: liver, lungs, Harderian gland; rat: liver, thyroid gland). Simvastatin is considered a non-genotoxic rodent carcinogen. As the incidence of tumours in rodents only increased, however, after the administration of extremely high doses (15 to 30 times higher concentration in the blood than when used in humans), it is assumed that these findings are of no relevance for the clinical use of the substance.

Although clinical studies with statins have not been associated with development of cataracts, animals (rats and dogs) develop this adverse effect at levels similar to those after clinical exposure. The clinical relevance of this is not yet known.

In animal studies, the active metabolite of simvastatin was only shown to produce foetal malformations at toxic doses. Following the administration of simvastatin, isolated cases of impaired fertility and testicular degeneration have been observed in rats and dogs respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

ascorbic acid
butylated hydroxyanisole (E320)
citric acid monohydrate
lactose monohydrate
magnesium stearate
microcrystalline cellulose
pregelatinised maize starch
talc

Tablet Coat

hypromellose
lactose monohydrate
titanium dioxide
triacetin
iron yellow (E172)
iron oxide red (E172)

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of the container

PP containers with PE caps (with optional PE ullage fillers)
Al/PVC/PVdC Blisters
Al/PVC/PVAC Blisters

Pack sizes for all pack types: 10, 20, 28, 30, 49, 50, 56, 60, 84, 90, 98, 100 and 250.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd
Station Close, Potters Bar,
Hertfordshire EN6 1TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04569/0517

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2007

10. DATE OF REVISION OF THE TEXT

19/09/2007

1. NAME OF THE MEDICINAL PRODUCT

Simvastatin 40mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg of active ingredient Simvastatin.

Excipient(s):
Lactose monohydrate (tablet core and tablet coat)
281.72 mg per film-coated tablet

Polydextrose (tablet coat only)
3.84 mg per film-coated tablet (containing NMT 4% glucose and NMT 2% sorbitol (E420))

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Simvastatin 10 mg film-coated tablets are presented as “dark peach to pink” coloured, oval shaped, film-coated tablets with “G” on one side and “SM” scoreline “10” on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia
To reduce increased plasma total and LDL cholesterol in patients with primary hypercholesterolaemia (type IIa) or combined hyperlipidaemia (type IIb) in combination with dietary measures when no adequate effect is obtained with dietary measures and other non-pharmacological measures alone (e.g. fitness training and weight loss).

Coronary heart disease
For secondary prevention of coronary heart disease in patients with elevated plasma cholesterol levels (>5.5 mmol/l).

Prophylaxis with simvastatin is indicated if total cholesterol-serum concentration is 5.5 mmol/l (212 mg/dl) or higher despite lipid-lowering diet and other non-pharmacological measures and should be carried out in conjunction with diet and other non-pharmacological measures (e.g. physical training and weight reduction).

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 hypercholesterolemia and high risk for cardiovascular complications.

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

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

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

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

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

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

Use in the elderly
No dosage adjustment is necessary.

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

4.3 Contra-indications

- Hypersensitivity to simvastatin or to any of the excipients
- Active liver disease or unexplained persistent elevations of serum transaminases
- Porphyria
- Myopathy (See Section 4.4)
- Concomitant administration of itraconazole, ketoconazole, itraconazole, HIV-protease inhibitors, delavirdine, mibefradil and amiodarone (see section 4.5).
- Pregnancy and lactation (see section 4.6)
- Women of child-bearing potential, unless adequate contraception is used.

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 of rhabdomyolysis.
In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:

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

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

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

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

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

Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)
The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone), as well as gemfibrozil, danazol, and ciclosporin (see section 4.2).

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

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

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

Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.

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

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

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

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

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

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 medicine.

The 40 mg film-coated tablets contain small amounts of glucose and sorbitol (E420) in the film-coating. Patients with rare hereditary problems of fructose intolerance or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates and niacin (nicotinic acid) (≥ 1g/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 and given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.

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

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

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

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

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

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

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 240ml of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

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

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

4.6 Pregnancy and lactation

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

Pregnancy
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 the 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 hypercholesterolemia. For these reasons simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant(see section 4.3).

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

4.7 Effects on ability to drive and to use machines

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

4.8 Undesirable effects

	Common (>1/100, <1/10)	Uncommon (>1/1000,<1/100)	Rare (>1/10000, <1/1000)
Blood and lymphatic system disorders			Anaemia
Nervous system disorders		Headache	Paresthesias Peripheral neuropathy Dizziness
Gastrointestinal disorders	Constipation Abdominal pain Flatulence Nausea	Dyspepsia Diarrhoea	Vomiting
Hepatic disorders			Icterus Hepatitis Pancreatitis
Skin and subcutaneous tissue disorders		Exanthema Skin rash Pruritus	Alopecia
Musculoskeletal, connective tissue and bone disorders			Myopathy Myalgia Muscular cramp Rhabdomyolysis
General disorders and administration site conditions		Asthenia	

Use of HMG-CoA-reductase inhibitors has rarely been associated with erectile dysfunction.

An apparent hypersensitivity syndrome has been reported in rare instances. It has been associated with some of the following symptoms: angioedema, lupus-like syndrome, polymyalgia rheumatica, vasculitis, thrombocytopenia, eosinophilia, elevation of ESR, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

Laboratory findings
Alkaline phosphatase and gamma-glutamyltranspeptidase elevations have been reported. Liver-function test abnormalities have generally been mild and transient. Increases in serum creatinine kinase levels caused by CK fraction deriving from skeletal muscle have been observed (see section 4.4).

In clinical trials markedly increased CK levels (> 10xULN) was reported in 0.2% of the patients treated with 40 mg daily, compared with 1.1% in patients treated with 80 mg daily.

Markedly increased and persistent transaminase levels (> 3xULN) were observed in less than 1% of the patients treated with doses up to 40 mg daily, but in 1.8% of the patients treated with 80 mg daily.

Adverse reactions - causal relationship unknown
The following adverse reactions have been reported very rarely (< 1/10000 including individual cases): depression, erythema multiforme including Stevens-Johnson syndrome, leucopenia, and purpura.

4.9 Overdosage

A few cases of overdose have been reported; no patient had any specific symptoms, and all patients recovered without sequelae. The highest dose taken was 450 mg.

In cases of overdose, general therapeutic measures should be adopted and liver function should be monitored

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitor
ATC-Code: C10A A01

Simvastatin is a synthetic blood lipid-lowering agent deriving from a fermentation product of *Aspergillus terreus.*

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed to the corresponding beta-hydroxyacid. This main metabolite of simvastatin inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase which catalyses an early step in the biosynthesis of cholesterol limiting the rate of the total reaction. In clinical studies, at daily doses of 10 to 80 mg, simvastatin reduced total plasma cholesterol, LDL and VLDL cholesterol. Simvastatin also slightly increased HDL cholesterol thus reducing the LDL/HDL ratio and total cholesterol/HDL ratio.

In a study of patients with hypertriglyceridaemia (TG concentration exceeding 2.25 mmol/l), simvastatin reduced the plasma triglyceride concentration by up to 30%.

Treatment with simvastatin also results in a substantial reduction of Apo-B.

In a controlled clinical study performed in 12 patients aged 15-39 suffering from homozygous familial hypercholesterolaemia, simvastatin administered at the 40 mg daily dose or at the 20 mg + 20 mg + 40 mg daily dose was effective in reducing LDL-cholesterol levels.

The active form of simvastatin specifically inhibits HMG-CoA reductase which catalyses the conversion of HMG-CoA to mevalonate. As the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol, treatment with simvastatin is not expected to cause accumulation of potentially toxic sterols. In addition, HMG-CoA is easily converted back into acetyl-CoA which is a common precursor for many biosynthetic reactions.

Simvastatin has been studied in the treatment of primary hypercholesterolaemia when satisfactory results have not been obtained with diet alone. Simvastatin was very effective in reducing total and LDL cholesterol in plasma in heterozygous familial and non-familial hypercholesterolaemia and in mixed hyperlipidaemia where particularly the cholesterol level is elevated. A clear effect was seen within two weeks and the maximum therapeutic response was achieved within 4 to 6 weeks. The response was maintained on continued treatment. Total cholesterol has been found to return to pre-treatment levels when simvastatin treatment is discontinued.

Although cholesterol is the precursor of all steroid hormones, simvastatin has not been shown to have any clinical effect on steroidogenesis. Simvastatin has not been shown to cause increase in biliary lithogenicity and, therefore, would not be expected to increase the incidence of cholelithiasis.

In the Scandinavian Simvastatin Survival Study (4S), the effect of simvastatin on total mortality was assessed in 4,444 patients between 35 and 70 years of age with coronary heart disease (with or without a history of myocardial infarction) and a baseline total serum cholesterol of 5.5 to 8.0 mmol/l and serum triglycerides ≤ 2.5 mmol/l following a two-month diet. The dose used was 20 to 40 mg/day. The median duration of treatment was 5.4 years. In this randomised, double-blind, placebo-controlled (n = 2223) multicentre study, treatment with simvastatin (n = 2221) resulted in mean reductions in total cholesterol, LDL cholesterol and triglycerides of 25%, 35%, and 10%, respectively, and a mean increase in HDL cholesterol of 8%. Simvastatin reduced the risk of total mortality by 30%, $p = 0.00003$ (182 deaths in the simvastatin group vs. 256 deaths in the placebo group), and the risk of CHD mortality by 42%, $p = 0.00001$ (111 vs. 189). Simvastatin also reduced the risk of major coronary events (CHD mortality and hospital-verified and silent non-fatal myocardial infarctions) by 34%, $p < 0.00001$ (431 patients vs. 622 patients with one or more events), and the risk of having a hospital-verified non-fatal myocardial infarction by 37%.

Furthermore, simvastatin reduced the risk of coronary revascularization procedures (coronary bypass grafts or percutaneous transluminal coronary angioplasty) by 37%, $p < 0.00001$ (252 patients vs. 383 patients).

No statistically significant difference was seen between groups in non-cardiovascular mortality. Simvastatin reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels.

Because there were only 53 female deaths, the effect of simvastatin on mortality in women could not be adequately assessed. However, simvastatin reduced the risk of having major coronary events by 34% in women, (p=0.012 60 women vs. 91 women with one or more events).

In a post hoc analysis performed on non-fatal cerebrovascular events (stroke, TIA), 75 patients receiving simvastatin and 102 patients receiving placebo were found to have experienced these events, indicating that the risk of these events was reduced by 28%, p = 0.033. The safety and tolerability of simvastatin were comparable to placebo.

In a placebo-controlled multicentre study involving 404 patients assessed with quantitative coronary angiography, simvastatin slowed the progression of coronary arterosclerosis and reduced the development of new lesions and new total occlusions. The clinical relevance of these data has not been established.

In controlled clinical studies in patients aged over 65 years receiving simvastatin, the efficacy expressed as lowering of total and LDL cholesterol levels seemed to be of the same order as in the general population on average. There was no increase in the frequency of clinical or laboratory adverse findings.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone which 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 flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption.

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

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

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

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential or toxicity to reproduction.

Administration of high dosage levels of simvastatin and related analogues to a variety of animal species has revealed a spectrum of changes in several tissues. Extensive data generated on several of these changes indicate that they represent an exaggeration of the biochemical effect of these drugs at the high end of the dose-response curve.

A battery of genetic toxicity studies (in vitro and in vivo) provided no evidence of a genotoxic potential.

In long-term studies conducted in rodents, high doses of simvastatin produced tumours in various organs (mouse: liver, lungs, Harderian gland; rat: liver, thyroid gland). Simvastatin is considered a non-genotoxic rodent carcinogen. As the incidence of tumours in rodents only increased, however, after the administration of extremely high doses (15 to 30 times higher concentration in the blood than when used in humans), it is assumed that these findings are of no relevance for the clinical use of the substance.

Although clinical studies with statins have not been associated with development of cataracts, animals (rats and dogs) develop this adverse effect at levels similar to those after clinical exposure. The clinical relevance of this is not yet known.

In animal studies, the active metabolite of simvastatin was only shown to produce foetal malformations at toxic doses. Following the administration of simvastatin, isolated cases of impaired fertility and testicular degeneration have been observed in rats and dogs respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
ascorbic acid
butylated hydroxyanisole (E320)
citric acid monohydrate
lactose monohydrate
magnesium stearate
microcrystalline cellulose
pregelatinised maize starch
talc

Tablet Coat
hypromellose
titanium dioxide
triacetin
iron oxide yellow (E172)
iron oxide red (E172)
polydextrose
macrogol 8000

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and content of container

PP containers with PE caps (with optional PE ullage fillers)
Al/PVC/PVdC Blisters
Al/PVC/PVAC Blisters

Pack sizes for all pack types: 10, 20, 28, 30, 49, 50, 56, 60, 84, 90, 98, 100 and 250.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd
Station Close, Potters Bar,
Hertfordshire EN6 1TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER
PL 04569/0518

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/09/2007

10. DATE OF REVISION OF THE TEXT
19/09/2007

1. NAME OF THE MEDICINAL PRODUCT

Simvastatin 80mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 80 mg of active ingredient Simvastatin.

Excipient(s):
Lactose monohydrate (tablet core and tablet coat)
576.24 mg per film-coated tablet

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Simvastatin 80 mg film-coated tablets are presented as pink to brick-red coloured, oval shaped, film-coated tablets with "G" on one side and "SM80" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia
To reduce increased plasma total and LDL cholesterol in patients with primary hypercholesterolaemia (type IIa) or combined hyperlipidaemia (type IIb) in combination with dietary measures when no adequate effect is obtained with dietary measures and other non-pharmacological measures alone (e.g. fitness training and weight loss).

Coronary heart disease
For secondary prevention of coronary heart disease in patients with elevated plasma cholesterol levels (>5.5 mmol/l).

Prophylaxis with simvastatin is indicated if total cholesterol-serum concentration is 5.5 mmol/l (212 mg/dl) or higher despite lipid-lowering diet and other non-pharmacological measures and should be carried out in conjunction with diet and other non-pharmacological measures (e.g. physical training and weight reduction).

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 hypercholesterolemia and high risk for cardiovascular complications.

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

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

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

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

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

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

Use in the elderly
No dosage adjustment is necessary.

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

4.3 Contra-indications

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

4.4 Special warnings and precautions for use

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

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

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

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

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

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

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

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

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

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

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

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

Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.

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

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

It is recommended that liver function tests be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80 mg should receive an additional test prior to titration, 3 months after titration to the 80 mg dose, and periodically thereafter (e.g., semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum

transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 x ULN and are persistent, simvastatin should be discontinued.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

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

The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates and niacin (nicotinic acid) (≥ 1g/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 and given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.

Pharmacokinetic interactions

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

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

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

Effects of other medicinal products on simvastatin

Interactions involving CYP3A4

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

Therefore, combination with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin

must be suspended during the course of treatment. Caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: ciclosporin, verapamil, diltiazem (see sections 4.2 and 4.4).

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

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 240ml of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

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

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

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

Pregnancy
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 the 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 hypercholesterolemia. For these reasons simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant(see section 4.3).

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

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

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

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

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

Blood and lymphatic system disorders:
Rare: anaemia

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

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

Hepato-biliary disorders:
Rare: hepatitis/jaundice

Skin and subcutaneous tissue disorders:
Rare: rash, pruritus, alopecia

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

General disorders and administration site conditions:
Rare: asthenia

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

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

4.9 Overdose

A few cases of overdose have been reported; no patient had any specific symptoms, and all patients recovered without sequelae. The highest dose taken was 450 mg.

In cases of overdose, general therapeutic measures should be adopted and liver function should be monitored

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitor
ATC-Code: C10A A01

Simvastatin is a synthetic blood lipid-lowering agent deriving from a fermentation product of *Aspergillus terreus.*

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed to the corresponding beta-hydroxyacid. This main metabolite of simvastatin inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase which catalyses an early step in the biosynthesis of cholesterol limiting the rate of the total reaction. In clinical studies, at daily doses of 10 to 80 mg, simvastatin reduced total plasma cholesterol, LDL and VLDL cholesterol. Simvastatin also slightly increased HDL cholesterol thus reducing the LDL/HDL ratio and total cholesterol/HDL ratio.

In a study of patients with hypertriglyceridaemia (TG concentration exceeding 2.25 mmol/l), simvastatin reduced the plasma triglyceride concentration by up to 30%.

Treatment with simvastatin also results in a substantial reduction of Apo-B.

In a controlled clinical study performed in 12 patients aged 15-39 suffering from homozygous familial hypercholesterolaemia, simvastatin administered at the 40 mg daily dose or at the 20 mg + 20 mg + 40 mg daily dose was effective in reducing LDL-cholesterol levels.

The active form of simvastatin specifically inhibits HMG-CoA reductase which catalyses the conversion of HMG-CoA to mevalonate. As the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol, treatment with simvastatin is not expected to cause accumulation of potentially toxic sterols. In addition, HMG-CoA is easily converted back into acetyl-CoA which is a common precursor for many biosynthetic reactions.
Simvastatin has been studied in the treatment of primary hypercholesterolaemia when satisfactory results have not been obtained with diet alone. Simvastatin was very effective in reducing total and LDL cholesterol in plasma in heterozygous familial and non-familial hypercholesterolaemia and in mixed hyperlipidaemia where particularly the cholesterol level is elevated. A clear effect was seen within two weeks and the maximum therapeutic response was achieved within 4 to 6 weeks. The response was maintained on continued treatment. Total cholesterol has been found to return to pre-treatment levels when simvastatin treatment is discontinued.

Although cholesterol is the precursor of all steroid hormones, simvastatin has not been shown to have any clinical effect on steroidogenesis. Simvastatin has not been shown to cause increase in biliary lithogenicity and, therefore, would not be expected to increase the incidence of cholelithiasis.

In the Scandinavian Simvastatin Survival Study (4S), the effect of simvastatin on total mortality was assessed in 4,444 patients between 35 and 70 years of age with coronary heart disease (with or without a history of myocardial infarction) and a baseline total serum cholesterol of 5.5 to 8.0 mmol/l and serum triglycerides ≤ 2.5 mmol/l following a two-month diet. The dose used was 20 to 40 mg/day. The median duration of treatment was 5.4 years. In this randomised, double-blind, placebo-controlled (n = 2223) multicentre study, treatment with simvastatin (n = 2221) resulted in mean reductions in total cholesterol, LDL cholesterol and triglycerides of 25%, 35%, and 10%, respectively, and a mean increase in HDL cholesterol of 8%. Simvastatin reduced the risk of total mortality by 30%, p = 0.00003 (182 deaths in the simvastatin group vs. 256 deaths in the placebo group), and the risk of CHD mortality by 42%, p = 0.00001 (111 vs. 189). Simvastatin also reduced the risk of major coronary events (CHD mortality and hospital-verified and silent non-fatal myocardial infarctions) by 34%, p < 0.00001 (431 patients vs. 622 patients with one or more events), and the risk of having a hospital-verified non-fatal myocardial infarction by 37%.

Furthermore, simvastatin reduced the risk of coronary revascularization procedures (coronary bypass grafts or percutaneous transluminal coronary angioplasty) by 37%, p < 0.00001 (252 patients vs. 383 patients).

No statistically significant difference was seen between groups in non-cardiovascular mortality. Simvastatin reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels.

Because there were only 53 female deaths, the effect of simvastatin on mortality in women could not be adequately assessed. However, simvastatin reduced the risk of having major coronary events by 34% in women, (p=0.012 60 women vs. 91 women with one or more events).

In a post hoc analysis performed on non-fatal cerebrovascular events (stroke, TIA), 75 patients receiving simvastatin and 102 patients receiving placebo were found to have experienced these events, indicating that the risk of these events was reduced by 28%, p = 0.033. The safety and tolerability of simvastatin were comparable to placebo.

In a placebo-controlled multicentre study involving 404 patients assessed with quantitative coronary angiography, simvastatin slowed the progression of coronary arterosclerosis and reduced the development of new lesions and new total occlusions. The clinical relevance of these data has not been established.

In controlled clinical studies in patients aged over 65 years receiving simvastatin, the efficacy expressed as lowering of total and LDL cholesterol levels seemed to be of the same order as in the general population on average. There was no increase in the frequency of clinical or laboratory adverse findings.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone which 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 flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption.

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

Distribution

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

Elimination

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

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

ascorbic acid
butylated hydroxyanisole (E320)
citric acid monohydrate
lactose monohydrate
magnesium stearate
microcrystalline cellulose
pregelatinised maize starch
talc

Tablet Coat

hypromellose
lactose monohydrate
titanium dioxide
triacetin
iron oxide red (E172)

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of the container

PP containers with PE caps (with optional PE ullage fillers)
Al/PVC/PVdC Blisters
Al/PVC/PVAC Blisters

Pack sizes for all pack types: 10, 20, 28, 30, 49, 50, 56, 60, 84, 90, 98, 100 and 250.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd
Station Close, Potters Bar,
Hertfordshire EN6 1TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04569/0519

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2007

10. DATE OF REVISION OF THE TEXT

19/09/2007

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

SIMVASTATIN 10 mg FILM-COATED TABLETS
SIMVASTATIN 20 mg FILM-COATED TABLETS
SIMVASTATIN 40 mg FILM-COATED TABLETS
SIMVASTATIN 80 mg FILM-COATED TABLETS

Read all of this leaflet carefully before you start taking this medicine • Keep this leaflet. You may want to read it again • If you have further questions, please ask your doctor or pharmacist • This medicine has been prescribed for you personally. 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

Simvastatin belongs to a group of medicines called lipid-lowering medicines. Simvastatin is part of your treatment to lower the levels of cholesterol in your blood. It can also be used to reduce the risk of heart problems caused by fats building up in your blood vessels. Your doctor is prescribing Simvastatin in order to reduce excessive cholesterol levels in your blood (hypercholesterolaemia), or to reduce a combination of excessive cholesterol levels and excessive lipid (fat) levels in your blood when the effect of other measures, such as diet, weight loss and physical exercise is not satisfactory enough. Simvastatin is also prescribed to reduce the risks of coronary heart disease (CHD). If you have CHD or if you are at risk of CHD (because you have diabetes, or if you have had a stroke or any other disorder affecting your blood vessels), Simvastatin may prolong your life. Simvastatin reduces the risk of heart attack or other heart-related problems, regardless of the amount of cholesterol in your blood. You will not notice much in terms of the effects of this medicine. You will only know whether it is working after a blood test has been done.

2. BEFORE YOU TAKE SIMVASTATIN

Do not take Simvastatin
- if you are allergic to simvastatin or any of the other ingredients in the tablet
- if you have liver problems
- if you are pregnant or breast-feeding
- if you are taking any of the following medicines: certain anti-fungal drugs (such as Itraconazole and Ketoconazole), medicines against HIV infection (such as Ritonavir and Indinavir), certain antibiotics (such as Erythromycin, Clarithromycin and Telithromycin) or Nefazodone (an antidepressant).

You should check with your doctor if you are unsure whether you can take Simvastatin.

Take special care with Simvastatin - Tell your doctor before taking Simvastatin:
- if you have muscle aches or pains or have a family history of muscle problems
- if you have a previous history of muscular problems with any medicines for lipids (such as statins) or cholesterol (such as fibrates)
- if you have kidney problems
- if you have a history of alcohol abuse
- if you have low levels of thyroid hormone
- if you are over the age of 70
- if you are taking other medicines.

Taking other medicines - You should not take the following tablets while you are taking Simvastatin unless specifically told so by your doctor. They could alter the amount of simvastatin in your blood:
- other lipid lowering medicine (eg. Fenofibrate, Gemfibrozil, Nicotinic Acid)
- immunosupressants (such as Ciclosporin)
- Amiodarone, Verapamil or Diltiazem (medicines for a heart condition)
- anticoagulants (such as Warfarin)
- Danazol (used to treat endometriosis and breast cysts in women).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. See also section "Do not take Simvastatin".

Taking Simvastatin with food and drink - Tablets may be taken with or without food. You should **avoid** drinking grapefruit juice while you are being treated with Simvastatin because it may alter the amount of Simvastatin in your blood. Your doctor will tell you to keep your alcohol intake to a minimum while you are taking Simvastatin. If you are worried about your drinking, discuss this with your doctor.

Pregnancy and breast feeding - Your **should not** take Simvastatin if you are pregnant, are trying to become pregnant or are breast feeding. If you become pregnant while taking Simvastatin **stop** taking them and contact your doctor as soon as possible. Ask your doctor or pharmacist for advice **before** taking any medicine.

Driving and using machines - Simvastatin is not expected to interfere with your ability to drive or use machines. However, when driving vehicles or operating machines, please be aware that dizziness has been reported rarely.

Important information about some of the ingredients of Simvastatin - Simvastatin Film-Coated Tablets contain **lactose** and **polydextrose** (40 mg strength only). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE SIMVASTATIN

Always take your tablets as your doctor has told you to. You should check with your doctor or pharmacist if you are unsure. • Take the tablets as a single dose in the evening. • Swallow the tablets whole with plenty of water. In homozygous familial hypercholesterolaemia, Simvastatin may be taken in 3 divided doses. **The usual dose for adults, including the elderly**, is 5-80 mg of Simvastatin per day. Your doctor will prescribe a low dose to start but may increase this, every 4 weeks, to a dose which suits you best, up to maximum dose of 80 mg a day. Simvastatin **should not** be given to children or adolescents. If you need to have surgery, tell the doctor that you are taking Simvastatin. The doctor may want you to stop taking them for a few days before your operation. You may need to have regular blood tests while you are taking these tablets.

If you take more Simvastatin than you should -
Contact your doctor or nearest hospital casualty department

immediately. Take the container and any remaining tablets with you.

If you forget to take Simvastatin - If you forget to take a dose take it as soon as you remember unless it is nearly time for your next dose. **Don't** take two doses together to make up for the one you have missed.

If you stop taking Simvastatin - Your doctor will tell you how long you need to keep taking your tablets. **Do not** suddenly stop taking this medicine without talking to your doctor first.

Regular exercise and a good diet are important in helping to control your blood fat levels. Your doctor will give you a low-cholesterol diet to follow during Simvastatin treatment. You must also follow the advice you have been given about your diet. Your doctor will have explained to you the importance of staying on a low fat diet and about risk factors such as smoking, high blood pressure, high blood sugar, being overweight and not taking exercise. **If you have any further questions on the use of this product, ask your doctor or pharmacist.**

4. POSSIBLE SIDE EFFECTS

Like most medicines, Simvastatin can sometimes cause side effects, although not everybody gets them. These side effects can include a reduction on the haemoglobin content of the blood (anaemia), headache, tingling of the limbs, fingers or toes, dizziness, constipation, abdominal pain, wind, indigestion, diarrhoea, feeling of being sick, vomiting, inflammation of the pancreas, yellowing of the skin or white of eyes (jaundice), inflammation of the liver (hepatitis), rash, itching, hair loss, muscle or joint pain, muscle cramps, muscle tenderness, muscle weakness, feeling usually tired. These side effects are seen in more than 1 in 10,000 patients but less than 1 in 1,000.

Stop taking Simvastatin and contact your doctor or hospital immediately if any of the following happen to you:

- swelling of the lips, tongue or face or difficulty breathing
- a severe skin rash (red, tender, itchy, burning or peeling skin). These are rare allergic reactions
- muscle or joint pain, muscle tenderness or muscle weakness, particularly if you have a fever, feel unusually tired, or have dark urine. On rare occasions there is a risk of muscle problems, which may be serious, including muscle breakdown, which can result in kidney damage
- yellowing of the skin or whites of the eyes, itching, and stomach pain. These are signs and symptoms of liver damage and hepatitis.

If any of the side effects mentioned above become serious, or if you notice any side effect not mentioned in this leaflet, please tell your pharmacist or doctor.

5. HOW TO STORE SIMVASTATIN TABLETS

Keep Simvastatin Film-Coated Tablets out of the reach and sight of children. Do not store above 25°C. Do not use Simvastatin Film-Coated Tablets after the expiry date, which is stated on the carton/bottle/blister after "EXP". The expiry date refers to the last day of the month. Medicines should not be disposed of 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 Film-Coated Tablets contain - Simvastatin comes as film-coated tablets in four strengths containing either 10 mg, 20 mg, 40 mg or 80 mg of the active ingredient simvastatin in each tablet. Each film-coated tablet also contains ascorbic acid, butylated hydroxyanisole (E320), citric acid monohydrate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised maize starch, hypromellose, talc, titanium dioxide, triacetin, glycerol triacetate, iron oxide yellow (E172) (20 mg and 40 mg only) and iron oxide red (E172). The 40 mg film-coated tablets also contain polydextrose and macrogol 8000.

What Simvastatin Film-Coated Tablets looks like and contents of the pack - Simvastatin 10 mg Film-Coated Tablets are dark peach to pink, oval shaped, film-coated tablets with "G" on one side and "SM" scoreline "10" on the other. Simvastatin 20 mg Film-Coated Tablets are dark tan, oval shaped, film-coated tablets with "G" on one side and "SM" scoreline "20" on the other. Simvastatin 40 mg Film-Coated Tablets are pink, oval shaped, film-coated tablets with "G" on one side and "SM40" on the other. Simvastatin 80 mg Film-Coated Tablets are pink to brick-red, oval shaped, film-coated tablets with "G" on one side and "SM80" on the other. Simvastatin Film-Coated Tablets come in blister packs of 10, 20, 28, 30, 49, 50, 56, 60, 84, 90, 98, 100 and 250 tablets. Not all pack sizes may be marketed.

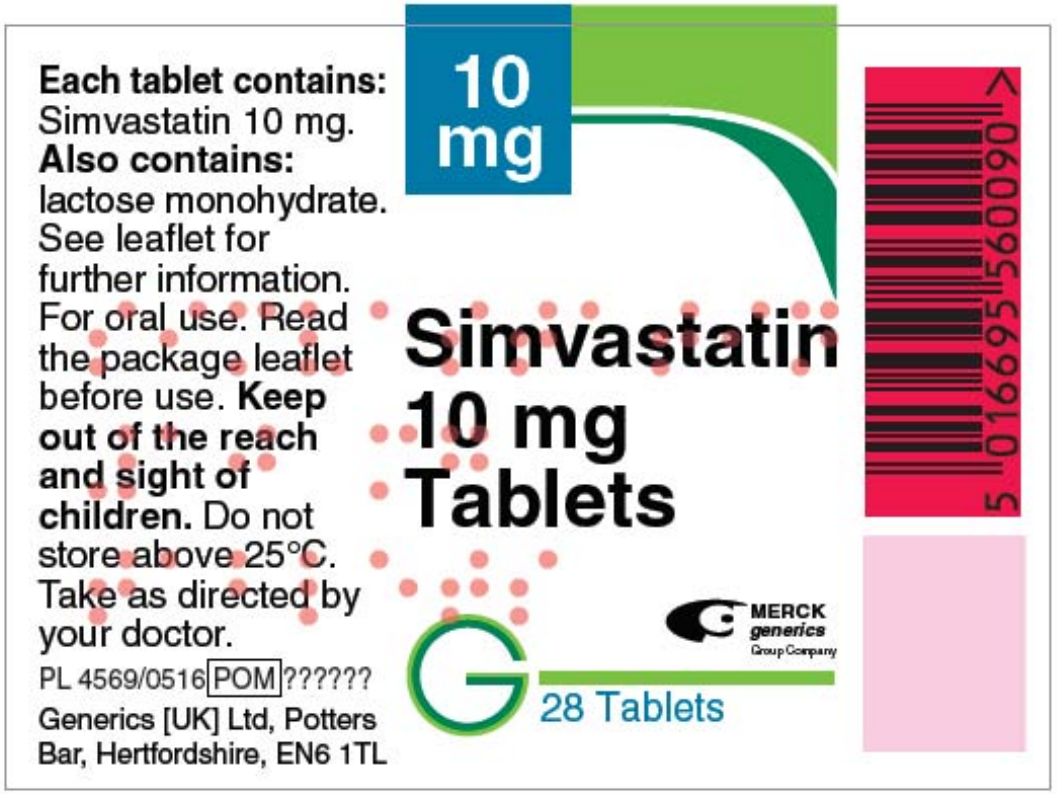
Marketing Authorisation Holder:
United Kingdom - Generics [UK] Limited, Station Close, Potters Bar, Hertfordshire, EN6 1TL.

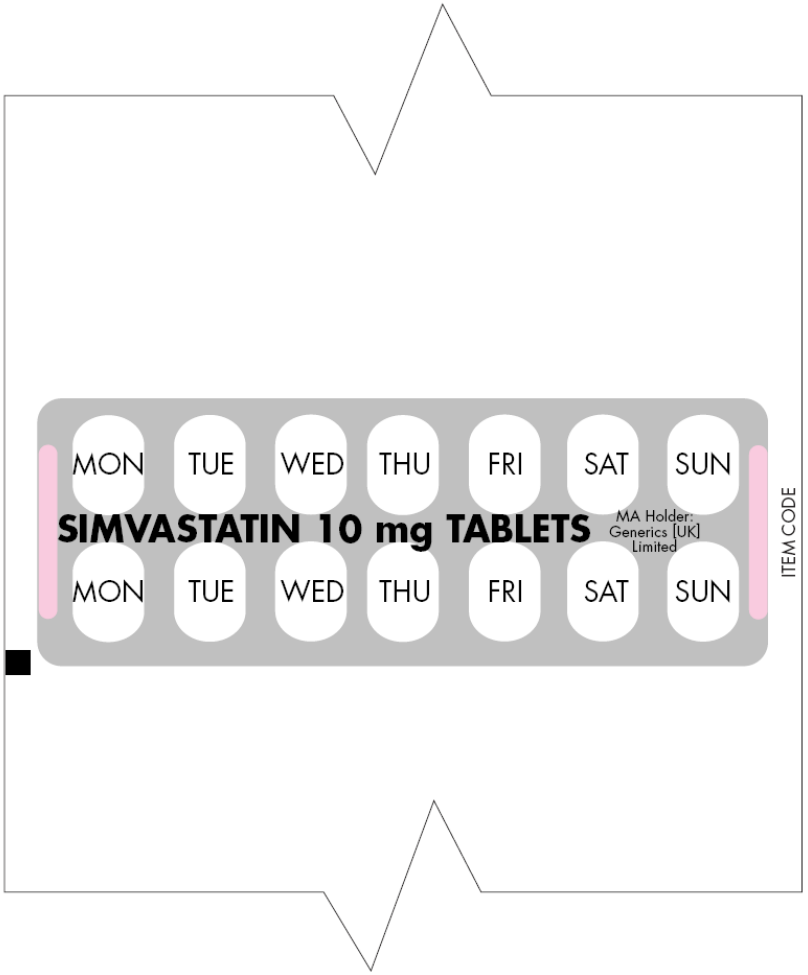
Manufacturer:
Generics [UK] Limited, Station Close, Potters Bar, Hertfordshire, EN6 1TL.
McDermott Laboratories t/a Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.
Merck Farma y Química, S.L. Polígono MERCK, E-08100 Mollet Del Vallés, Barcelona, Spain.

This medicinal product is authorised in the Member States of the EEA under the following names:
Austria - Simvarcana 20 mg, 40 mg Filmtabletten
Belgium - Simvafour 20 mg, 40 mg filmomhulde tabletten and Simvastatine Mylan 80 mg filmomhulde tabletten
Czech Republic - Simvastatin Mylan 10 mg, 20 mg, 40 mg
Denmark - Simvastatin Generics 10 mg, 20 mg, 40 mg
Finland - Simvastatin Scand Pharm 10 mg, 20 mg, 40 mg, 80 mg tabletti
France - Simvastatin Merck Generiques 10, 20, 40 mg and Simvastatin Mylan 80 mg
Germany - Simvastatin dura 10 mg, 20 mg, 40 mg Filmtabletten and Simvadura 80 mg Filmtabletten
Greece - Simvastatin Generics 10 mg, 20 mg, 40 mg, 80 mg
Ireland - Simvastatin 10 mg, 20 mg, 40 mg, 80 mg Film Coated Tablets
Italy - Simvastatina Mylan Generics 10 mg, 20 mg, 40 mg
Luxembourg -Simvacor 20 mg, 40 mg and Simvastatine Mylan 80 mg
Netherlands - Simvastatine Mylan 10 mg, 20 mg, 40 mg, 80 mg Filmomhulde tabletten
Poland - Simvagen 10 mg, 20 mg, 40 mg, 80 mg
Portugal - Simvastatina Laquifa 10 mg, 20 mg, 40 mg Comprimidos Revestidos
Slovenia - Simvastatin Mylan 10 mg, 20 mg, 40 mg filmsko oblozene tablete
Sweden - Simvastatin Scand Pharm 10 mg, 20 mg, 40 mg, 80 mg
United Kingdom - Simvastatin 10 mg, 20 mg, 40 mg, 80 mg Film-Coated Tablets.

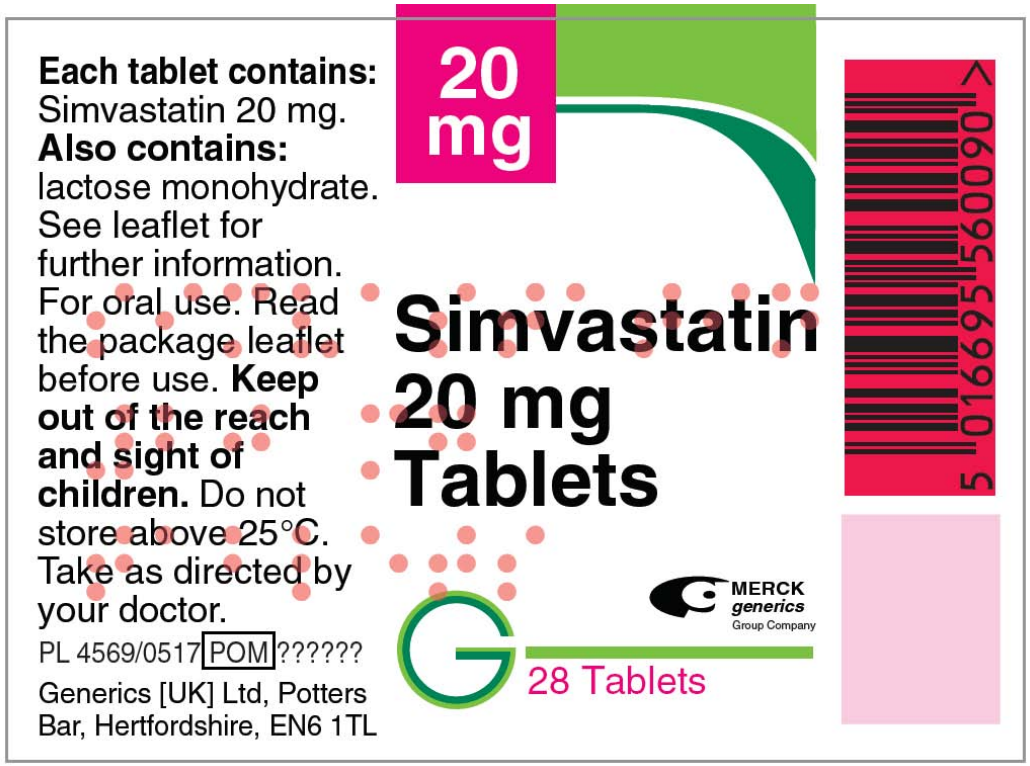
Date of revision: March 2008 008-740-01 ????????

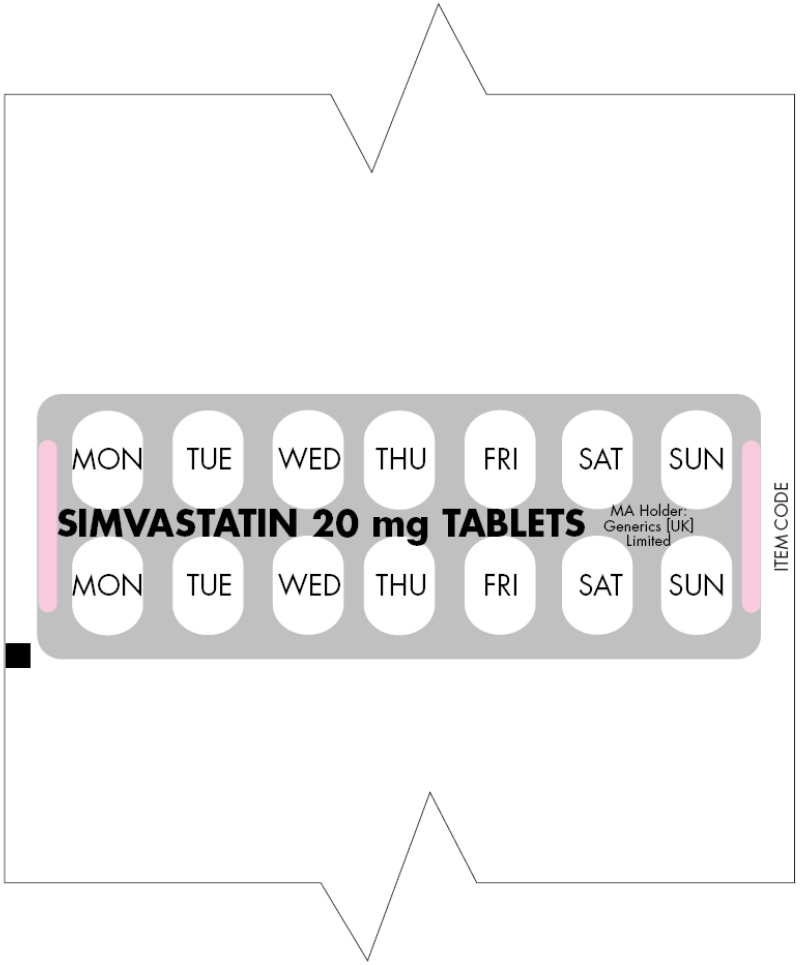
Module 4
Labelling


Each tablet contains:
Simvastatin 10 mg.
Also contains:
lactose monohydrate.
See leaflet for further information.
For oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not store above 25°C.
Take as directed by your doctor.
PL 4569/0516 POM ??????
Generics [UK] Ltd, Potters Bar, Hertfordshire, EN6 1TL
10 mg
Simvastatin 10 mg Tablets
MERCK generics Group Company
28 Tablets
5 016695 560090

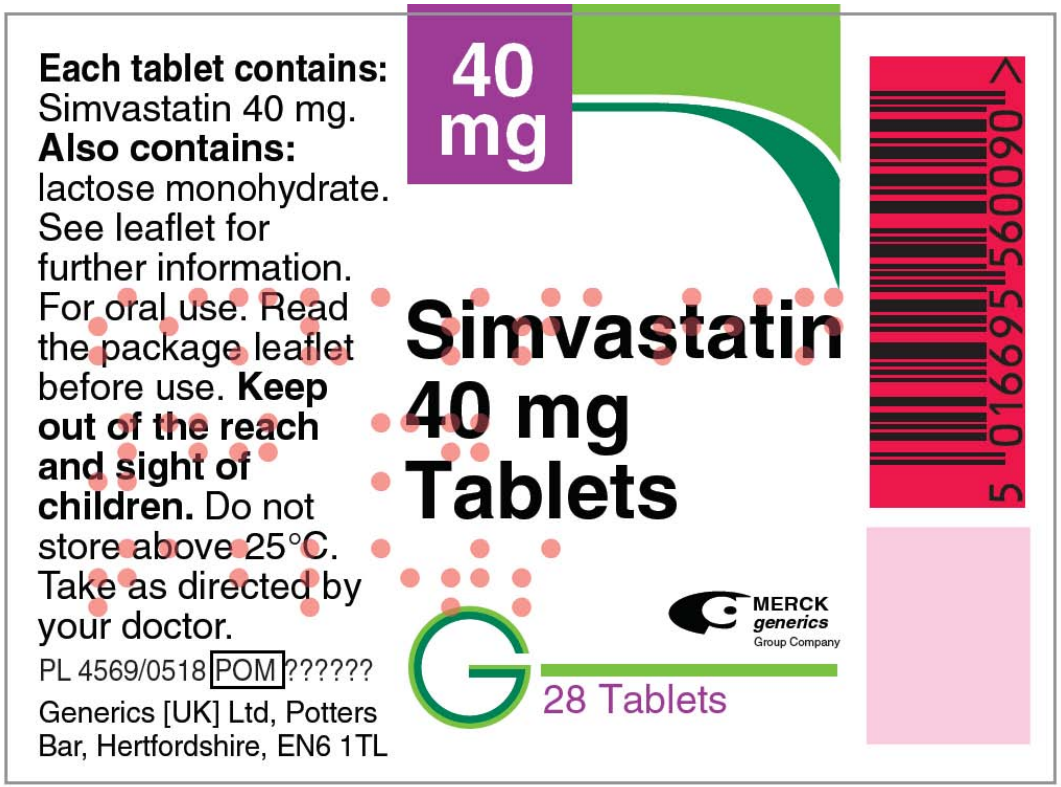

MON TUE WED THU FRI SAT SUN
SIMVASTATIN 10 mg TABLETS
MA Holder: Generics [UK] Limited
MON TUE WED THU FRI SAT SUN
ITEM CODE

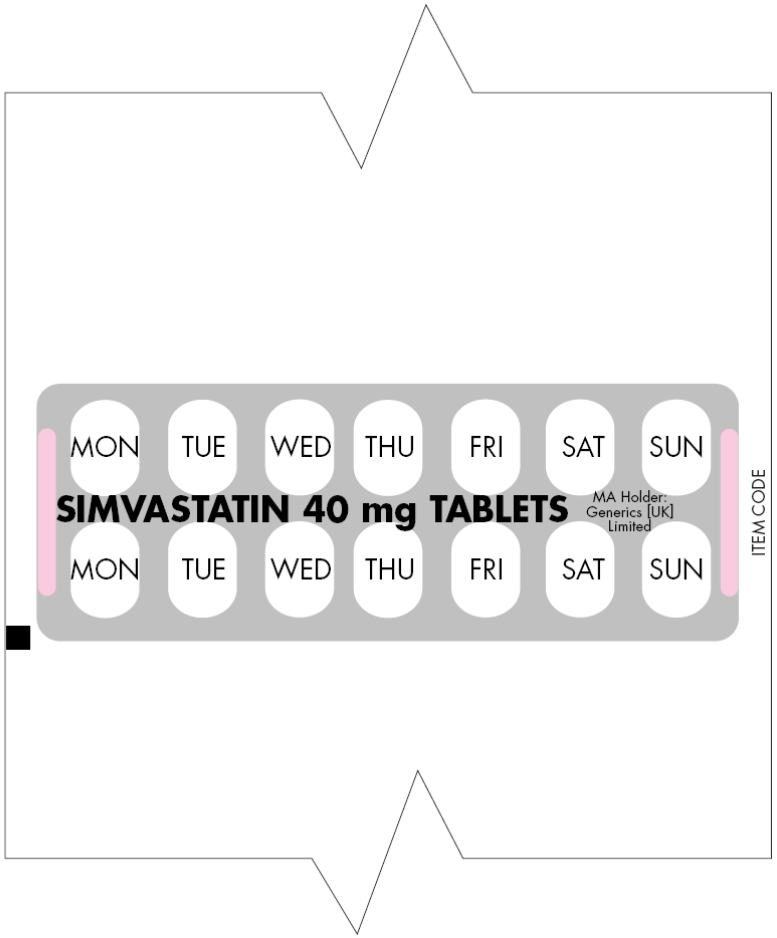

Simvastatin 20 mg Tablets
28 Tablets
20 mg
Simvastatin 20 mg Tablets
28 Tablets
Simvastatin 20 mg Tablets
28 Tablets
Simvastatin 20 mg Tablets
28 Tablets
Each tablet contains: Simvastatin 20 mg. Also contains: lactose monohydrate. See leaflet for further information. For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children. Do not store above 25°C.
Take as directed by your doctor.
PL 4569/0517 POM ??????
Generics [UK] Ltd,
Potters Bar, Hertfordshire, EN6 1TL
5 016695 450551 >
MERCK generics
Group Company
Affix Dispensing Label Here
Simvastatin 20 mg Tablets
20 mg
28 Tablets


Each tablet contains:
Simvastatin 20 mg.
Also contains:
lactose monohydrate.
See leaflet for further information.
For oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not store above 25°C.
Take as directed by your doctor.
PL 4569/0517 POM ??????
Generics [UK] Ltd, Potters Bar, Hertfordshire, EN6 1TL
20 mg
Simvastatin 20 mg Tablets
MERCK generics Group Company
28 Tablets
5 016695 560090

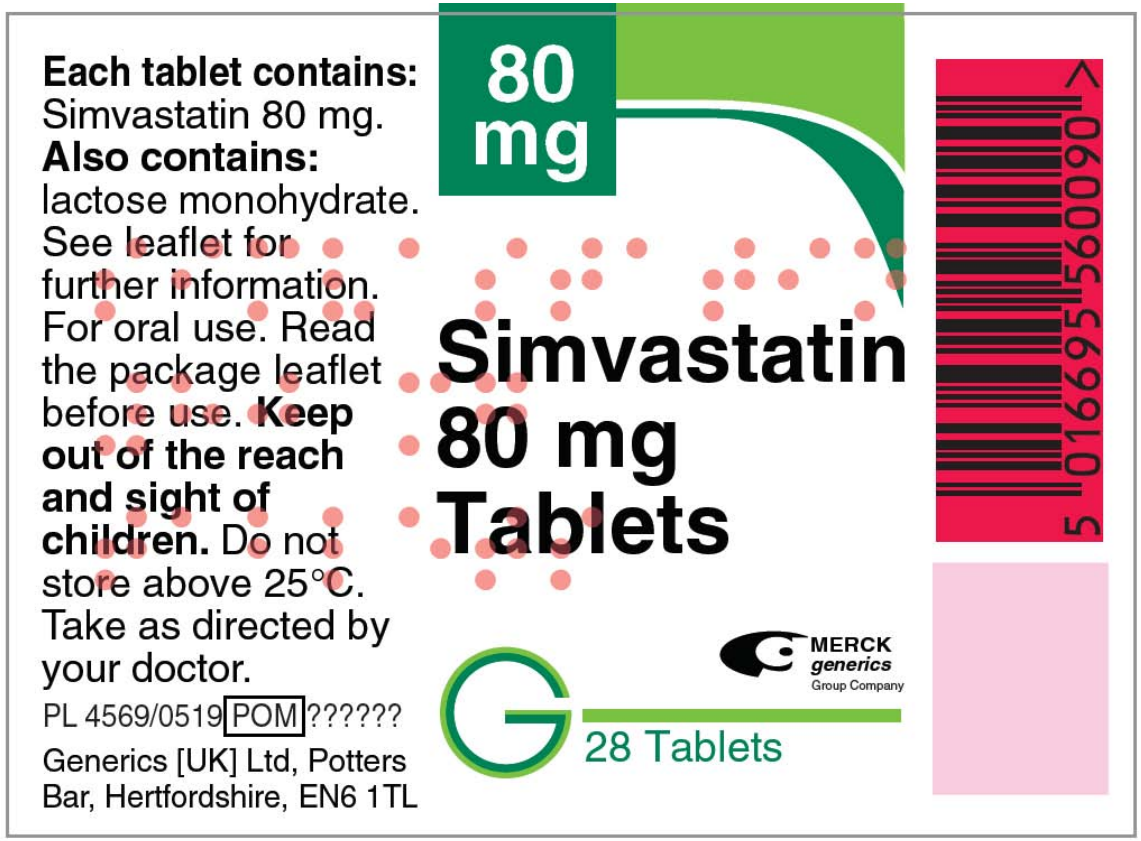

MON TUE WED THU FRI SAT SUN
SIMVASTATIN 20 mg TABLETS
MA Holder: Generics [UK] Limited
MON TUE WED THU FRI SAT SUN
ITEM CODE

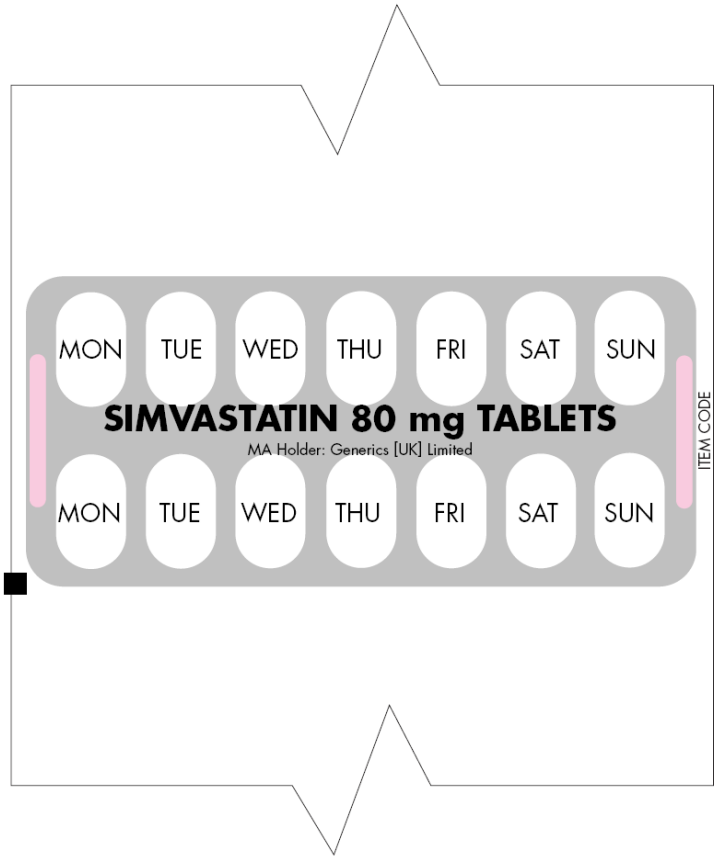

Simvastatin 40 mg Tablets
28 Tablets
40 mg
Simvastatin 40 mg Tablets
28 Tablets
Simvastatin 40 mg Tablets
28 Tablets
Simvastatin 40 mg Tablets
28 Tablets
Each tablet contains: Simvastatin 40 mg. Also contains: lactose monohydrate. See leaflet for further information. For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children. Do not store above 25°C.
Take as directed by your doctor.
PL 4569/0518 POM ??????
Generics [UK] Ltd,
Potters Bar, Hertfordshire, EN6 1TL
5 016695 450551 >
MERCK generics
Group Company
Affix Dispensing Label Here
Simvastatin 40 mg Tablets
28 Tablets
40 mg


Each tablet contains:
Simvastatin 40 mg.
Also contains:
lactose monohydrate.
See leaflet for further information.
For oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not store above 25°C.
Take as directed by your doctor.
PL 4569/0518 POM ??????
Generics [UK] Ltd, Potters Bar, Hertfordshire, EN6 1TL
40 mg
Simvastatin 40 mg Tablets
MERCK generics Group Company
28 Tablets
5 016695 560090


MON TUE WED THU FRI SAT SUN
SIMVASTATIN 40 mg TABLETS
MA Holder: Generics [UK] Limited
MON TUE WED THU FRI SAT SUN
ITEM CODE


Simvastatin 80 mg Tablets
28 Tablets
80 mg
Simvastatin 80 mg Tablets
28 Tablets
Simvastatin 80 mg Tablets
28 Tablets
Simvastatin 80 mg Tablets
28 Tablets
Each tablet contains: Simvastatin 80 mg. Also contains: lactose monohydrate. See leaflet for further information. For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children. Do not store above 25°C.
Take as directed by your doctor.
PL 4569/0519 POM ????????
Generics [UK] Ltd, Potters Bar, Hertfordshire, EN6 1TL
5 016695 450551
MERCK generics Group Company
Affix Dispensing Label Here
28 Tablets
80 mg
Simvastatin 80 mg Tablets


Each tablet contains:
Simvastatin 80 mg.
Also contains:
lactose monohydrate.
See leaflet for further information.
For oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not store above 25°C.
Take as directed by your doctor.
PL 4569/0519 POM??????
Generics [UK] Ltd, Potters Bar, Hertfordshire, EN6 1TL
80 mg
Simvastatin 80 mg Tablets
5 016695 560090 >
MERCK generics Group Company
28 Tablets


MON TUE WED THU FRI SAT SUN
SIMVASTATIN 80 mg TABLETS
MA Holder: Generics [UK] Limited
MON TUE WED THU FRI SAT SUN
ITEM CODE

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

On 16th October 2006, Czech Republic, Greece, France, Poland and Slovenia granted Generics (UK) Limited Marketing Authorisations (licences) for the medicinal products Simvastatin 10mg, 20mg, 40mg and 80mg Tablets (PL 04569/0516-9; UK/H/0613/001-4/E01). These applications were granted via a repeat-use Mutual Recognition Procedure (MRP), with the UK as Reference Member State (RMS). National licences had been granted in the UK on 18th March 2003 and these applications have previously been through a first-wave MRP in Austria, Belgium, Germany, Denmark, Greece, Finland, Ireland, Italy, Luxembourg, The Netherlands, Portugal and Sweden (which was successfully concluded on 19th January 2004).

These are applications made under Article 10.1 of 2001/83 EC, claiming to be generic medicinal products of Zocor 10mg, 20mg, 40mg and 80mg Tablets (Merck, Sharp and Dohme, UK), which were granted licences in the EU over 10 years ago.

Simvastatin is a HMG-CoA reductase inhibitor. After absorption, it undergoes rapid enzymatic hydrolysis of the lactone ring to form the principal metabolite simvastatin–β-hydroxyacid. The β-hydroxyacid acts a potent reversible competitive inhibitor of HMG-CoA reductase, which catalyses the conversion of hydroxymethyl glutarate to mevalonate. However, at therapeutic doses, the enzyme is not completely blocked, thereby allowing biologically necessary amounts of mevalonate to be available. Because the conversion of HMG-CoA to mevalonate is an early and rate-limiting step in the biosynthesis of cholesterol, therapy with simvastatin would not be expected to cause an accumulation of potentially toxic sterols. In addition, HMG-CoA is metabolised readily back to acetyl CoA, which participates in many biosynthetic processes in the body.

No new preclinical or clinical studies were conducted, which is acceptable given that the applications are claiming to be generic medicinal products to medicines that have been licensed for over 10 years. The RMS has been assured that the bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation. For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Simvastatin 10mg Tablets Simvastatin 20mg Tablets Simvastatin 40mg Tablets Simvastatin 80mg Tablets
Name(s) of the active substance(s) (INN)	Simvastatin
Pharmacotherapeutic classification (ATC code)	Catdiovascular system: Serum lipid reducing agents (C10 A A01)
Pharmaceutical form and strength(s)	10mg, 20mg, 40mg and 80mg Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/0613/001-04/E01
Reference Member State	United Kingdom
Member States concerned	10mg: Czech Republic, France, Poland, Slovenia 20mg: Czech Republic, France, Poland, Slovenia 40mg: Czech Republic, France, Poland, Slovenia 80mg: France, Greece, Poland
Date of first authorisation	18th March 2003
Marketing Authorisation Number(s)	PL 04569/0516-9
Name and address of the authorisation holder	Generics [UK] Ltd, Station Close, Potters Bar, Hertfordshire, EN6 1TL, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

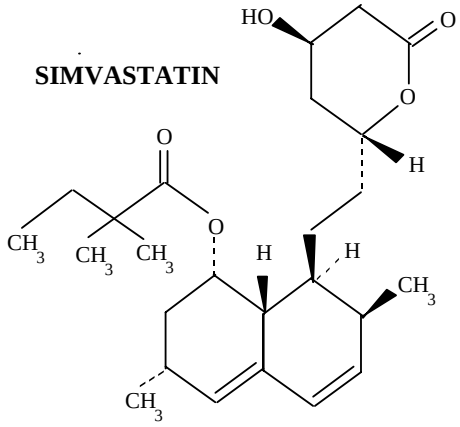
Active Substance

INN: Simvastatin

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

Molecular Formula: $C_{25}H_{38}O_5$

Chemical Structure:



Molecular Weight: 418.6

Appearance: White to off-white powder

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

Chirality: Simvastatin is a chiral compound and has seven asymmetric centres.

Simvastatin is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance simvastatin. Analytical methods are those of the European Pharmacopoeia, with additional tests for residual solvents that comply with the relevant ICH guidelines. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications have been provided for all packaging used for the active substance. The primary packaging has been shown to comply with current legislation concerning contact with food.

A suitable retest period has been determined, based on stability data generated in accordance with current guidelines.

Other Ingredients
Other ingredients consist of pharmaceutical excipients lactose monohydrate, cellulose microcrystalline, maize starch pregelatinised, ascorbic acid, citric acid monohydrate, butylated hydroxyanisole (E320), magnesium stearate, talc and purified water. The tablet coating is composed of hypromellose, lactose monohydrate, titanium dioxide, triacetin (10mg, 20mg and 80mg only) iron oxide yellow (E172 – 20mg and 40mg only), polydextrose (40mg only), macrogol 8000 (40mg only) and iron oxide red (E172).

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of butylated hydroxyanisole (which is complaint with the US Pharmacopoeia monograph), and iron oxide red, iron oxide yellow and polydextrose (which have suitable in-house specifications).

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

Pharmaceutical Development
The objective of the pharmaceutical development programme was to produce products with 10mg, 20mg, 40mg and 80mg simvastatin that are tolerable and can be considered as generic products to the originator products Zocor10mg, 20mg, 40mg and 80mg Tablets.

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

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

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

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System
All strengths of tablet are packaged in:
1. aluminium/polyvinylchloride/polyvinylidene chloride blister strips
2. aluminium/polyvinylchloride/polyvinyl acrylate blister strips
3. polypropylene containers with polyethyelene caps.

Pack sizes have been stated as being 10, 20, 28, 30, 49, 50, 56, 60, 84, 90, 98, 100 or 250 tablets. The applicant has stated that not all packaging will be marketed in the UK, but has provided assurances that they will submit mock-ups before launching any packaging types into the market.

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

Stability of the product
Stability studies were performed on batches of all strengths of finished product in accordance with current guidelines. The results support a shelf-life of 3 years, with the storage instructions "Do not store above 25 °C."

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

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and Labels are pharmaceutically acceptable.

The marketing authorisation holder has committed to updating the marketing authorisation license with a revised PIL and results of user testing, in accordance with Article 59 of Council Directive 2001/83/EC, no later than 1st July 2008.

Expert Report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

MAA Forms
The MAA forms are pharmaceutically satisfactory.

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

III.2 PRE-CLINICAL ASPECTS
These applications for generic products claims essential similarity to Zocor 10mg, 20mg, 40mg and 80mg Tablets (Merck, Sharp and Dohme), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type. The preclinical expert report has been written by an appropriately qualified person and is a suitable summary of the preclinical aspects of the dossier.

III.3 CLINICAL ASPECTS
III.3.1 Clinical Pharmacology
Three bioequivalence studies were performed, comparing the proposed 10mg, 40mg and 80mg test products with their equivalent strengths of Zocor Tablets (Merck, Sharp and Dohme, UK). All studies were single-dose, crossover studies, with plasma samples collected pre- and up to 28 hours post dose.

The pharmacokinetic results for both simvastatin and its hydroxymetabolite from all three studies are presented in the tables below.

Test 10mg tablets versus Zocor 10mg Tablets (Merck, Sharp and Dohme)

	Simvastatin		Hydroxymetabolite	
Parameter	**Test Agent, mean**	**Reference UK, mean**	**Test Agent, mean**	**Reference UK, mean**
C_{max} ng/ml	10.52	9.14	2.44	2.21
T_{max} hours	2.02	1.94	5.00	4.78
AUCα ng.h/ml	47.51	38.26	21.74	19.17
T½ hours	6.17	6.29	4.69	4.33

Test 40mg tablets versus Zocor 40mg Tablets (Merck, Sharp and Dohme)

	Simvastatin		Hydroxymetabolite	
Parameter	**Test Agent, mean**	**Reference UK, mean**	**Test Agent, mean**	**Reference UK, mean**
C_{max} ng/ml	7.60	7.45	3.79	3.50
T_{max} hours	1.86	2.00	4.31	4.40
AUCα ng.h/ml	37.18	44.33	30.60	29.40
T½ hours	7.53	7.31	6.02	6.17

Test 80mg tablets versus Zocor 80mg Tablets (Merck, Sharp and Dohme)

	Simvastatin		Hydroxymetabolite	
Parameter	**Test Agent, mean**	**Reference UK, mean**	**Test Agent, mean**	**Reference UK, mean**
C_{max} ng/ml	19.05	19.15	4.46	4.39
T_{max} hours	2.45	2.68	5.33	5.64
AUCα ng.h/ml	137.23	134.65	47.77	50.34
T½ hours	8.99	8.63	7.52	7.46

The C_{max} and AUCα values lie within the acceptable limits for bioequivalence to be assumed between the test products and the reference products for both simvastatin and its hydroxymetabolite.

III.3.2 Clinical Efficacy

No new data.

III.3.3 Clinical Safety

No new data

Module 1 – Administrative information

MAA forms

The MAA forms are medically satisfactory.

Summary of Product Characteristics (SPC)

The SPCs are medically satisfactory and consistent with those for the reference products.

Patient Information Leaflet (PIL)

The PIL is medically satisfactory.

Packaging

All packaging is medically satisfactory.

Module 2 – Clinical overall summary

A clinical overall summary, written by an appropriately qualified person, has been provided and is satisfactory, non-critical summary of Module 5.

Conclusion

The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of Simvastatin 10mg, 20mg, 40mg and 80mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

Bioequivalence has been demonstrated between the applicant's 10mg, 40mg and 80mg tablets and their equivalent strength Zocor Tablets. As the 20mg and 40mg tablets meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 40mg strength can be extrapolated to the 20mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product in the RMS.

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with simvastatin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
28/03/2008	Type IB	To change the name of the medicinal product in Italy, The Netherlands, Slovenia and the Czech Republic.	Granted 06/06/2008
17/04/2008	Type IA	To register a change in the name of the MA Holder from either 'Merck Generics Belgium BVBA/sprl' to 'Mylan BVBA/sprl' (BE, LU), 'Merck NM AB' to 'Mylan AB' (SE), 'Merck Dura GmbH' to 'Mylan Dura GmbH' (DE), 'Merck Generics Italia SpA' to 'Mylan S.p.A.' (IT) or 'Merck Generics B.V.' to 'Mylan B.V.' (NL). Address changes are registered for the MA Holder in DE and IT only.	Granted 01/05/2008