Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Simvastatin Pharma 40mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg of simvastatin.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

Oblong, biconvex, white to off-white tablets with a scoreline on one 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 adminstration

Route of Administration
Oral

Recommended Dosage Schedule
The patient should be placed on a conventional cholesterol-lowering diet before initiating simvastatin treatment and should continue on this diet during treatment with simvastatin.

Simvastatin film-coated tablets should be taken with water. The tablets can be taken either on an empty stomach or after a meal.

Hypercholesterolaemia
The usual starting dose is 10 mg/day given as a single dose in the evening.

Adjustment of dosage should be based on the measurement of plasma cholesterol levels and overall cardiovascular risk assessment. Measurements should be made at intervals of not less than four weeks. The usual maximum daily dose is 40 mg. In patients with severe hypercholesterolaemia not corrected by the 40 mg daily dose and at high cardiovascular risk, the dosage can exceptionally be increased up to 80 mg daily (as a single dose in the evening or in three divided

doses of 20 mg, 20 mg and a 40 mg dose taken in the evening).
If LDL cholesterol levels fall below 1.94 mmol/l (75 mg/dl) or total plasma cholesterol falls below 3.6 mmol/l (140 mg/dl), reduction of the simvastatin dose should be considered.

Coronary heart disease and elevated cholesterol levels
The usual starting dose is 20 mg/day given as a single dose in the evening. If adjustment of the dose is required, it should be made as specified above (see the hypercholesteraemia sub-section). There is no evidence of the efficacy of doses less than 20 mg/day in this indication.

Concomitant therapy
Simvastatin is effective alone and in combination with bile-acid sequestrants (colestyramine, colestipol).
In the case of concomitant use of cholesterol-lowering agents like colestipol and colestyramine, simvastatin should be taken one hour before or at least four hours after taking of the resins to avoid reduction of the absorption of simvastatin.
In patients taking ciclosporin, fibrates or niacin concomitantly with simvastatin, the maximum recommended dose is 10 mg/day (see section 4.4 - sub-section muscle effects and section 4.5).

Impaired renal function
Because simvastatin is not excreted to a significant degree via the kidneys, a dose reduction is generally not necessary in patients with moderate renal insufficiency.
In patients with severe renal insufficiency (creatinine clearance below 30 ml/min), use of daily dosages of more than 10 mg should be considered carefully and, if this dosage is necessary, treatment should be started with caution (see section 4.4).

Use in children (< 18 years)
The use of simvastatin in children is not recommended, as safety and efficacy studies have not been established (see section 4.4).

Use in elderly patients
The efficacy and safety of simvastatin were not investigated in elderly post-infarction patients > 70 years (see section 5.1).

4.3 Contraindications

- Hypersensitivity to simvastatin or to any of the excipients.
- Active liver disease or unexplained persistent elevation of serum transaminase values.
- Porphyria.
- Myopathy (see section 4.4).
- Concomitant administration of ketoconazole, itraconazole, HIV-protease inhibitors, delavirdine and mibefradil (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 special precautions for use

Muscle effects
Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (CK) (> 10X the upper limit of normal [ULN]). Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely. In the Scandinavian Simvastatin Survival Study, there was one case of myopathy among 1399 patients taking simvastatin 20 mg and no cases among 822 patients taking 40 mg daily for a median duration of 5.4 years. In two 6-month controlled clinical studies, there was one case of myopathy among 436 patients taking 40 mg and five cases among 669 patients taking 80 mg. Overall study results suggest that the muscular effects are dose-dependent, and the monitoring of muscular enzymes should be intensified when simvastatin is prescribed at the highest dosages.

The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the designs of these studies.

Myopathy caused by drug interactions
The incidence and severity of myopathy are increased by concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates, and lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid).

In addition, the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Simvastatin and other HMG-CoA reductase inhibitors are metabolized by the cytochrome P450 isoform 3A4. Certain drugs that have a significant inhibitory effect at therapeutic doses on this metabolic pathway can substantially raise the plasma levels of HMG-CoA reductase inhibitors and thus increase the risk myopathy. These include cyclosporin, the tetralol-class calcium channel blocker mibefradil, verapamil, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin and clarithromycin, telithromycin, HIV-protease inhibitors, delavirdine and the antidepressant nefazodone.

Reducing the risk of myopathy

1 General measures

Patients starting therapy with simvastatin should be advised of the risk of myopathy and told to report promptly unexplained muscle pain, tenderness or weakness. A CK level above 10x ULN in a patient with unexplained muscle symptoms indicates myopathy. Simvastatin therapy should be discontinued if myopathy is diagnosed or suspected. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved.

Of the patients with rhabdomyolysis, many had complicated medical histories. Some had pre-existing renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with simvastatin should be stopped a few days before elective major surgery and when a major acute medical or surgical condition supervenes.

2 Measures to reduce the risk of myopathy caused by medicinal product interactions (see above)

Physicians contemplating combined therapy with simvastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

Although combinations of fibrates or niacin with low doses of simvastatin have been used without myopathy in small, short-term clinical trials with careful monitoring the combined use of simvastatin with fibrates or niacin is not recommended unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination.
The combination of simvastatin with other fibrates or niacin should explicitly be restricted to patients with severe combined hyperlipidaemia and a high cardiovascular risk.
Addition of these drugs to simvastatin typically provides little additional reduction in LDL-cholesterol, but further reductions of triglycerides and further increases in HDL cholesterol may be obtained. If one of these drugs must be used with simvastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.
Concomitant administration of simvastatin with gemfibrozil should be avoided due to the pharmacokinetic interaction (see section 4.5).

In patients taking concomitant cyclosporin, fibrates or niacin, the dose of simvastatin should generally not exceed 10 mg/day (see section 4.2, sub-section concomitant therapy), as the risk of myopathy increases substantially at higher doses. Concomitant use of simvastatin with ketoconazole, itraconazole, HIV-protease inhibitors, delavirdine and mibefradil is contraindicated (see section 4.3). Concomitant use of simvastatin with erythromycin, clarithromycin, telithromycin, verapamil or nefazodone is not recommended.

Interruption of simvastatin therapy during a course of treatment with systemic antifungal azole or a macrolide antibiotic should be considered if there is no alternative to a short course of treatment with either of these agents. Concomitant

use with other medicines also known to have a significant inhibitory effect on cytochrome P450 3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

Concomitant intake of grapefruit juice and simvastatin is not recommended (see section 4.5).

Hepatic effects
Minor asymptomatic transient rises in serum transaminase may occur soon after initiation of therapy with simvastatin which do not require the drug to be discontinued. There is no evidence that these changes are due to hypersensitivity to simvastatin.

In two controlled clinical studies in 1,105 patients, the six month incidence of persistent hepatic transaminase elevations considered drug-related was 0.7% and 1.8% at the 40 and 80 mg dose respectively.

It is recommended that liver-function tests be performed before treatment begins, and periodically thereafter, (e.g. twice a year) for the first year of treatment or until one year after the last elevation in dose in all patients. Patients titrated to the 80 mg dose should receive an additional test at three months. 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 three times the upper limit of normal and are persistent, the drug should be discontinued.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

There is a risk for increased effect of vitamin K antagonists (see section 4.5, sub-section coumarin derivatives).

Impaired renal function
Simvastatin should be used with caution in severe renal impairment (creatinine clearance < 30 ml/min) (See section 4.2).

Secondary hypercholesterolaemia
In case of secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, first treat the underlying disease.

Excipient
The tablets contain very small amounts of butylhydroxyanisole (E320). Butylhydroxyanisole is an irritant to the eyes, skin and mucous membranes.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Gemfibrozil and other fibrates, plasma lipid-lowering doses of niacin (nicotinic acid) (≥ 1 g/day).
When these medicinal products are used concomitantly with simvastatin, the risk of myopathy is increased and concurrent use should be avoided. The concurrent use of fibrates is not recommended (see section 4.4, sub-section muscle effects).

Interaction with cytochrome P450 3A4
Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 may increase the risk of myopathy by increasing the activity of HMG-CoA reductase inhibitor in plasma during simvastatin therapy. Such inhibitors include ciclosporin, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors and nefazodone.

Combination with ketoconazole, itraconazole, HIV-protease inhibitors, delavirdine and mibefradil is contraindicated. Caution should be exercised when combining simvastatin and nefazodone, verapamil, erythromycin, clarithromycin or telithromycin. (see section 4.3 and section 4.4, sub-section muscle effects).

Grapefruit juice contains one or more ingredients inhibiting cytochrome P450 3A4 and may therefore increase the plasma concentrations of drugs metabolised via the cytochrome P450 3A4. Concomitant intake of grapefruit juice and simvastatin is not recommended.

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

Digoxin
Concomitant administration of simvastatin and digoxin in healthy volunteers resulted in a slight elevation (less than 0.3 ng/ml) in plasma digoxin concentration (ascertained by radio-immuno-assay) compared to test subjects receiving placebo in combination with digoxin.

Coumarin derivatives
In two clinical studies, one in healthy volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day was found to moderately potentiate the effect of coumarin anticoagulants. The prothrombin time, reported as the International Normalised Ratio (INR), was increased from 1.7 to 1.8 in the test subjects and from 2.6 to 3.4 in the patients.

In patients treated with coumarin derivatives, prothrombin time should be determined before starting therapy with simvastatin and frequently at the beginning of treatment 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. If the dose of simvastatin is changed, the same procedure should be repeated. No haemorrhages or prothrombin time changes have occurred in connection with simvastatin treatment in patients not taking anticoagulants.

Other concomitant therapy
In clinical studies, simvastatin was used concomitantly with ACE inhibitors, beta-blockers, calcium antagonists, diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

Pregnancy
Simvastatin is contraindicated during pregnancy.

Atherosclerosis develops slowly and therefore discontinuation of antihyperlipidaemic medication during pregnancy should have little impact on long-term treatment results of primary hypercholesterolaemia.
Moreover, cholesterol and other products of cholesterol synthesis are important for fetal development, e.g. synthesis of steroids and cell membranes.
Because simvastatin and other HMG-CoA reductase inhibitors decrease the synthesis of cholesterol and possibly other products of the cholesterol synthesis chain, simvastatin is contraindicated for use in pregnancy and should only be used in women of child bearing potential, if adequate contraceptive methods are used. If the patient becomes pregnant while taking simvastatin, the treatment should be discontinued and the patient informed of the potential adverse effect of the drug to the foetus.

A few reports have been received of congenital malformations following intrauterine exposure to HMG-CoA reductase inhibitors.

In a prospective review of 100 pregnancies in women given simvastatin or another HMG-CoA reductase inhibitor, the incidences of congenital malformations, spontaneous abortions and fetal death or stillbirths was not higher than that usually expected. As the safety of simvastatin in pregnant women has not been established and there is no apparent benefit to therapy with simvastatin during pregnancy, treatment should be immediately discontinued as soon as pregnancy is recognised.

Lactation
No data on the excretion of simvastatin and its metabolites in breast milk are available. Because many medicinal products are excreted in breast milk and because simvastatin may have serious adverse effects on infants, treatment with simvastatin is contraindicated during breastfeeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

	Common (>1/100)	Uncommon (>1/1,000, <1/100)	Rare (<1/1,000)
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: depression, erythema multiforme including Stevens-Johnson syndrome, leucopenia, and purpura.

4.9 Overdose

A few cases of overdosage 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 inhibitors
ATC Code: C10AA01

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 multicenter study involving 404 patients assessed with quantitative coronary angiography, simvastatin slowed the progression of coronary arteriosclerosis 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 a pharmacologically inactive lactone, which to a large extent is hydrolysed to the corresponding beta-hydroxyacid in the body. This beta-hydroxyacid, L-654,969, is a potent inhibitor of HMG-CoA reductase. After the administration of a simvastatin dose, both active and latent inhibitors are detected in the plasma.

Absorption
The amount of L-654,969 reaching the general circulation following an oral dose of simvastatin was assessed, using an intravenous reference dose of L-654,969. Less than 5% of the oral dose was detected in plasma as L-654,969. Simvastatin is readily absorbed from the gastrointestinal tract and a considerable part of the absorbed dose is extracted from blood by the liver before entering the general circulation. Therefore, the bioavailability of the active drug is low. Concomitant food intake does not affect absorption.

Simvastatin and the metabolites are mainly eliminated by biliary excretion. The maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after ingestion of the drug. The effect of the dose on the relative concentrations of the inhibitors was investigated by giving the subjects 5, 10, 20, 60, 90 or 120 mg of simvastatin. Increases in dose were not found to cause substantial deviation from linearity of AUC of HMG-CoA reductase inhibitors in the general circulation.

Distribution
In human blood, simvastatin and L-654,969 are almost completely bound to plasma proteins (>95%). The major metabolites of simvastatin in human plasma are L-654,969 and four other less active metabolites.

Elimination
Half-lives for systemic circulating HMG-CoA reductase inhibitors are about 2 hours. In a distribution study, the subjects were given 100 mg (20 µCi) of ^{14}C-labelled simvastatin as five 20 mg capsules, after which blood, urine and stool samples were taken.

Within 96 hours, 13% of the radioactivity was excreted in urine and 60% in faeces. The radioactivity detected in the faeces consisted of biliary excreted metabolites and unchanged drug as well as unabsorbed drug.
Less than 0.5% of the dose was excreted in urine as HMG-CoA reductase inhibitors within 96 hours. In plasma, active and total inhibitors amounted to 14% and 28% of the area under the concentration-time curve (AUC) for total radioactivity, respectively, indicating that most compounds in plasma were inactive or only mildly active.

5.3 Preclinical safety data

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. These changes were not unexpected in view of the large doses used, the potency of these drugs in inhibiting mevalonate synthesis, and the essential role of the target enzyme in maintenance of cellular homeostasis.

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.

Thus, morphological changes in the livers of rats, squamous epithelial hyperplasia of the forestomach of rats and mice, and hepatotoxicity in rabbits have all been shown to be directly related to inhibition of HMG-CoA reductase.
Cataracts have been detected at high dosage levels in dog studies with simvastatin, although at a very low incidence. While there is no clear correlation between the magnitude of serum lipid-lowering and the development of cataracts, a consistent relationship has been observed between high serum levels of drug and cataract development with simvastatin and related HMG-CoA reductase inhibitors.

Serum levels (expressed as total inhibitors) in dogs receiving the minimally cataractogenic dose of simvastatin of 50 mg/kg/day are six times higher than those in man receiving the maximally anticipated therapeutic dose of 1.6 mg/kg (based on a 50 kg man).

Elevated serum transaminases have been observed in dogs receiving simvastatin. These occur either as chronic low-level elevations or as transient enzyme spikes in approximately 10-40% of the dogs receiving this drug. None of the dogs experiencing these transaminase elevations demonstrated any symptoms of illness; and none of the transaminase elevations have progressed to levels associated with frank hepatic necrosis, despite continued drug administration. No histopathological changes have been identified in the liver of any dogs receiving simvastatin.

Testicular degeneration has been seen in two dog safety studies with simvastatin. Special studies designed to further define the nature of these changes have not met with success, since the effects are poorly reproducible and unrelated to dose, serum cholesterol levels, or duration of treatment. Simvastatin has been administered for up to 2 years to dogs at a dose of 50 mg/kg/day without any testicular effects.

Skeletal muscle necrosis was seen in one study in rats given 90 mg/kg b.d., but this was a lethal dosage in rats.

Genetic toxicology and carcinogenicity: An extensive battery of in vitro and in vivo genetic toxicity tests have been conducted on both simvastatin and the corresponding open acid L-654,969. These include assays for microbial mutagenesis, mammalian cell mutagenesis, single stranded DNA breakage, and tests for chromosome aberrations. The results of these studies provided no evidence of an interaction between simvastatin or L-654,969 with genetic material at the highest soluble non-cytotoxic concentration tests in in-vitro assay systems or at maximally tolerated doses tested in vivo.
Initial carcinogenicity studies conducted in rats and mice with simvastatin employed doses ranging from 1 mg/kg/day to 25 mg/kg/day. No evidence of a treatment-related incidence of tumour types was found in mice in any tissue. A statistically significant ($p<0.05$) increase in the incidence of thyroid follicular cell adenomas was observed in female rats receiving 25 mg/kg of simvastatin per day (15.5 times the maximum recommended human dose).

This benign tumour type was limited to female rats; no similar changes were seen in male rats or in female rats at lower dosages (up to 5 mg/kg/day). These tumours are a secondary effect reflective of a simvastatin-mediated enhancement of thyroid hormone clearance in the female rat. No other statistically significant increased incidence of tumour types was identified in any tissues in rats receiving simvastatin.

Data from both of these studies indicated that squamous epithelial hyperplasia of the forestomach occurred at all dosage levels. These gastric changes are confined to an anatomical structure which is not found in man. Moreover, identical cells found in other locations (e.g. oesophagus and anorectal junction of the rat, mouse and dog) are unaffected.
Results of a 73-week carcinogenicity study in mice receiving simvastatin doses up to 400 mg/kg/day (250 times the maximum recommended human dose, based on a 50 kg person) exhibited increased incidences of hepatocellular

adenomas and carcinomas, pulmonary adenomas and Harderian gland adenomas. A no-effect dose of 25 mg/kg/day (15.5 times the maximum recommended human dose) was established in this study and from the results of the initial 92-week carcinogenicity study in mice. In an additional 106-week rat carcinogenicity study, treatment-related increases in the incidences of lens opacities (after 103 weeks) and hepatocellular neoplasms were observed at doses 31 to 62.5 times the maximum recommended human dose and at exposures (based on 24-hour plasma AUC of total inhibitors) more than 3.5 times that achieved in male volunteers administered a maximum daily dose of 80 mg simvastatin. The no-effect dose remains at 25 mg/kg/day (15.5 times the maximum recommended human dose) as established in the initial carcinogenicity study. An increase in the incidence of thyroid hyperplastic lesions was also observed; however, this is consistent with the previous finding that this is a species-specific response and has no implications for man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose anhydrous
Microcrystalline cellulose
Pregelatinised maize starch
Butylhydroxyanisole
Magnesium stearate
Talc

Film-coating

Hydroxypropyl cellulose
Hypromellose
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

2 years

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

10, 14, 20, 28, 30, 50, 56, 60, 84, 98, 100 tablet, per blister card 10, 14 or 20 tablets (PVC/PE/PVDC/A1 blister or PVC/PE/PVDC/A1 blister in A1 sachet).

49, 50, 56 or 100 tablets, per blister card 5, 7, 10 or 14 tablets (perforated unit dose blister for hospital use – PVC/PE/PVDC/A1 blister).

100, 250 or 300 tablets packed in HDPE tablet containers.

Not all package sizes may be marketed.

6.6 Instructions for use and handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Nycomed Danmark Aps
Langebjerg 1
DK-4000 Roskilde
Denmark

8 MARKETING AUTHORISATION NUMBER

PA 838/5/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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