Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Simvastatin 40 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40mg of simvastatin and 262.92mg lactose monohydrate.

For a full list of excipients see Section 6.1

3 PHARMACEUTICAL FORM

Film coated tablet.

Brick red-coloured, oval biconvex film-coated tablets with "40" imprinted on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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).

Hyperlipidaemia
In patients with primary hypercholesterolaemia, heterozygous and homozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia, Simvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, low density lipoprotein LDL-cholesterol, apolipoprotein B and triglycerides when response to diet and other non-pharmacological measures prove inadequate**.** Simvastatin also raises HDL-cholesterol and therefore lowers the LDL/HDL and total cholesterol/HDL ratios.

As with any cholesterol-lowering therapy other modifiable risk factors should also be considered when treatment is started.

Homozygous familial hypercholesterolaemia
Simvastatin is indicated as an adjunct to diet and other non dietary measures in reducing elevated total cholesterol, LDL-cholesterol and apolipoprotein B in patients with homozygous familial hypercholesterolaemia when response to these measures is inadequate.

4.2 Posology and method of administration

Oral administration.

The patient should be placed on a standard cholesterol-lowering diet before receiving Simvastatin and should continue on this diet during treatment with Simvastatin.

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

Hyperlipidaemia
For patients with hyperlipideamia the recommended dose is 10 mg once daily taken in the evening. The dose range is 10 mg to 80 mg a day in single doses taken in the evening. A marked response to treatment should be seen within two weeks with maximum therapeutic response reached by four to six weeks which is maintained for the course of therapy. When therapy is ceased the total cholesterol levels have been shown to return to pretreatment levels. Adjustment of dosage, if required, should be made as specified above (see 4.2 'Posology and method of administration', *Coronary heart disease).*

Homozygous familial hypercholesterolaemia
Based on the results of a controlled clinical study, the recommended dosage for patients with homozygous familial hypercholesterolaemia is a single dose in the evening of 40 mg/day Simvastatin, or 80 mg/day in three divided doses of 20 mg, 20 mg and a 40 mg dose taken in the evening. 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.

Concomitant therapy
Simvastatin is effective alone or in combination with bile-acid sequestrants.

In patients taking cyclosporin, fibrates or niacin concomitantly with Simvastatin, the maximum recommended dosage is 10 mg/day (see 4.4 'Special warnings and special precautions for use', *Muscle effects* and 4.5 'Interaction with other medicaments and other forms of interaction').

Dosage in renal insufficiency
Because Simvastatin does not undergo significant renal excretion, modification of dosage should not be necessary in patients with moderate renal insufficiency.

However, in patients with severe renal insufficiency (creatinine clearance <30 ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see *Pharmaconkinetic properties)*

Use in Elderly: Although experience in elderly patients is limited, efficacy using standard doses appears similar to that seen in the population as a whole. There is no apparent increase in the frequency of clinical or laboratory adverse findings.

Children: Studies to show safety and effectiveness in children have not been carried out.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Myopathy / Rhabdomylosis
Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine phosphokinase (CPK) (>10X the upper limit of normal [ULN]). Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and very rare fatalities have occured. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

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.

Myopathy caused by drug interactions
Concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy increase the incidence and severity.

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 metabolised by the cytochrome P450 isoform 3A4 (CYP3A4). Certain drugs that have a significant inhibitory effect at therapeutic doses on this metabolic pathway and can substantially raise the plasma levels of HMG-CoA reductase inhibitors and thus increase the risk of myopathy. Such drugs include cyclosporine, the tetralol class calcium channel blocker mibefradil, itraconazole, ketoconazole and anti-fungal azoles, the macrolide antibiotics and erythromycin and clarithromycin, and the anti-depressant nefazodone.

Reducing the risk of myopathy

1. General measures
When patients are started on therapy with simvastatin they should be advised of the risk of myopathy and told to report promptly unexplained muscle pain, tenderness or weakness. A CPK level above 10x ULN in a patient with unexplained muscle symptoms indicates myopathy. 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. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CPK increases resolved.

Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:
• Elderly (age >70 years)
• Renal impairment
• Uncontrolled hypothyroidism
• Personal or familial history of hereditary muscular disorders
• Previous history of muscular toxicity with a statin or fibrate
• Alcohol abuse.
In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with a different member of the class should only be initiated with caution.
If CK levels are significantly elevated at baseline (> 5 x ULN), treatment should not be started.

Many of the patients which presented with rhabdomyolysis, 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 any major acute medical or surgical condition supervenes.

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 (≥1 g/day) of niacin or by concomitant use of amiodarone or verapamil with higher doses of simvastatin (see sections 4.2 and 4.5). There is also a slight increase in risk when diltiazem is used with simvastatin 80 mg.

Consequently, regarding CYP3A4 inhibitors, the use of simvastatin concomitantly with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated (see sections 4.3 and 4.5). If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment.

Moreover, caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: ciclosporin, verapamil, diltiazem (see sections 4.2 and 4.5). Concomitant intake of grapefruit juice and simvastatin should be avoided.
The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with ciclosporin, danazol, gemfibrozil, or lipid-lowering doses (≥1 g/day) of niacin. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. The benefits of the combined use of simvastatin 10 mg daily with other fibrates (except fenofibrate), niacin, cyclosporine or danazol should be carefully weighed against the potential risks of these combinations. (See sections 4.2 and 4.5.)
Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.
The combined use of simvastatin at doses higher than 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

Hepatic effects
In clinical studies, persistent increases (to> 3 x ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When simvastatin was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels.
It is recommended that liver function tests be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80¯mg dose should receive an additional test prior to titration, 3 months after titration to the 80¯mg dose, and periodically thereafter (e.g. semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 x ULN and are persistent, simvastatin should be discontinued.
The product should be used with caution in patients who consume substantial quantities of alcohol.
As with other lipid-lowering agents, moderate (< 3 x ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Hypertriglyceridaemia
Although simvastatin can lower the levels of triglycerides, it is not indicated where hypertriglyceridaemia is the major abnormality (ie Types I, IV andV hyperlipidaemia)

Interstitial lung disease

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

Ophthalmic examination
In the absence of any drug therapy, an increase in the prevalence of lens opacities with time is expected as a result of ageing. Current long-term data from clinical trials do not indicate an adverse effect of simvastatin on the human lens.

Use in the elderly
Although experience in elderly patients is limited, efficacy using standard doses appears similar to that seen in the population as a whole. There is no apparent increase in the frequency of clinical or laboratory adverse findings.

Paediatric use
Studies to show safety and effectiveness in children have not been established. Therefore Simvastatin is not recommended for paediatric use.

Excipient
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, lipid-lowering doses (≥ 1g/day) of niacin (nicotinicacid): These drugs have shown to increase the risk of myopathy when given concomitantly with simvastatin, probably because they can produce myopathy when given alone. There is no current evidence to suggest that these agents affect the pharmacokinetics of simvastatin.

CYP3A4 interations: Simvastatin does not have CYP3A4 inhibitory effect and therefore it is not expected to affect the plasma levels of drugs which are metabalised by CYP3A4.
However simvastatin acts as a substrate for CYP3A and therefore potent inhibitors of CYP3A4 may increase the risk of myopathy by increasing the plasma levels of HMG-CoA reductase inhibitory activity during simvastatin therapy. These include ciclosporin, the tetralol-class channel blocker mibefradil, the azole antifungals itraconazole and ketoconazole, the macrolide antibiotics, erythromycin and clarithromycin, HIV protease inhibitors and the antidepressant nefazodone.
It has been found that grapefruit juice contains one or more components that inhibit CYP3A4. The effects of a typical consumption of one 240ml glass per a day is minimal and of no clinical relevance. However, very large quantities (over 1 litre daily) significantly increase the plasma levels of HMG-CoA reductase inhibitory activity during simvastatin therapy and should be avoided.

Propranolol: There was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of Simvastatin and propranolol in normal healthy volunteers.

Digoxin: Concomitant administration of simvastatin and digoxin resulted in a slight elevation (less than 0.3 ng/ml) in drug concentrations (as measured by a digoxin radio-immuno-assay) in plasma compared to concomitant administration of placebo and digoxin.

Coumarin derivatives: In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International 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. 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, 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy: Simvastatin is contra-indicated in pregnancy. As atherosclerosis is a chronic process the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidaemia. Simvastatin and inhibitors of HMG-CoA reductase decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway. Since, cholesterol and these other products are essential components for foetal development, including synthesis of steroids and cell membranes, simvastatin is contra-indicated for use in pregnancy and women of child bearing potential unless such patients are highly unlikely to conceive.

An interval of at least one month between the end of therapy with simvastatin and planned conception is advisable.

If the patient becomes pregnant while taking simvastatin, treatment should be discontinued immediately and the patient apprised of the potential hazard to the foetus.

A few reports have been received of congenital abnormalities in infants whose mothers were treated during pregnancy with HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and foetal death/stillbirths did not exceed what would be expected in the general population. As safety 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.

Breast-feeding mothers: It is not known whether simvastatin or its metabolites are excreted in human milk. Therefore simvastatin is not recommended during lactation.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

The frequencies of the following adverse events, which have been reported during clinical studies and/or post-marketing use, are categorized based on an assessment of their incidence rates in large, long-term, placebo-controlled, clinical trials including HPS and 4S with 20,536 and 4,444 patients, respectively (see section 5.1). For HPS, only serious adverse events were recorded as well as myalgia, increases in serum transaminases and CK. For 4S, all the adverse events listed below were recorded. If the incidence rates on simvastatin were less than or similar to that of placebo in these trials, and there were similar reasonably causally related spontaneous report events, these adverse events are categorized as “rare”.
In HPS (see section 5.1) involving 20,536 patients treated with 40 mg/day of 'Zocor' (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with 'Zocor' 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 'Zocor' 40 mg compared with 5.1 % in patients treated with placebo). The incidence of myopathy was < 0.1 % in patients treated with 'Zocor' 40 mg. Elevated transaminases (> 3 x ULN confirmed by repeat test) occurred in 0.21 % (n = 21) of patients treated with 'Zocor' 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

Psychiatric disorders:

Unknown: sleep disturbances, including insomnia and nightmares, memory loss and depression.

Nervous system disorders:

Rare: headache, paresthesia, dizziness, peripheral neuropathy

Respiratory disorders thoracic and mediastinal disorders:

Unknown: Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

Gastro-intestinal 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
Reproductive system and breast disorders:

Unknown: sexual dysfunction.

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 overdosage have been reported; no patient had any specific symptoms, and all patients recovered without sequelae. The maximum dosage taken was 450 mg. General measures should be adopted and liver function should be monitored.

The maximum plasma concentration of inhibitors occurred within 1.3 and 2.4 hours of administration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code C10 A 01 - Serum Lipid Reducing Agents - Cholesterol and Triglyceride Reducers - HMG Co A reductase Reducers

Involvement of LDL cholesterol in atherogenesis has been well documented in both clinical and pathological studies, as well as in many animal experiments. Epidemiological studies show that risk factors for coronary heart disease include raised LDL cholesterol and lowered HDL (high-density lipoprotein) cholesterol .

Simvastatin has been shown to reduce both normal and elevated LDL-cholesterol concentrations. LDL is formed from VLDL and is catabolised predominantly by the high-affinity LDL receptor. The mechanism of simvastatin lowering LDL may involve both reduction of VLDL-cholesterol concentration and induction of the LDL receptor, leading to both reduced production and increased catabolism of LDL cholesterol.

Apolipoprotein B also shown to fall substantially during treatment with simvastatin. One molecule of apoprotein B is found with each LDL particle, and since there is little apolipoprotein B found in other lipoproteins, this strongly suggests that simvastatin does not merely cause cholesterol to be lost from LDL but also may reduce the concentration of circulating LDL particles.

In addition, simvastatin increases HDL cholesterol and reduces plasma triglycerides. As a result of these changes the ratios of total to HDL cholesterol and LDL to HDL cholesterol are reduced.

In controlled clinical study of 12 patients between the ages of 15 and 39 years with homozygous familial hypercholesterolemia, a single daily dose of 40mg or three divided doses or 80mg/day divided into three doses, the mean LDL-cholestrol reduction for the 40mg and 80mg doses were 14% and 25%, respectively. One patient with absent LDL - cholesterol receptor function had an LDL - cholesterol reduction of 41% with an 80mg dose.

In the Scandinavian Simvastatin Survival Study (4S), the effect of simvastatin on total mortality was assessed in 4,444 patients with coronary heart disease (CHD) and baseline total cholesterol of 212 – 309 mg/dl (5.5 to 8.0 mmol/l). In this multicentre, randomised, double-blind, placebo-controlled study, patients with previous angina or myocardial infarction (MI) were treated with standard care, including diet and simvastatin 20 – 40 mg/day or placebo for a median duration 5.4 years. Over the course of the study, treatment with simvastatin led to mean reductions in total cholesterol, LDL cholesterol, LDL cholesterol and triglycerides of 25%, 3% an 10 %, respectively, and a mean increase in HDL cholesterol of 8%. Simvastatin significantly reduced the risk of death by 30%, of CHD death by 42%, and of having a hospital-verified non-fatal myocardial infarction by 37%. Furthermore simvastatin reduced the risk for undergoing myocardial revascularisation procedures (coronary artery by-pass grafting or percutaneous transluminal coronary angioplasty) by 37%.

In a *post hoc* analysis performed on fatal plus non-fatal cerebrovascular events (stroke and transient ischaemic attacks), there were 75 patients with such events in the simvastatin group and 102 in the placebo group (risk reduction 28%, p=0.033).

In a multicentre, placebo-controlled clinical trial in 404 patients using quantitative coronary angiography, simvastatin slowed the progression of coronary atherosclerosis and reduced the development of both new lesions and new total occlusions, whereas coronary atherosclerosis lesions steadily worsened s in patients receiving standard care.

The active form is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyses the conversion of HMG-CoA 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 step in the biosynthetic pathway 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.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone which is readily hydrolysed *in vivo* to the corresponding ß-hydroxyacid, L-654,969, a potent inhibitor of HMG-CoA reductase.
Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the ß-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors).
Both are measured in plasma following administration of simvastatin. In a disposition study with ^{14}C-labelled simvastatin, 100 mg (20 uCi) of drug was administered as capsules (5 x 20 mg), and blood, urine, and faeces collected.

Thirteen per cent of the radioactivity was recovered in the urine and 60% in faeces. The latter represents absorbed drug equivalents excreted in bile as well as any unabsorbed drug. Less than 0.5% of the dose was recovered in urine as HMG-CoA reductase inhibitors. In plasma, the inhibitors account for 14% and 28% (active and total inhibitors) of the AUC of total radioactivity, indicating that the majority of chemical species present were inactive or weak inhibitors.

The major metabolites of simvastatin present in human plasma are L-654,969 and four additional active metabolites. Both simvastatin and L-654,969 are highly bound to human plasma proteins >94%).

The bioavailability of L-654,969 to the systemic circulation following an oral dose of simvastatin was estimated using an i.v. reference dose of L-654,969; the value was found to be less than 5% of the dose. By analogy to the dog model, simvastatin is well absorbed and undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. Consequently, availability of active drug to the general circulation is low.

In dose-proportionality studies, utilising doses of simvastatin of 5, 10, 20, 60, 90 and 120 mg, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before a test meal.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of drug occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1.3 to 2.4 hours post-dose.

5.3 Preclinical safety data

The oral LD_{50} of simvastatin in mice is approximately 3.8 g/kg and in rats approximately 5 g/kg.

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. The serum levels in dog receiving a minimal cataratagenic dose of simvastatin of 50mg/kg/day were found to be six times higher than the maximum anticipated therapeutic dose of 1.6mg/kg in a man.

In dogs receiving simvastatin, elevated serum transaminases have been found. They occur as either a chronic low level elevation or as transient enzyme spikes in 10 - 40% of dogs. None of the dogs showing elevated serum transaminases demonstrated any symptoms of illness and none of these transaminase elevations led associated hepatic necrosis, despite continued drug administration. There were no histopathological changes identified in the liver of any dogs receiving simvastin.

In two dog studies with simvastatin testicular degeneration was identified. However, similar studies to further define the actual nature of these changes has not been successful due to the effects being difficult to reproduce and unrelated to dose, serum cholesterol levels or duration of treatment. A dose of 50mg/kg/day administered to dogs for a period of two years has not shown 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.

There are extensive battery of *in vivo* and *in vitro* genetic toxicity tests which have been conducted both with simvastatin and the corresponding open acid L-654,969. These tests include assays for microbial mutagenesis, mammalian cell mutagenesis, single stranded DNA breakage and tests for chromosome aberrations. The results of these tests concluded no evidence of interaction between simvastatin or L-654,969 with genetic material at both the highest soluble non cytotoxic concentrations in *in vitro* assays or maximal tolerated doses in *in vivo* tests.

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 ($p \leq 0.05$) 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.

In both these studies there was squamous epithelial hyperplasia in the forestomach of the rodent at all doses. However, these changes are confined to the anatomical structure which is not present in man.

Results from a 73 week carcinogenicity study in mice receiving simvastatin of doses up to 400mg/kg/day (250 times the maximum recommended human dose based on a 50kg person) showed increased hepatocellular adenomas and carcinomas, pulmonary adenomas and Harderian gland adenomas. At 25mg/kg/day no effects were reported which is 15.5 times the maximum therapeutic dose in humans. In an additional 106 week study on rats there was increased incidence of lens opacities and hepatocellular neoplasms at doses 31 - 62.5 times higher than the maximum therapeutic dose in humans. There was also an increase in the thyroid hyperplastic lesions , however, these were consistent with findings that this is species specific response and have no implications in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose Monohydrate
Microcrystalline cellulose
Pregelatinised starch
Butylated hydroxyanisole
Ascorbic acid
Anhydrous citric acid
Colloidal anhydrous silica
Talc
Magnesium Stearate

Film-Coating
Hypromellose
Red Iron Oxide E172
Yellow Iron Oxide E172
Triethyl citrate
Titanium Dioxide E171
Talc
Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/PVDC/ Aluminum blister pack containing 14 tablets, 2 blister per carton

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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C/Anabel Segura 11
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8 MARKETING AUTHORISATION NUMBER

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