SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

SIMVACOR®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Simvastatin 10 mg /tab

* Simvastatin $C_{25}H_{38}O_5$

[1S-[1α,3α,7β,8β(2S*,4S*),8αβ]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl-2,2-dimethylbutanoate

Butanoic acid, 2,2-dimethyl-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*, 4S*), 8αβ]]

3 PHARMACEUTICAL FORM

Film coated tablets

SIMVACOR® `tablets 10mg are pink, round, film-coated, flat on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia:

SIMVACOR® is indicated as an adjunct to diet for treatment of primary hypercholesterolaemia or combined (mixed) hyperlipidaemia, when response to diet or other non-pharmacological measures (exercise, loss of weight) is inadequate.

SIMVACOR® is also indicated as an adjunct to diet for treatment of homozygous familial hypercholesterolaemia and as an adjunct to other lipid lowering treatments (e.g. LDL-apheresis) when response to these measures is inadequate.

Cardiovascular prevention:

Simvacor is indicated in patients with obvious atherosclerosis or diabetes mellitus for reducing the risk of coronary mortality and morbidity, and in patients with normal or elevated

cholesterol levels as an adjunct to the treatment of other risk factors and other heart-protective therapy (see 5.1).

4.2 Dosage and administration

Dose range is 5 to 80 mg a day in single doses taken at night. Adjustment of dosage, if required, should be made at intervals of not less than four weeks up to a maximum of 80 mg/day taken at night in single doses. The 80 mg dose is indicated only for patients with severe hypercholesterolemia and if there is high risk of coronary heart disease.

Hypercholesterolaemia: The patient should be placed on a standard cholesterol- lowering diet before receiving SIMVACOR® and should continue on this diet during treatment with the drug. The recommended starting dose is 10-20 mg once daily taken in the evening. In case that a greater reduction of LDL-C levels is required (>45%), the recommended starting dose is 20-40 mg once daily taken in the evening. Adjustment of dosage, if required, should be as specified above.

Homozygous familial hypercholesterolaemia: Based on the results of a controlled clinical study, the recommended dosage is SIMVACOR® 40 mg/day taken as a single dose in the evening, or 80 mg /day in three divided doses of 20 mg, 20 mg and a 40 mg dose taken in the evening.

SIMVACOR® 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: For patients at high risk of coronary heart disease (CHD, with or without hyperlipidaemia), the usual recommended dose of SIMVACOR® is 20-40 mg/day taken as a single dose in the evening. The treatment with the drug should start at the same time with diet and exercise. Adjustment of dosage, if required, should be made as specified above.

Concomitant therapy: SIMVACOR® is effective alone or in combination with bile-acid sequestrants. The drug should be administered 2 hours before or 4 hours after the administration of the bile-acid sequestrants. In patients taking ciclosporin, gemfibrozil or other fibrates (except fenofibrate) or lipid lowering doses of niacin (≥1g/day) concomitantly with SIMVACOR®, the maximum recommended dosage is 10 mg/day. In patients taking amiodarone or verapamil concomitantly with SIMVACOR®, the maximum recommended dosage is 20 mg/day. (see 4.4 and 4.5).

Dosage in renal insufficiency: Since SIMVACOR® does not undergo significant renal excretion, modification of dosage should not be necessary in patients with moderate renal insufficiency.

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

Use in the elderly: No adjustment of dosage is needed.

Children and adolescents: the safety and efficacy of the drug for children and adolescents has not been established. Therefore SIMVACOR® is not recommended for use in children.

4.3 Contra-indications

SIMVACOR® is contra-indicated in the following cases:

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

4.4 Special warnings and precautions for use

Myopathy / rhabdomyolysis

Simvastatin, as other inhibitors of HMG-CoA reductase, occasionally cause myopathy, which is manifested as muscle pain, sensitivity or weakness associated with elevated creatine kinase (CK) (>10X the upper normal limit [ULN]). Myopathy is sometimes revealed as rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rarely deaths have been reported. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

The risk of myopathy / rhabdomyolysis is dose-dependent. In clinical studies, when the patients were carefully monitored and some interacting drugs were excluded, the incidence was about 0,03% for the 20 mg, 0,08% for the 40 mg and 0,4% for the 80 mg dosages.

Control of creatine kinase

Creatinine kinase levels (CK) should not be controlled after tiring exercise or in case of any obvious different reason for its increase, as this complicates its evaluation. If CK levels have

been notably increased since the beginning of the treatment (>5x ULN), they should be re-measured 5-7 days later for the verification of the results.

Before treatment

Patients starting therapy with simvastatin should be advised of the risk of myopathy and told to report promptly unexplained muscle pain, tenderness or weakness.

The drug should be used with caution in patients with predisposing factors for rhabdomyolysis. In order to establish an initial rate of reference, CK should be measured before the beginning of treatment in the following cases:

- Elderly (>70 years of age)
- Renal insufficiency
- Non-controlled hypothyroid
- Individual or familial history of hereditary muscular disorders
- Past history of muscle toxicity following administration of statin or fibrate
- Alcohol abuse

In these cases, the risk and potential benefit of the therapy should be weighed, and clinical observation is recommended. If a patient has previously showed muscle disorder due to administration of a statin or a fibrate, therapy with a different drug of the same class should be administered with caution. If CK levels are notably elevated before initiation of the therapy (>5x ULN), treatment with SIMVACOR should not start.

During treatment

If muscle pain, weakness or cramps occur during treatment with a statin, CK levels should be measured. In case that these levels are notably high (>5x ULN) during lack of hard exercise, therapy must be discontinued. If muscular symptoms are more severe and cause daily discomfort, even for CK levels <5x ULN, discontinuation of the therapy should be taken into consideration. If there is suspicion of myopathy for any reason, therapy should be discontinued.

If symptoms stop and CK levels return to normal, treatment with a statin should be re-initiated or there should begin treatment with a different statin in the lowest possible dose and under close clinical observation.

The treatment with simvastatin should be interrupted for a few days before a serious selective surgical operation and before any major medical or surgical state.

Measures to reduce the risk of myopathy caused by drug interactions (also see 4.5):

The risk of myopathy and rhabdomyolysis was significantly increased by concomitant administration of simvastatin with potent CYP3A4 inhibitors (itraconazole, ketoconazole,

erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone), as well as gemfibrozil, ciclosporin and danazol (see 4.2).

The risk of myopathy and rhabdomyolysis was increased by concomitant administration of simvastatin with other fibrates, lipid lowering doses of niacin (≥1 g/day) or by concomitant administration of amiodarone or verapamil with larger doses of simvastatin (see 4.2 and 4.5). The risk is also slightly increased by the administration of diltiazem with simvastatin 80 mg.

Therefore, as far as CYP3A4 inhibitors are concerned, the concomitant administration of simvastatin with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contra-indicated (see 4.3 and 4.5). If therapy with itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin cannot be avoided, the treatment with simvastatin should be interrupted. Furthermore, concomitant use of less potent CYP3A4 inhibitors (cilosporin, verapamil, diltiazem) should be administered with caution (see 4.2 and 4.5). Concomitant use of simvastatin and grapefruit juice should be avoided.

In patients taking concomitant ciclosporin, gemfibrozil, or lipid-lowering doses of niacin (>1 g/day), the dose of simvastatin should not exceed 10 mg/day. The concomitant use of simvastatin with gemfibrozil should be avoided unless the benefit of combined therapy outweighs the increased risk. The benefit of combined therapy of simvastatin 10 mg/day with other fibrates (except fenofibrate), niacin or ciclosporin should be carefully weighed towards the potential risk (see 4.2 and 4.5).

The concomitant administration of simvastatin and fenofibrate should be done carefully as both these dugs may induce myopathy when administered alone.

The concomitant administration of simvastatin in doses >20 mg/day with amiodarone or verapamil should be avoided unless the clinical benefit outweighs the increased risk of myopathy (see 4.2 and 4.5).

Hepatic effects :

In clinical studies, there has been reported a persistent increase (>3x ULN) of serum transaminase levels in some adult patients who received simvastatin. When simvastatin was interrupted or discontinued, the transaminase levels slowly returned to pre-treatment levels.

It is recommended that liver function tests be performed before treatment begins, and periodically thereafter if necessary. Patients titrated to the 80 mg doses should receive an additional test before titration, 3 months after titration in the 80 mg dosage and periodically thereafter (e.g. twice a year) 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 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.

As with other lipid lowering factors, there has been reported a mild increase (<3x ULN) of serum transaminase levels following treatment with simvastatin. These changes, which occurred right after the initiation of the treatment, were usually transient and asymptomatic and did not require the drug to be discontinued.

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

Diabetes Mellitus:

Some evidence suggests that statins as a class raise blood glucose and in some patients, are high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

4.5 Interaction with other medicaments and other forms of interaction

Pharmacodynamic interactions

Interactions with lipid lowering medicaments which may induce myopathy when administered alone.

The risk of myopathy, including rhabdomyolysis, was increased by the concomitant administration of fibrates and niacin (nicotinic acid) (≥1 g/day). Furthermore, there is a pharmacokinetic interaction with gemfibrozil, which leads to increased plasma levels of simvastatin (see Pharmacokinetic interactions and 4.2 and 4.4). There is no indication that, during simultaneous administration of simvastatin and fenofibrate, the risk of myopathy exceeds the total risks of every drug individually. Sufficient data are not available regarding pharmaceutical alertness and pharmacokinetics of other fibrates.

Pharmacokinetic interactions

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

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

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

Effects of other medicinal products on Simvastatin

Interactions concerning CYP3A4

Simvastatin is a substrate for cytochrome P450 3A4. Potent inhibitors of P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the plasma levels of HMG-CoA

reductase inhibitory activity during simvastatin therapy. These inhibitors include itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone. The simultaneous administration of itraconazole increased the acid of simvastatin (active β-hydroxy metabolite) more than 10 times. Telithromycin increased the acid of simvastatin 11 times.

For this reason, the combination with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contra-indicated. If therapy with itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin cannot be avoided, simvastatin therapy should be interrupted. Caution is required during the concomitant use of simvastatin and less powerful CYP3A4 inhibitors: ciclosporin, verapamil, diltiazem (see 4.2 and 4.4).

Ciclosporin

The risk of myopathy and rhabdomyolysis increased by concomitant administration of ciclosporin especially with large simvastatin doses (see 4.2 and 4.4). Therefore, in patients taking ciclosporin, the daily dosage of simvastatin should not exceed 10 mg. Although the mechanism is not fully understood, cyclosporine increases the AUC of simvastatin's acid, partly due to CYP3A4 inhibition.

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 AUC of simvastatin's acid 1,9 times probably due to inhibition of glycouronic reactions (see 4.2 and 4.4).

Amiodarone and verapamil

The risk of myopathy and rhabdomyolysis increases by concomitant administration of amiodarone or verapamil with large simvastatin doses (see 4.4). From an ongoing study, incidence of myopathy has been reported in 6% of the patients taking simvastatin 80 mg and amiodarone.

A data analysis from clinical studies showed almost 1% incidence of myopathy in patients taking simvastatin 40 or 80 mg and verapamil. In a pharmacokinetic study, concomitant administration with verapamil increased 2,3 times the exposure to simvastatin's acid, partly due to CYP3A4 inhibition. For this reason, in patients receiving concomitant treatment with

amiodarone or verapamil, the daily simvastatin dosage should not exceed 20 mg unless the clinical benefit seems to outweigh the increased risk for myopathy and rhabdomyolysis.

Diltiazem

A data analysis from clinical studies showed 1% incidence of myopathy in patients taking simvastatin 80 mg and diltiazem. The risk of myopathy in patients taking 40 mg did not increase by concomitant administration of diltiazem (see 4.4). In a pharmacokinetic study, concomitant administration of diltiazem increased 2,7 times the exposure to simvastatin's acid, obviously due to CYP3A4 inhibition. For this reason, in patients receiving concomitant treatment with diltiazem, the daily simvastatin dosage should not exceed 40 mg unless the clinical benefit seems to outweigh the increased risk for myopathy and rhabdomyolysis.

Grapefruit juice

Grapefruit juice inhibits cytochrome P450 3A4. The concomitant use of large quantities (over 1L daily) of grapefruit juice and simvastatin increased 7 times the exposure to simvastatin's acid. Consumption of 240 ml grapefruit juice in the morning and of simvastatin in the evening also led to a 1,9 times increase. The consumption of grapefruit juice during simvastatin therapy should be avoided.

Orally administered anticoagulants

In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20 - 40 mg/day modestly potentiate the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. There have been very rare reports of increased INR. 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.

Effect of simvastatin on the pharmacokinetics of other products

Simvastatin does not have an inhibitory effect on P450 3A4. Therefore, it is not expected to affect the plasma levels of other drugs metabolized through cytochrome P450 3A4.

4.6 Pregnancy and lactation

Pregnancy

SIMVACOR® is contra-indicated in pregnancy (see 4.3).

The safety of SIMVACOR® in pregnant women has not been established. There are no controlled clinical studies with simvastatin in pregnant women. There have been rare reports of congenital anomalies following endometrial exposure to HMG-CoA reductase inhibitors. However, in a review of approximately 200 prospectively followed pregnancies in women exposed during the first 3 months of pregnancy to simvastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies did not exceed what would be expected in the general population. This number of pregnancies was statistically sufficient in order to exclude an increase in congenital anomalies over 2,5 times the initial incidence.

There is no evidence that the incidence of congenital anomalies in children, whose parents receive SIMVACOR® or another structurally related HMG-CoA reductase inhibitor, is different than the one observed in the general population. However, the mother's treatment with SIMVACOR® may reduce the foetal levels of mevalonic compounds, which are the precursors for cholesterol biosynthesis. Atherosclerosis is a chronic process and the discontinuation of lipid -lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolaemia. For this reason, SIMVACOR® should not be administered to pregnant women and to women trying to conceive or suspecting to be pregnant. SIMVACOR® therapy must be discontinued during pregnancy or as soon as pregnancy is recognized (see 4.3).

Lactation

It is not known whether simvastatin or its metabolites are excreted in human milk. Because some other drugs are excreted in human milk and due to the possibility of serious side-effects, women taking SIMVACOR® should not breast-feed their children (see 4.3).

4.7 Affects on ability to drive and operate machines

SIMVACOR® has an insignificant or no effect on the ability to drive and use machines. However, when driving or using machines, there should be taken into consideration some rare reports of dizziness from the post-marketing experience of the drug.

4.8 Side effects

The incidence of the following side-effects, reported during clinical studies and/or with the post-marketing experience of the drug, are categorised by the rate of their occurrence during

long-term, controlled by placebo clinical studies which include the HPS study and the 4S study in 20,536 and 4,444 patients respectively (see 5.1). During the HPS study, only serious side-effects as well as myalgia and elevation of serum transaminase and of CK, were reported. During the 4S study all of the side-effects were reported. If the incidences with simvastatin were lower than or equal to the placebo in these studies, and there was relevant reports of similar etiology, these side-effects are categorized as ‘’rare’’.

In the HPS study for heart protection, (see 5.1) which included 20,536 patients receiving 40 mg/day SIMVASTATIN (n=10,269) or placebo (n=10,267), safety profiles were comparable between patients taking 40 mg SIMVASTATIN and patients taking placebo during the 5 years, average, of the study. The rate of interruption due to side-effects was comparable (4.8% in patients taking SIMVASTATIN 40 mg compared to 5.1% in those taking placebo). The incidence of myopathy was <0,1% in patients taking SIMVACOR® 40 mg. Increased transaminase levels (>3x ULN were established by repeated tests) occurred in 0,21% (n=21) of the patients taking SIMVASTATIN compared to the 0,09% (n=9) of those receiving placebo.

The incidences of side-effects were categorised according to the following:

Very frequent (>1/10), Frequent (≥1/100, <1/10), Not frequent (≥1/1,000, <1/100), Rare (≥1/10,000, <1/1,000), Very rare (<1/10,000), including individual reports.

Blood and lymphatic disorders

Rare: anaemia

Disorders of the nervous system

Rare: headache, paraesthesia, peripheral neuropathy, dizziness

Gastrointestinal disorders

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

Hepatic and bile disorders

Rare: hepatitis, jaundice

Skin disorders

Rare: rash, itching, alopecia

Disorders in the myoskeletal system of the binding tissue and the bones

Rare: myopathy, rhabdomyolysis (see 4.4), myalgia, muscle spasms

General disorders and states of administration route

Rare: asthenia

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

Laboratory test findings :

Rare: increases of serum transaminases (alanine aminotransferase, aspartic aminotransferase, γ-glutamyl transpeptidase) (see 4.4 *Hepatic Effects*), elevated alkaline phosphatase and elevated CK serum levels (see 4.4).

Class Effects

- Sleep disturbances, including nightmares
- Memory loss
- Sexual dysfunction
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30kg/m^2, raised triglycerides, history of hypertension).

4.9 Overdosage

A few cases of overdosage have been reported. The maximum dosage taken was 3,6 g. All patients recovered without sequelae. There is no special treatment in case of overdosage. In this case, measures of symptomatic treatment, as well as supporting measures should be adopted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: HMG-CoA reductase inhibitor

ATC code: C10A A01

After being orally administered, simvastatin , an inactive lactone, is hydrolyzed through the liver to its active β-hydroxyoxy form that strongly inhibits the HMG-CoA reductase (3-hydroxy-3 methylglutaryl CoA reductase). This enzyme catalyses HMG-CoA conversion to mevalonate, an early and defining step in the biosynthetic pathway of 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 the LDL-lowering effect of simvastatin may involve both reduction of the VLDL-cholesterol concentration and induction of the LDL receptors, leading to reduced production and/or increased catabolism of LDL-cholesterol. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately 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.

High risk of coronary heart disease (CHD) or pre-existing coronary heart disease

In the heart protection Study (HPS), the effect of therapy with simvastatin was assessed in 20,536 patients (40-80 years old) with or without hyperlipidaemia, and coronary heart disease, another or diabetes mellitus. In this study 10,269 patients received SIMVASTATIN 40 mg /day and 10,267 patients received placebo for an average of 5 years. On initiation, 6,793 patients (33%) had LDL-C levels below 116 mg/dl, 5,063 patients (25%) had between 116 and 135 mg/dl and 8,680 patients (42%) had above 135 mg/dl.

Therapy with 40 mg/day simvastatin, compared to the placebo, reduced the risk of total mortality significantly (1,328 [12,9%] for patients taking simvastatin and 1,507 [14,7%] for patients taking placebo (p=0,0003) , due to reducing CHD deaths by 18% (587[5,7%] and 707 [6,9%], (p=0,0005), (absolute decrease of the risk to 1,2 %). The reduction in non-vascular deaths is not significantly important. SIMVASTATIN also reduced the risk of major coronary episodes (combined final target, including non-fatal infarctions or CHD deaths) by 27% (p<0,0001). Simvastatin reduced the need for undergoing myocardial revascularization procedures (including coronary artery by-pass grafting or percutaneous transluminal coronary angioplasty) as well as peripheral and other non-coronary revascularization procedures by 30% (p<0,0001) and 16% (p=0,0006) respectively. Simvastatin reduced the risk of brain episode by 25% (p<0,0001) responding to reduction of ischaemic episode by 30% (p<0,0001). Furthermore, in the subgroup of patients with diabetes, Simvastatin reduced the risk of vascular complications in greater extent, including revascularization procedures of peripheral vessels (surgery or angioplasty), by 21% (p=0,0293).

The equivalent reduction in the episode incidence was similar in every subgroup studied, including those without coronary heart disease but with angio-encephalic disease or peripheral vascular disease, those whose age when initiating the study was below or over 70 years, with

or without hypertension, and especially those whose LDL-C when initiating the study was 3,0 mmol/l.

In the Scandinavian Simvastatin Survival Study (4S), the effect on total mortality of therapy with simvastatin was assessed in 4,444 patients with coronary heart disease (CHD) and baseline total cholesterol 212-309 mg/dl (5,5 to 8,0 mmol/l). In this multicentre, randomised, double-blind, placebo-controlled study, patients with angina or history of myocardial infarction (EM) received treatment concomitantly with diet, regular observation, and either SIMVASTATIN 20-40 mg /day (n=2,221) or placebo (n=2,223) for an average of 5,4 years. Simvastatin reduced the risk of death by 30% (absolute decrease of the risk to 3,3 %). The risk of CHD death was reduced by 42% (absolute decrease of the risk to 3,5%). SIMVASTATIN also reduced the risk of major coronary episodes (CHD death and hospital-verified non-fatal myocardial infarction) by 34%. Furthermore, simvastatin reduced the risk for fatal and non-fatal angio-cerebral episodes (transient ischemic episode) by 28%. There was no statistically significant difference concerning mortality between the groups.

Primary hypercholesterolaemia and combined hyperlipidaemia

In studies comparing the safety and efficacy of simvastatin 10, 20, 40 and 80 mg /day in patients with hypercholesterolaemia, the average LDL-C reduction was 30, 38, 41 and 47% respectively. During studies in patients with combined (mixed) hyperlipidaemia taking simvastatin 40 and 80 mg, the average triglyceride reduction was 28 and 33% (placebo: 2%) respectively and the average HDL-C increase was 13 and 16% (placebo: 3%) respectively.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone which is readily hydrolysed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver. The degree of hydrolysis in man is very slow.

Absorption

In man simvastatin is well absorbed and undergoes extensive first-pass excretion in the liver. The excretion in the liver depends on the hepatic blood flow. The liver is the primary site of action for the active form. The availability of β-hydroxyacid to the systemic circulation following an oral dose of simvastatin, was found to be less than 5% of the dose. The maximum plasma concentration of active metabolites is achieved within 1-2 hours after simvastatin administration. Simultaneous food consumption did not affect absorption.

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

Distribution

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

Excretion

Simvastatin is a substrate for CYP3A4 (see 4.3 and 4.5). The major metabolites of simvastatin present in human plasma are β-hydroxyacid and four additional active metabolites. After oral administration of labelled simvastatin in man, 13% of the radioactivity was excreted in urine and 60% in faeces within 96 hours. The ratio which was excreted in faeces represents the absorbed drug, equivalent to the one excreted in bile as well as the non-absorbed drug. The elimination half-life of the β-hydroxyacid following intravenous injection was about 1,9 hours. Only 0,3% of the intravenous dose, IV, was excreted in urine in the form of inhibitors.

5.3 Preclinical safety data

Data from conventional animal studies about pharmacodynamics, toxicity, genotoxicity and carcinogenesis have showed that there are no other risks for patients than those expected according to the pharmacological mechanism. Simvastatin in the highest tolerable dosage in rats and rabbits did not cause any fetal dysplasia and had no effect on fertility, reproduction or foetal growth.

6 PHARMACEUTICAL DATA

6.1 List of Excipients

Lactose monohydrate, microcrystalline cellulose, pregelatinized maize starch, butylhydroxyanisole, ascorbic acid, citric acid monohydrate, magnesium stearate.

Coating: Hydroxypropylmethylcellulose, hydroxypropylcellulose, titanium dioxide (E171), talc, iron oxide (E172).

6.2 Incompatibilities

Not known.

6.3 Shelf life

The shelf life of the product is 36 months under normal conditions.

6.4 Special precautions for storage

SIMVACOR® should be stored at room temperature (≤ 25°C).

6.5 Nature and contents of container

10 mg: Pale pink round film-coated tablets in PVC/aluminium blister.

Each blister contains 10 tablets. Each box contains :

10 mg: 1 blister of 10 tablets and a patient information leaflet.

6.6 Instructions for use and handling

SIMVACOR® should be taken under physician's prescription.

7 MARKETING AUTHORIZATION HOLDER

KLEVA SA. - Pharmaceutical Industry

189, Parnithos Ave., 136.75 Athens

Greece

Tel. : 30 210 2402404-7

Fax : 30 210 2460206

8 MARKETING AUTHORIZATION NUMBER(S)

MA122/02401

9 DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORISATION

18th April 2006

10 DATE OF REVISION OF THE TEXT

1st August 2012