

## New Zealand Datasheet

### Name of Medicine

SIMVAREX

Simvastatin

10 mg, 20 mg 40 mg and 80 mg tablets

### Presentation

SIMVAREX 10 mg tablets are light pink coloured oval shaped biconvex film coated tablets imprinted SVN 10 on one side and NEO on the other.

SIMVAREX 20 mg tablets are tan coloured oval shaped biconvex film coated tablets imprinted SVN 20 on one side and NEO on the other.

SIMVAREX 40 mg tablets are pink coloured oval shaped biconvex film coated tablets imprinted SVN 40 on one side and NEO on the other.

SIMVAREX 80 mg tablets are pink coloured capsule shaped biconvex film coated tablet (17.8 mm x 5.4 mm) imprinted SVN 80 on one side and NEO on the other.

### Uses

#### Actions

SIMVAREX (simvastatin) is a lipid-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*.

After oral ingestion, simvastatin, an inactive lactone, is hydrolysed to the corresponding  $\beta$ -hydroxyacid form. This is a principal metabolite and an inhibitor of HMG-CoA reductase, the enzyme that catalyses an early and rate-limiting step in the biosynthesis of cholesterol. Clinical studies show simvastatin to be highly effective in reducing total-C, LDL-C, TG, and very-low-density lipoprotein cholesterol VLDL-C concentrations, and increasing HDL-C in heterozygous familial and non-familial forms of hypercholesterolemia, and in mixed hyperlipidemia when elevated cholesterol was cause for concern and diet alone has been insufficient. Marked responses are seen within 2 weeks, and maximum therapeutic responses occur within 4-6 weeks. The response is maintained during continuation of therapy. When therapy with SIMVAREX tablets is stopped, cholesterol and lipids return to pretreatment levels.

The active form of simvastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyses the conversion of HMG-CoA to mevalonate. Because the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway of cholesterol, therapy with SIMVAREX tablets would not be expected to cause an accumulation of potentially toxic sterols. In addition, HMG-CoA is also metabolised readily back to acetyl-CoA, which participates in many biosynthetic processes in the body.

In animal studies, after oral dosing, simvastatin had high selectivity for the liver, where it achieved substantially higher concentrations than in non-target tissues. Simvastatin undergoes extensive first-pass extraction in the liver, the primary site of action, with subsequent excretion of medicine in the bile. Systemic exposure of the active form of simvastatin in humans has been found to be less than 5% of the oral dose. Of this, 95% is bound to human plasma proteins.

SIMVAREX tablets raise HDL-C and therefore lowers the LDL-C/HDL-C and total-C/HDL-C ratios.

### **Clinical Studies**

In the Scandinavian Simvastatin Survival Study (4S), the effect on total mortality of therapy with simvastatin for a median of 5.4 years was assessed in 4,444 patients with coronary heart disease (CHD) and baseline total-C 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomised, double-blind, placebo-controlled study, SIMVAREX reduced the risk of death by 30%, of CHD death by 42%, and of having a hospital-verified nonfatal myocardial infarction by 37%. simvastatin reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%. In patients with diabetes mellitus the risk of a major coronary event was reduced by 55%. Furthermore, simvastatin significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischemic attacks) by 28%.

In the Heart Protection Study (HPS), the effects of therapy with simvastatin for a mean duration of 5 years were assessed in 20,536 patients, with or without hyperlipidemia, who were at high risk of coronary heart disease (CHD) events because of diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or CHD. At baseline, 33% had LDL levels below 116 mg/dL; 25% had levels between 116 mg/dL and 135 mg/dL; and 42% had levels greater than 135 mg/dL.

In this multicenter, randomised, double-blind, placebo-controlled study, simvastatin 40 mg/day compared with placebo reduced the risk of total mortality by 13%, due to a reduction in CHD deaths (18%). Simvastatin also decreased the risk of major coronary events (a composite endpoint comprising non-fatal MI or CHD deaths) by 27%. Simvastatin reduced the need for undergoing coronary revascularization procedures (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) and peripheral and other non-coronary revascularization procedures by 30% and 16%, respectively. Simvastatin reduced the risk of stroke by 25%, attributable to a 30 % reduction in ischemic stroke. Furthermore, simvastatin reduced the risk of hospitalisation for angina pectoris by 17%. The risks of major coronary events and major vascular events (a composite endpoint comprising major coronary events, stroke, or revascularization procedures) were reduced by about 25% in patients with or without CHD, including diabetics and patients with peripheral or cerebrovascular disease. In addition, within the subgroup of patients with diabetes, simvastatin reduced the risk of developing macrovascular complications, including peripheral revascularization procedures (surgery or angioplasty), lower limb amputations, or leg ulcers by 21%. The risk reductions produced by simvastatin in both major vascular events and major coronary events were evident and consistent regardless of patient age, gender, baseline LDL-C, HDL-C, TG, apolipoprotein A-I, or apolipoprotein B level, presence or absence of hypertension, creatinine levels up to the entry limit of 2.3 mg/dL, presence or absence of baseline cardiovascular medications (i.e., aspirin, beta blockers, angiotensin converting enzyme (ACE) inhibitors, or calcium channel blockers), smoking status, alcohol intake, or obesity. By 5 years, 32% of patients in the placebo group were taking a statin (outside of the study protocol), so that the observed risk reductions underestimate the real effect of simvastatin.

## Pharmacokinetics

Simvastatin is an inactive lactone which is readily hydrolysed in vivo to the corresponding  $\beta$ -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  $\beta$ -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 <sup>14</sup>C-labelled simvastatin, 100mg (20 uCi) of medicine was administered as capsules (5 x 20mg), and blood, urine, and faeces collected. Thirteen percent of the radioactivity was recovered in the urine and 60 percent in faeces. The latter represents absorbed medicine equivalents excreted in bile as well as unabsorbed medicine. Less than 0.5 percent of the dose was recovered in urine as HMG-CoA reductase inhibitors. In plasma, the inhibitors account for 14 percent and 28 percent (active and total inhibitors) of the AUC of total radioactivity, indicating that the majority of chemical species present were inactive or weak inhibitors.

Both simvastatin and L-654,969 are bound to human plasma proteins (95%). The major metabolites of simvastatin present in human plasma are L-654,969 and four additional active metabolites. The availability of L-654,969 to the systemic circulation following an oral dose of simvastatin was estimated using an IV reference dose of L-654,969; the value was found to be less than 5 percent 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 medicine equivalents in the bile. Consequently, availability of active medicine to the general circulation is low.

In dose-proportionality studies utilising doses of simvastatin of 5, 10, 20, 60, 90 and 120mg 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 medicine 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.

In a study of patients with severe renal insufficiency (creatinine clearance <30ml/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately two-fold higher than those in healthy volunteers.

In a study of 12 healthy volunteers, simvastatin at the maximal 80-mg dose had no effect on the metabolism of the probe CYP3A4 substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and therefore, is not expected to affect the plasma levels of other medicines metabolised by CYP3A4.

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see Warnings and Precautions, Myopathy/Rhabdomyolysis and Medicine Interactions).

No pharmacokinetic studies have been conducted to date in elderly patients or in patients with renal or hepatic dysfunction.

## **Indications**

### **Patients at High Risk of Coronary Heart Disease (CHD) or With Existing CHD**

In patients at high risk of CHD (with or without hyperlipidemia but with a total cholesterol of > 3.5 mmol/L), i.e., patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD, SIMVAREX tablets are indicated to:

- Reduce the risk of total mortality by reducing CHD deaths;
- Reduce the risk of major vascular events (a composite of non-fatal myocardial infarction, CHD death, stroke, or revascularization procedures);
- Reduce the risk of major coronary events (a composite of non-fatal myocardial infarction or CHD deaths);
- Reduce the risk of stroke;
- Reduce the need for coronary revascularization procedures (including coronary artery bypass grafting and percutaneous transluminal coronary angioplasty);
- Reduce the need for peripheral and other non-coronary revascularization procedures;
- Reduce the risk of hospitalisation for angina pectoris.

In patients with diabetes, SIMVAREX tablets reduce the risk of developing peripheral macrovascular complications (a composite of peripheral revascularization procedures, lower limb amputations, or leg ulcers).

In hypercholesterolemic patients with coronary heart disease, SIMVAREX tablets slow the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

### **Patients with Hyperlipidemia**

- SIMVAREX tablets are indicated as an adjunct to diet to reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), triglycerides TG, and, apolipoprotein B (apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia including heterozygous familial hypercholesterolemia (Fredrickson type IIa), or combined (mixed) hyperlipidemia (Fredrickson type IIb) when response to diet and other non-pharmacological measures is inadequate. SIMVAREX tablets therefore lower the LDL-C/HDL-C and total-C /HDL-C ratios.
- SIMVAREX tablets are indicated for the treatment of patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia) with a baseline LDL cholesterol of < 3.37mmol/L and baseline triglyceride of > 2.26 mmol/L, despite adequate dietary intervention.
- SIMVAREX tablets are indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia) not responding to diet alone with VLDL/TG ratios > 0.25, and raised total cholesterol, TG and Apo-E levels.

- SIMVAREX tablets are also indicated as an adjunct to diet and other non-dietary measures for the treatment of patients with homozygous familial hypercholesterolemia to reduce elevated total-C, LDL-C and apoB.

## **Dosage and Administration**

The dosage range for SIMVAREX tablets is 5-80mg/day, given as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80mg/day given as a single dose in the evening. SIMVAREX tablets may be taken with or without food.

### **Patients at High Risk of Coronary Heart Disease (CHD) or With Existing CHD**

The usual starting dose of SIMVAREX tablets is 40mg/day given as a single dose in the evening in patients at high risk of CHD (with or without hyperlipidemia) i.e., patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD. Medicine therapy can be initiated simultaneously with diet and exercise.

### **Patients with Hyperlipidemia (Who are not in the risk categories above)**

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

The usual starting dose is 20 mg/day given as a single dose in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40mg/day given as a single dose in the evening. Patients who require only a moderate reduction of LDL-C may be started at 10mg. Adjustments of dosage including starting dose, if required, should be made as specified above.

### **Patients with Homozygous Familial Hypercholesterolemia**

Based on results of a controlled clinical study, the recommended dosage for patients with homozygous familial hypercholesterolemia is SIMVAREX tablets 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. SIMVAREX tablets 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**

SIMVAREX tablets are effective alone or in combination with bile acid sequestrants.

In patients taking cyclosporine, danazol, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses (> 1 g/day) of niacin concomitantly with SIMVAREX tablets, the dose of SIMVAREX should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with SIMVAREX tablets, the dose of SIMVAREX tablets should not exceed 20 mg/day. (See Warnings and Precautions: Myopathy/Rhabdomyolysis and Interactions).

### **Dosage in Renal Insufficiency**

Because SIMVAREX tablets do 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.

## Contraindications

- Hypersensitivity to any component of this preparation.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and nursing (see also Warnings and Precautions, Use in Pregnancy and Use in Lactation).

## Warnings and Precautions

### ***Myopathy/Rhabdomyolysis***

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

The risk of myopathy/rhabdomyolysis is increased by concomitant use of simvastatin with the following:

Potent inhibitors of CYP3A4, eg., itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone, particularly with higher doses of simvastatin (see below; Medicine Interactions, CYP3A4 Interactions, Pharmacokinetics).

#### Other medicines:

Gemfibrozil and other fibrates (except fenofibrate), or lipid-lowering doses (> 1g/day) of niacin, particularly with higher doses of simvastatin (see Interactions, Interactions with lipid-lowering medicines that cause myopathy when given alone). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent.

Cyclosporine or danazol particularly with higher doses of simvastatin (See Interactions, *Other medicine interactions*, Pharmacokinetics).

Amiodarone or verapamil with higher doses of simvastatin (see Interactions, *Other medicine interactions*). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

Diltiazem: In a pharmacokinetic study, co-administration of diltiazem and simvastatin resulted in a mean 70% increase in systemic exposure to total simvastatin-derived HMG-CoA reductase inhibitory activity. Patients on diltiazem treated concomitantly with simvastatin 80 mg have a slightly increased risk of myopathy. The risk of myopathy is approximately 1% in these patients. In clinical studies, the risk of myopathy in patients taking simvastatin 40 mg with diltiazem was similar to that in patients taking simvastatin 40 mg without diltiazem (see Medicine Interactions, Other medicine interactions).

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

**Consequently:**

1. Use of simvastatin concomitantly with potent CYP3A4 inhibitors (eg, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone) should be avoided. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.
2. The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine, danazol, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses ( $\geq 1$  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 medicine combination. The benefits of the use of simvastatin in patients receiving other fibrates (except fenofibrate), niacin, cyclosporine or danazol should be carefully weighed against the risks of these drug combinations. Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone. Addition of fibrates or niacin to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. Combinations of fibrates or niacin with low doses of simvastatin have been used without myopathy in small, short-term clinical studies with careful monitoring.
3. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. 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.
4. All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and/or a CK level  $>10$  times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.
5. Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency

usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

### ***Hepatic Effects***

It is recommended that liver function tests (LFT) be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80mg dose should receive an additional test prior to titration, 3 months after titration to the 80mg 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 3X ULN and are persistent, the medicine should be discontinued.

In clinical studies persistent increases (to more than 3X ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When the medicine was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. Some of these patients had abnormal LFT prior to therapy with simvastatin and/or consumed substantial quantities of alcohol.

In the 4S, the number of patients with more than one transaminase elevation to >3X ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). The frequency of single elevations of SGPT (ALT) to 3X ULN was significantly higher in the simvastatin group in the first year of the study (20 vs. 8,  $p=0.023$ ), but not thereafter. Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group ( $n=2,221$ ) and 5 in the placebo group ( $n=2,223$ ). Of the 1986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to > 3X ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. All of the patients in this study received a starting dose of 20mg of simvastatin; 37% were titrated to 40mg.

In 2 controlled clinical studies in 1105 patients, the 6 month incidence of persistent hepatic transaminase elevations considered medicine-related was 0.7% and 1.8% at the 40 and 80 mg dose respectively.

In the Heart Protection Study, in which 20, 536 patients were randomised to receive SIMVAREX 40mg/day or placebo, the incidences of elevated transaminases (> 3X ULN confirmed by repeat test) were 0.21% ( $n = 21$ ) for patients treated with simvastatin and 0.09% ( $n = 9$ ) for patients treated with placebo.

The medicine 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.

As with other lipid-lowering agents, moderate (less than 3X 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.

### ***Ophthalmic Evaluations***

In the absence of any medicine therapy, there is generally an increase in the prevalence of lens opacities with time as a result of ageing. Current long term data from clinical studies do not indicate an adverse effect of simvastatin on the human lens.

### **Use in Pregnancy**

SIMVAREX tablets are contraindicated during pregnancy.

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

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

### **Use in Lactation**

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

### **Paediatric Use**

Safety and effectiveness in children have not been established.

SIMVAREX is not recommended for paediatric use at this time.

### **Elderly**

For patients over the age of 65 years who received simvastatin in controlled clinical studies, efficacy, as assessed by reduction in total and LDL- C levels, appears similar to that seen in the population as a whole, and there is no apparent increase in the frequency of clinical or laboratory adverse findings.

### **Animal Toxicology**

#### **Reproductive and Developmental Toxicity**

At maximally tolerated doses in both the rat and the rabbit, simvastatin produced no foetal malformations and had no effects on fertility, reproductive function or neonatal development. However, in rats, an oral dose of 60 mg/kg/day of the hydroxy acid, pharmacologically active metabolite of simvastatin resulted in decreased maternal body weight and an increased incidence of foetal resorptions and skeletal malformations compared with controls. Subsequent studies conducted at dosages of up to 60 mg/kg/day with this metabolite showed that these resorptions and skeletal malformations were consequences of maternal toxicity (forestomach lesions associated with maternal weight loss) specific to rodents and are highly unlikely to be due to a direct effect on the developing foetus. Although no studies have been conducted with simvastatin, maternal treatment of pregnant rats with a closely related HMG-CoA reductase inhibitor at dosages of 80 and 400 mg/kg/day (10- and 52-fold the maximum recommended therapeutic dose based on mg/m<sup>2</sup> body surface area) has been shown to reduce the foetal plasma levels of mevalonate.

### **Genetic Toxicology and Carcinogenicity**

An extensive battery of *invitro* and *in vivo* genetic toxicity tests have been conducted on both simvastatin and its 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 noncytotoxic concentrations tested 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 1mg/kg/day to 25mg/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 25mg/kg of simvastatin per day (more than an order of magnitude greater than the maximum 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 5mg/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 evidence 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 humans. Moreover, identical cells found in other locations (e.g. oesophagus and anorectal junction of the rat, mouse and dog) are unaffected.

Results of an additional 73-week carcinogenicity study in mice receiving simvastatin doses up to 400 mg/kg/day (more than 2 orders of magnitude greater than the maximum human dose) exhibited increased incidences of hepatocellular adenomas and carcinomas, pulmonary adenomas and harderian gland adenomas. A no-effect dose of 25 mg/kg/day (again, more than an order of magnitude greater than the maximum human dose) was established in this study and from the results of the initial 92-week carcinogenicity study in mice.

Results of an additional 106-week carcinogenicity study in rats receiving simvastatin doses ranging from 50 mg/kg/day to 100 mg/kg/day (more than an order of magnitude

greater than the maximum human dose) exhibited a treatment-related increase in the incidence of hepatocellular neoplasms. The no-effect dose remains at 25 mg/kg/day (more than an order of magnitude greater than the maximum 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.

### **Effects on Ability to Use and Drive Machinery**

SIMVAREX tablets are presumed to be safe and unlikely to produce an effect on the ability to drive or use machinery.

### **Adverse Effects**

SIMVAREX tablets are generally well-tolerated; for the most part adverse effects have been mild and transient in nature. Less than 2 percent of patients were discontinued from controlled clinical studies due to adverse effects attributable to simvastatin tablets.

In the pre-marketing controlled clinical studies, adverse effects occurring with a frequency of 1 percent or more and considered by the investigator as possibly, probably or definitely medicine-related were: abdominal pain, constipation and flatulence. Other adverse effects occurring in 0.5 - 0.9 percent of patients were asthenia and headache.

Myopathy has been reported rarely.

In the Heart Protection Study involving 20, 536 patients treated with 40mg/day of simvastatin (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with simvastatin and patients treated with placebo over the mean 5 years of the study. In this mega-trial, only serious adverse effects and discontinuations due to any adverse effects were recorded. Discontinuation rates due to adverse effects were comparable (4.8% in patients treated with simvastatin compared with 5.1% in patients treated with placebo). The incidence of myopathy was < 0.1% in patients treated with simvastatin. Elevated transaminases (>3X ULN confirmed by repeat test) occurred in 0.21% (n = 21) of patients treated with simvastatin compared with 0.09% (n = 9) of patients treated with placebo.

In 4S, involving 4444 patients treated with 20-40 mg/day of simvastatin (n=2221) or placebo (n=2223), the safety and tolerability profiles were comparable between treatment groups over the median 5.4 years of the study.

The following additional adverse effects were reported either in uncontrolled clinical studies or in marketed use: nausea, diarrhoea, rash, dyspepsia, pruritis, alopecia, dizziness, depression, memory loss, muscle cramps, myalgia, pancreatitis, paresthesia, peripheral neuropathy, vomiting and anaemia. Rarely rhabdomyolysis and hepatitis/jaundice , and very rarely hepatic failure have occurred. 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, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

Another reported adverse effect not considered to be medicine related was chest pain.

### **Laboratory Test Findings**

Marked and persistent increases of serum transaminases have been reported infrequently. Elevated alkaline phosphatase and (-glutamyl transpeptidase have been reported. Liver function test abnormalities have generally been mild and transient. Increases in CK levels, derived from skeletal muscle, have been reported (see Warnings and Precautions).

### **Adverse Effects - Causal Relationship Unknown**

The following adverse effects have been reported; however, a causal relationship to therapy with SIMVAREX tablets has not been established: depression, erythema multiforme including Stevens-Johnson syndrome, leukopenia and purpura.

## **Interactions**

### **CYP3A4 Interactions**

Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other medicines metabolised by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of simvastatin. (See Warnings and Precautions, *Myopathy/Rhabdomyolysis*, and, Pharmacokinetics).

Itraconazole

Ketoconazole

Erythromycin

Clarithromycin

Telithromycin

HIV protease inhibitors

Nefazodone

### **Interactions with lipid-lowering medicines that can cause myopathy when given alone**

The risk of myopathy is also increased by the following lipid-lowering medicines that are not potent inhibitors of CYP3A4, but which can cause myopathy when given alone.

(See Warnings and Precautions: *Myopathy/Rhabdomyolysis*).

Gemfibrozil

Other fibrates (except fenofibrate)

When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent.

Niacin (nicotinic acid) (> 1 g/day)

### **Other medicine interactions**

Cyclosporine or Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol particularly with higher doses of simvastatin (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*, Pharmacokinetics)

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*).

Diltiazem: Patients on diltiazem treated concomitantly with simvastatin 80 mg have a slightly increased risk of myopathy (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*).

### **Other interactions**

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of medicines metabolised by CYP3A4. The effect of typical consumption (one 250-ml glass daily) is minimal (13% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the area under the concentration-time curve) 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 (see Warnings and Precautions: *Myopathy/Rhabdomyolysis* and Pharmacokinetics).

### **Coumarin Derivatives**

In two clinical studies, one in normal volunteers and the other in hypercholesterolemic 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 or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Medicine interaction studies were performed with the following compounds.

### **Propranolol**

In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of SIMVAREX and propranolol.

### **Digoxin**

Concomitant administration of SIMVAREX tablets and digoxin in normal volunteers resulted in a slight elevation (less than 0.3ng/ml) in medicine concentrations (as measured by a digoxin radioimmunoassay) in plasma compared to concomitant administration of placebo and digoxin.

### **Other Concomitant Therapy**

In clinical studies, simvastatin was used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta blockers, diuretics and nonsteroidal anti-inflammatory medicines (NSAIDs) without evidence of clinically significant adverse interactions.

### **Overdosage**

A few cases of overdosage have been reported; the maximum dose taken was 3.6g. All patients recovered without sequelae. General measures should be adopted.

### **Pharmaceutical Precautions**

Store below 25°C.

## Medicine Classification

Prescription Medicine.

## Package Quantities

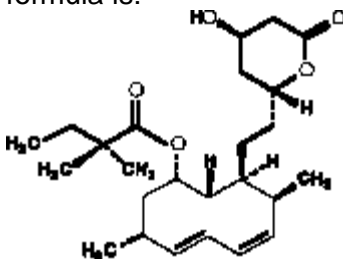
SIMVAREX 10mg, 20 mg, 40 mg and 80 mg tablets are available in blister packs of 30 tablets.

## Further Information

### Chemistry

SIMVAREX tablets contain simvastatin, which is described chemically as: [1S[1(,3(,7(,8((2S\*,4S\*),8α β)]-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.

Its empirical formula is C<sub>25</sub>H<sub>38</sub>O<sub>5</sub> and its molecular weight is 418.57. Its structural formula is:



Simvastatin is a white crystalline powder, practically insoluble in water and freely soluble in chloroform, methanol and ethanol.

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## Date of Preparation

21 July 2008