NAME OF THE MEDICINAL PRODUCT

ZOCOR Heart-Pro® 10mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Simvastatin 10 mg
For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Peach-coloured, oval-shaped tablets marked 'MSD-735'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To reduce the risk of a first major coronary event (non fatal myocardial infarction and coronary heart disease (CHD) deaths) in individuals who are likely to be at moderate risk (approximately 10-15% 10-year risk of a first major event) of CHD, i.e.:

- Men aged 55 years and above.
- Men aged 45-54 years and women aged 55 years and above who have one or more of the following:
    - o Family history of coronary heart disease in a first-degree relative (parent or sibling); CHD in male first degree relative below 55 years or female first degree relative below 65 years.
    - o Smoker (is currently a smoker or has been a smoker in the last 5 years).
    - o Overweight (Body Mass Index > 25kg/m2) or truncal obesity (waist: 40 inches or 102cm in men; 35 inches or 88cm in women).
    - o Of South Asian ethnic origin i.e. from the Indian subcontinent that includes India, Bangladesh, Pakistan or Sri Lanka.

Zocor Heart-Pro® should be taken as part of a programme of actions designed to reduce the risk of CHD. These include cessation of smoking, eating a healthy diet, weight loss and regular exercise.

4.2 Posology and method of administration

Route of administration is oral.
Zocor Heart-Pro® is given as a single 10mg dose in the evening.
Simvastatin treatment can be initiated simultaneously with diet, exercise and smoking cessation.
Use in the elderly: No dosage adjustment is necessary.
Children: The experience in children is limited. Zocor Heart-Pro® is not indicated for paediatric use.

4.3 Contraindications

Hypersensitivity to simvastatin or any of the excipients; previous history of muscular toxicity with a statin or fibrate; individuals already taking prescription cholesterol lowering drugs; concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone); active liver disease or unexplained persistent elevations of serum transaminases; pregnancy and breast feeding (see also 4.6 'Pregnancy and lactation'); women of childbearing potential.

4.4 Special warnings and precautions for use

Zocor Heart-Pro® treatment is not intended for individuals who are known to have:
- Existing coronary heart disease
- Diabetes
- History of stroke or peripheral vascular disease

• Diagnosis of the genetic disorder called Familial Hypercholesterolaemia
Individuals with these conditions are at higher risk of cardiovascular disease and should be managed under the supervision of a physician.
Individuals who have been diagnosed as having hypertension are also at increased risk of cardiovascular disease. Therefore, these individuals should consult their doctor before undertaking treatment with Zocor Heart-Pro®.
If an individual is found to have a fasting LDL-C level of 5.5 mmol/l or greater before or during treatment, they should be advised to consult their doctor, since it is unlikely that simvastatin 10mg will give a satisfactory reduction in cholesterol.
Reducing the risk of myopathy:
Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria and very rarely fatalities have occurred.

1. General measures

All individuals starting therapy with Zocor Heart-Pro® must be advised of the risk of myopathy and told to immediately stop taking Zocor Heart-Pro® until they consult with a physician, if they experience unexplained generalised muscle pain, tenderness or weakness (e.g. muscle pain not associated with flu, unaccustomed exercise, or recent strain or injury). A creatine kinase (CK) level should be measured in people with these symptoms.
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.
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. Such patients merit closer monitoring *(see 4.4, Special warnings and precautions for use)*.
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.
People aged >70 years or with hypothyroidism, renal impairment, a personal or family history of hereditary muscle disorders should not take Zocor Heart-Pro® except on medical advice.

2. Measures to reduce the risk of myopathy caused by drug interactions (see above)

Use of simvastatin concomitantly with itraconazole, ketoconazole, erythromycin, telithromycin, clarithromycin, HIV protease inhibitors or nefazodone, should be avoided. If treatment with itraconazole, ketoconazole, erythromycin, telithromycin or clarithromycin is unavoidable, therapy with simvastatin should be suspended during the course of treatment. Concomitant use with other medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk. (*See 4.5 Interactions with other medicinal products and other forms of interaction).*
The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of fusidic acid with statins (section 4.5). If the combination proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.5). Temporary suspension of simvastatin treatment may be considered.
Hepatic effects: In clinical studies with higher doses of simvastatin, persistent increases (to more than 3X ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. These changes appear to be less common with lower doses. When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels.
As with other lipid lowering agents, moderate (less than 3X ULN) elevations of serum transaminase 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.
The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a known past history of liver disease. Individuals consuming more than the nationally recommended upper limit for weekly units of alcohol (28 for men and 21 for women) should not take Zocor Heart-Pro® without medical supervision. Active liver diseases or unexplained persistent transaminase elevations are contra-indications to the use of simvastatin.
If an individual develops symptoms or signs of liver disease (e.g. jaundice) while taking Zocor Heart-Pro® the drug should be discontinued immediately and medical advice should be sought.

This product contains lactose. Individuals 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

Interaction studies have only been performed in adults.

Pharmacodynamic interactions.

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

The risk of myopathy, including rhabdomyolysis, is increased during the concomitant administration with fibrates and niacin (nicotinic acid) (≥1 g/day). Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see Pharmacokinetic interactions and section 4.4). 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. Adequate pharmacovigilance and pharmacokinetic data are not available for 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 4.3 and 4.4).

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting agents	*Prescribing recommendations*
Potent CYP3A4 inhibitors: Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone	**Contraindicated with simvastatin**
Gemfibrozil	Avoid but if necessary, do not exceed 10 mg simvastatin daily
Ciclosporin Danazol Other fibrates (except fenofibrate) Niacin (≥1 g/day)	Do not exceed 10 mg simvastatin daily
Fusidic acid	Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Effects of other medicinal products on simvastatin.

Interactions involving CYP3A4.

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4

increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, telithromycin, clarithromycin, HIV protease inhibitors and nefazodone. Concomitant administration of itraconazole resulted in a more than 10 fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11 – fold increase in exposure to simvastatin acid. Therefore, combination with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: ciclosporin (see sections 4.2 and 4.4).

Ciclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin particularly with higher doses of simvastatin (see section 4.4). Therefore, the dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with ciclosporin. Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.

Danazol

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with higher doses of simvastatin. Therefore, the dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with danazol

Gemfibrozil

Gemfibrozil increases the AUC of simvastatin 1.9-fold possibly due to inhibition of the glucuronidation pathway (see section 4.4). Therefore the dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with gemfibrozil.

Fusidic acid

The risk of myopathy may be increased by concomitant administration of fusidic acid with statins, including simvastatin. Isolated cases of rhabdomyolysis have been reported with simvastatin. Temporary suspension of simvastatin treatment may be considered. If it proves necessary, patients on fusidic acid and simvastatin should be closely monitored (see section 4.4).

Grapefruit juice

Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 litre daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 ml of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

Effects of simvastatin on the pharmacokinetics of other medicinal products.

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

Oral anticoagulants

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. Very rare cases of elevated INR have been reported. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs.
Once a stable prothrombin time has been documented, prothrombin times can be monitored at the

intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

4.6 Pregnancy and lactation

Pregnancy

Zocor Heart-Pro® is contra-indicated during pregnancy (see section 4.3).
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 Zocor Heart-Pro® or another closely related HMG‑CoA reductase inhibitor differs from that observed in the general population, maternal treatment with Zocor Heart-Pro® may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, Zocor Heart-Pro® should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Zocor Heart-Pro® should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. *(See section 4.3 and 5.3.)*

Lactation

It is not known whether simvastatin or its metabolites are excreted in human milk. Simvastatin should be avoided during lactation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Simvastatin is generally well tolerated; for the most part, side effects have been usually mild and transient in nature. Less than 2% of patients on simvastatin were discontinued from controlled clinical studies due to side effects attributable to simvastatin.
In the pre-marketing controlled clinical studies, the most commonly reported side effects were abdominal pain, constipation, flatulence, asthenia and headache.
The following adverse effects have been reported:

<u>Blood and lymphatic system disorders:</u>

Anaemia

<u>Nervous system disorders:</u>

Headache, paraesthesia, dizziness, peripheral neuropathy

<u>Gastrointestinal disorders:</u>

Constipation, abdominal pain, flatulence, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis

<u>Hepato-biliary disorders:</u>

Hepatitis/jaundice, hepatic failure

Skin and subcutaneous tissue disorders:

Rash, pruritus, alopecia

Musculoskeletal, connective tissue and bone disorders:

Myopathy, rhabdomyolysis (see section 4.4), myalgia, muscle cramps

General disorders and administration site conditions:

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:

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Serum lipid reducing agents
ATC Code: C10 AA01
The involvement of LDL cholesterol in atherogenesis has been well documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that high LDL cholesterol and low HDL (high-density lipoprotein) cholesterol are both risk factors for coronary heart disease.
Simvastatin 10 mg/day reduces Low Density Lipoprotein Cholesterol (LDL-C) by around 27%. This degree of reduction has been shown to reduce the risk of a first major coronary event by about one third after 3 years of treatment.
After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active beta-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy-3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.
Zocor Heart-Pro® has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolised predominantly by the high-affinity LDL receptor. The mechanism of the LDL-lowering effect of Zocor Heart-Pro® may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with Zocor Heart-Pro®. In addition, Zocor Heart-Pro® moderately increases HDL-C and reduces plasma TG. As a result of these changes the ratios of total to HDL-C and LDL- to HDL-C are reduced.

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 14C-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 availability 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

Based on conventional animal studies regarding pharmacodynamics, repeated dose toxicity, genotoxicity and carcinogenicity, there are no other risks for the individual than may be expected on account of the pharmacological mechanism. At maximally tolerated doses in both the rat and the rabbit, simvastatin produced no foetal malformations and had no effects on fertility, reproductive function or neonatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic acid (E300)
Butylated hydroxyanisole (E320)
Citric acid monohydrate (E330)
Lactose
Magnesium stearate (E572)
Microcrystalline cellulose (E460)
Pregelatinised maize starch
Hydroxypropylcellulose (E463)
Methylhydroxy-propylcellulose (E464)
Talc (E553(b))
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister packs of opacified trilaminate film composed of polyvinylchloride/polyethylene/polyvinylidene chloride (PVC/PE/PVDC) lidded with aluminium foil containing 28 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

McNeil Ltd.
Saunderton
High Wycombe
Buckinghamshire HP14 4HJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 13249/0039

23/07/2004