Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zocor 20 mg Film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20mg of simvastatin.

Excipients:
Contains Lactose Monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from Poland:
Tan-coloured, oval-shaped, film-coated tablets, marked “MSD 740” on one side and not marked on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypercholesterolaemia
Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Cardiovascular prevention
Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy (see section 5.1).

4.2 Posology and method of administration

The dosage range is 5-80 mg/day given orally 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 80-mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks (see sections 4.4 and 5.1).

Hypercholesterolaemia
The patient should be placed on a standard cholesterol-lowering diet, and should continue on this diet during treatment with Zocor. The usual starting dose is 10-20 mg/day given as a single dose in the evening. Patients who require a large reduction in LDLC (more than 45 %) may be started at 20-40 mg/day given as a single dose in the evening. Adjustments of dosage, if required, should be made as specified above.

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

Concomitant therapy
Zocor is effective alone or in combination with bile acid sequestrants. Dosing should occur either> 2 hours before or> 4 hours after administration of a bile acid sequestrant.

In patients taking ciclosporin, danazol, gemfibrozil, other fibrates (except fenofibrate) concomitantly with Zocor, the dose of Zocor should not exceed 10 mg/day. In patients taking amiodarone orverapamil concomitantly with Zocor, the dose of Zocor should not exceed 20 mg/day. In patients taking diltiazem or amlodipine concomitantly with Zocor, the dose of Zocor should not exceed 40 mg/day. (See sections 4.4 and 4.5.)

Dosage in renal insufficiency
No modification of dosage should 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 dosage adjustment is necessary.

Use in children and adolescents (10 – 17 years of age)
For children and adolescents (boys Tanner Stage II and above and girls who are at least one year post-menarche, 10-17 years of age) with heterozygous familial hypercholesterolaemia, the recommended usual starting dose is 10 mg once a day in the evening. Children and adolescents should be placed on a standard cholesterol-lowering diet before simvastatin treatment initiation; this diet should be continued during simvastatin treatment.The recommended dosing range is 10-40 mg /day. Doses should be individualized according to the recommended goal of therapy as recommended by the paediatric treatment recommendations (see sections 4.4 and 5.1). Adjustments should be made at intervals of 4 weeks or more.

The experience in pre-pubertal children is limited. Zocor is not recommended for paediatric use.

4.3 Contraindications

• Hypersensitivity to simvastatin or to any of the excipients

• Active liver disease or unexplained persistent elevations of serum transaminases

• Pregnancy and lactation (see section 4.6)

• Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) (see section 4.5).

4.4 Special warnings and precautions for use

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 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 rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/ rhabdomyolysis is dose related. In a clinical trial database in which 41,413 patients were treated with Zocor with 24,747 (approximately 60 %) of whom were enrolled in studies with a median folllow-up of at least 4 years, the incidence of myopathy was approximately 0.03 %, 0.08 % and 0.61 % at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which patients with a history of myocardial infarction were treated with Zocor 80mg/day (mean follow-up by 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occured during the first year of treatment. The incidence of myopathy during each subsequent year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%. (See sections 4.8 and 5.1).

Creatine Kinase measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment
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.

Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:

• Elderly (age ≥ 65 years)

• Female Gender

• Renal impairment

• Uncontrolled hypothyroidism

• Personal or familial history of hereditary muscular disorders

• Previous history of muscular toxicity with a statin or fibrate

• Alcohol abuse.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with a different member of the class should only be initiated with caution. If CK levels are significantly elevated at baseline (> 5 x ULN), treatment should not be started.

Whilst on treatment
If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (> 5 x ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are < 5 x ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

A higher rate of myopathy has been observed in patients titrated to the 80 mg dose (see section 5.1). Periodic CK measurements are recommended as they may be useful to identify subclinical cases of myopathy. However, there is no

assurance that such monitoring will prevent myopathy.

Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)
The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone), as well as gemfibrozil, ciclosporin, and danazol (see section 4.2).

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of other fibrates or by concomitant use of amiodarone or verapamil with higher doses of simvastatin (see sections 4.2 and 4.5). The risk is increased when by concomitant use of diltiazem or amlodipine with simvastatin 80 mg (see sections 4.2 and 4.5). The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of fusidic acid with statins (see section 4.5).

Consequently, regarding CYP3A4 inhibitors, the use of simvastatin concomitantly with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated (see sections 4.3 and 4.5). If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Moreover, caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: ciclosporin, verapamil, diltiazem (see sections 4.2 and 4.5). Concomitant intake of grapefruit juice and simvastatin should be avoided.

The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with ciclosporin, danazol, gemfibrozil, or lipid-lowering doses (≥ 1 g/day) of niacin. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. The benefits of the combined use of simvastatin 10 mg daily with other fibrates (except fenofibrate),ciclosporin or danazol should be carefully weighed against the potential risks of these combinations. (See sections 4.2 and 4.5.)

Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.

The combined use of simvastatin at doses higher than 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

The combined use of simvastatin at doses higher than 40 mg daily with diltiazem or amlodipine should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of HMG-CoA reductase inhibitors and lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid), either of which can cause myopathy when given alone.

Physicians contemplating combined therapy with simvastatin and lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when the dose of either medicinal product is increased.

In an interim analysis of an ongoing clinical outcomes study, an independent safety monitoring committee identified a higher than expected incidence of myopathy in Chinese patients taking simvastatin 40 mg and nicotinic acid/laropiprant 2000 mg/40 mg. Therefore, caution should be used when treating Chinese patients with simvastatin (particularly doses of 40 mg or higher) co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin. Because the risk of myopathy with statins is dose-related, the use of simvastatin 80 mg with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin is not recommended in Chinese patients. It is unknown whether there is an increased risk of myopathy in other Asian patients treated with simvastatin

co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) or products containing niacin.

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, persistent increases (to> 3 x ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When simvastatin was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels.

It is recommended that liver function tests be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80-mg dose should receive an additional test prior to titration, 3 months after titration to the 80-mg dose, and periodically thereafter (e.g., semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 x ULN and are persistent, simvastatin should be discontinued.

The product should be used with caution in patients who consume substantial quantities of alcohol.

As with other lipid-lowering agents, moderate (< 3 x ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Interstitial lung disease

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

Use in children and adolescents (10-17 years of age **)**

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys Tanner Stage II and above and in girls who were at least one year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. (See sections 4.2, 4.8, and 5.1.) Adolescent females should be counselled on appropriate contraceptive methods while on simvastatin therapy (see sections 4.3 and 4.6). In patients aged < 18 years, efficacy and safety have not been studied for treatment periods> 48 weeks' duration and long-term effects on physical, intellectual, and sexual maturation are unknown. Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-pubertal children and pre-menarchal girls.

Excipient
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.

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 concomitant administration with fibrates. Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see below *Pharmacokinetic interactions* and sections 4.2 and 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. Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (see section 4.4).

Pharmacokinetic interactions

Prescribing recommendations for interacting agents are summarized 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 10 mg simvastatin daily
Ciclosporin Danazol	Do not exceed 10 mg simvastatin daily
Other fibrates (except fenofibrate)	
Amiodarone Verapamil	Do not exceed 20 mg simvastatin daily
Diltiazem Amlopidine	Do not exceed 40 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

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, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active betahydroxyacid 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, verapamil, diltiazem (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 sections 4.2 and 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 (see sections 4.2 and 4.4).

Gemfibrozil

Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway (see sections 4.2 and 4.4).

Amiodarone

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with higher doses of simvastatin (see section 4.4). In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Calcium Channel Blockers
• *Verapamil*

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of verapamil with simvastatin 40 mg or 80 mg (see section 4.4). In a pharmacokinetic study, concomitant administration with verapamil resulted in a 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Diltiazem

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg (see section 4.4). The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant diltiazem (see section 4.4). In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with diltiazem, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

• ***Amlodipine***

Patients on amlodipine treated concomitantly with simvastatin 80 mg have an increased risk of myopathy. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant amlodipine. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.
Niacin (nicotinic acid)

Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid). In a pharmacokinetic study, the co-administration of a single dose of nicotinic acid prolonged-release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin

and simvastatin acid and in the C_{max} of simvastatin acid plasma concentrations.

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 Normalized 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 Fertility, pregnancy and lactation

Pregnancy

Zocor is contraindicated 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 Zocor 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 or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with Zocor 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 should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Zocor should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See sections 4.3 and 5.3.)

Lactation

It is not known whether simvastatin or its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions, women taking Zocor should not breast-feed their infants (see section 4.3).

4.7 Effects on ability to drive and use machines

Zocor 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

The frequencies of the following adverse events, which have been reported during clinical studies and/or post-marketing use, are categorized based on an assessment of their incidence rates in large, long-term, placebo-controlled, clinical trials including HPS and 4S with 20,536 and 4,444 patients, respectively (see section 5.1). For HPS, only serious adverse events were recorded as well as myalgia, increases in serum transaminases and CK. For 4S, all the adverse events listed below were recorded.

If the incidence rates on simvastatin were less than or similar to that of placebo in these trials, and there were similar reasonably causally related spontaneous report events, these adverse events are categorized as “rare”.

In HPS (see section 5.1) involving 20,536 patients treated with 40 mg/day of Zocor (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with Zocor 40 mg and patients treated with placebo over the mean 5 years of the study. Discontinuation rates due to side effects were comparable (4.8 % in patients treated with Zocor 40 mg compared with 5.1 % in patients treated with placebo). The incidence of myopathy was < 0.1 % in patients treated with Zocor 40 mg. Elevated transaminases (> 3 x ULN confirmed by repeat test) occurred in 0.21 % (n = 21) of patients treated with Zocor 40 mg compared with 0.09 % (n = 9) of patients treated with placebo.

The frequencies of adverse events are ranked according to the following: Very common > 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1000, < 1/100), Rare (≥ 1/10,000, < 1/1000), Very Rare (< 1/10,000) not known (cannot be estimated from the available data).

Investigations:

Rare: increases in serum transaminases (alanine aminotransferase, asparate aminotransferase, y-glutamyl transpeptidase) (see section 4.4 Hepatic effects), elevated alkaline phosphatase; increase in serum CK levels (see section 4.4).

Blood and lymphatic system disorders:
Rare: anaemia

Nervous system disorders:
Rare: headache, paresthesia, dizziness, peripheral neuropathy
Very Rare: memory impairment

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

Skin and subcutaneous tissue disorders:
Rare: rash, pruritus, alopecia

Musculoskeletal, connective tissue and bone disorders:

Rare: myopathy, rhabdomyolysis (see section 4.4), myalgia, muscle cramps

* In a clinical trial, myopathy occurred commonly in patients treated with Zocor 80 mg/day compared to patients treated with 20 mg/day (1.0 % vs 0.02%, respectively).

General disorders and administration site conditions:
Rare: asthenia

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

Hepatobiliary disorders:

Rare: hepatitis/jaundice

Very rare: hepatic failure

Psychiatric disorders:

Very rare: insomnia

The following adverse events have been reported with some statins:

• sleep disturbances, including insomnia and nightmares

• sexual dysfunction

• depression

• exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

Children and adolescents (10-17 years of age)

In a 48-week study involving children and adolescents (boys Tanner Stage II and above and girls who were at least one year post-menarche) 10-17 years of age with heterozygous familial hypercholesterolaemia (n = 175), the safety and tolerability profile of the group treated with Zocor was generally similar to that of the group treated with placebo. The long-term effects on physical, intellectual, and sexual maturation are unknown. No sufficient data are currently available after one year of treatment. (See sections 4.2, 4.4, and 5.1.).

4.9 Overdose

To date, a few cases of overdosage have been reported; the maximum dose taken was 3.6 g. 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: HMG-CoA reductase inhibitor

ATC-Code: C10A A01

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active betahydroxyacid 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 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 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. In addition, Zocor 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.

<u>High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease</u>
In the Heart Protection Study (HPS), the effects of therapy with Zocor were assessed in 20,536 patients (age 40-80 years), with or without hyperlipidaemia, and with coronary heart disease, other occlusive arterial disease or diabetes mellitus. In this study, 10,269 patients were treated with Zocor 40 mg/day and 10,267 patients were treated with placebo for a mean duration of 5 years. At baseline, 6,793 patients (33 %) had LDLC levels below 116 mg/dL; 5,063 patients (25 %) had levels between 116 mg/dL and 135 mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

Treatment with Zocor 40 mg/day compared with placebo significantly reduced the risk of all cause mortality (1328 [12.9 %] for simvastatin-treated patients versus 1507 [14.7 %] for patients given placebo; $p = 0.0003$), due to an 18 % reduction in coronary death rate (587 [5.7 %] versus 707 [6.9 %]; $p = 0.0005$; absolute risk reduction of 1.2 %). The reduction in non-vascular deaths did not reach statistical significance. Zocor also decreased the risk of major coronary events (a composite endpoint comprised of non-fatal MI or CHD death) by 27 % ($p < 0.0001$). Zocor 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 % ($p < 0.0001$) and 16 % ($p = 0.006$), respectively. Zocor reduced the risk of stroke by 25 % ($p < 0.0001$), attributable to a 30 % reduction in ischemic stroke ($p < 0.0001$). In addition, within the subgroup of patients with diabetes, Zocor reduced the risk of developing macrovascular complications, including peripheral revascularization procedures (surgery or angioplasty), lower limb amputations, or leg ulcers by 21 % ($p = 0.0293$). The proportional reduction in event rate was similar in each subgroup of patients studied, including those without coronary disease but who had cerebrovascular or peripheral artery disease, men and women, those aged either under or over 70 years at entry into the study, presence or absence of hypertension, and notably those with LDL cholesterol below 3.0 mmol/l at inclusion.

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with Zocor on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomised, double-blind, placebo-controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet, standard care, and either Zocor 20-40 mg/day (n = 2,221) or placebo (n = 2,223) for a median duration of 5.4 years. Zocor reduced the risk of death by 30 % (absolute risk reduction of 3.3 %). The risk of CHD death was reduced by 42 % (absolute risk reduction of 3.5 %). Zocor also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent nonfatal MI) by 34 %.

Furthermore, Zocor significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischemic attacks) by 28 %. There was no statistically significant difference between groups in non-cardiovascular mortality.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) evaluated the effect of treatment with Zocor 80 mg versus 20 mg (median follow-up 6.7 yrs) on major vascular events (MVEs; defined as fatal CHD, non-fatal MI, coronary revascularization procedure, non-fatal or fatal stroke, or peripheral revascularization procedure) in 12,064 patients with a history of myocardial infarction. There was no significant difference in the incidence of MVEs between the 2 groups; Zocor 20 mg (n = 1553; 25.7 %) vs. Zocor 80 mg (n = 1477; 24.5 %); RR 0.94, 95 % CI: 0.88 to 1.01. The absolute difference in LDL-C between the two groups over the course of the study was 0.35 ± 0.01 mmol/L. The safety profiles were similar between the two treatment groups except that the incidence of myopathy was approximately 1.0 % for patients on Zocor 80 mg compared with 0.02 % for

patients on 20 mg. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1 %.

Primary Hypercholesterolaemia and Combined Hyperlipidaemia
In studies comparing the efficacy and safety of simvastatin 10, 20, 40 and 80 mg daily in patients with hypercholesterolemia, the mean reductions of LDL-C were 30, 38, 41 and 47 %, respectively.
In studies of patients with combined (mixed) hyperlipidaemia on simvastatin 40 mg and 80 mg, the median reductions in triglycerides were 28 and 33 % (placebo: 2 %), respectively, and mean increases in HDL-C were 13 and 16 % (placebo: 3 %), respectively.

Clinical Studies in Children and Adolescents (10-17 years of age)

In a double-blind, placebo-controlled study, 175 patients (99 boys Tanner Stage II and above and 76 girls who were at least one year post-menarche) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (heFH) were randomized to simvastatin or placebo for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level> 189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

Zocor significantly decreased plasma levels of LDL-C, TG, and Apo B. Results from the extension at 48 weeks were comparable to those observed in the base study. After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the Zocor 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

After 24 weeks of simvastatin treatment (with dosages increasing from 10, 20 and up to 40 mg daily at 8- week intervals), Zocor decreased the mean LDL-C by 36.8 % (placebo: 1.1 % increase from baseline), Apo B by 32.4 % (placebo: 0.5 %), and median TG levels by 7.9 % (placebo: 3.2 %) and increased mean HDL-C levels by 8.3 % (placebo: 3.6 %). The long-term benefits of Zocor on cardiovascular events in children with heFH are unknown.

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolaemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone, which is readily hydrolyzed in vivo to the corresponding betahydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

The pharmacokinetic properties have been evaluated in adults. Pharmacokinetic data in children and adolescents are not available.

Absorption

In man simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the betahydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption.

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

Distribution

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

Elimination

Simvastatin is a substrate of CYP3A4 (see sections 4.3 and 4.5). The major metabolites of simvastatin present in human plasma are the beta-hydroxyacid and four additional active metabolites. Following an oral dose of radioactive simvastatin to man, 13 % of the radioactivity was excreted in the urine and 60 % in the faeces within 96 hours. The amount recovered in the faeces represents absorbed medicinal product equivalents excreted in bile as well as unabsorbed medicinal product. Following an intravenous injection of the beta-hydroxyacid metabolite, its half-life averaged 1.9 hours. An average of only 0.3 % of the IV dose was excreted in urine as inhibitors.

5.3 Preclinical safety data

Based on conventional animal studies regarding pharmacodynamics, repeate dose toxicity, genotoxicity and carcinogenicity, there are no other risks for the patient 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

Tablet Core
Ascorbic acid
Butylated hydroxyanisole
Citric acid monohydrate
Lactose Monohydrate
Magnesium stearate
Microcrystalline cellulose
Pregelatinised maize starch

Tablet Coating
Hypromellose
Hyprolose
Talc
Titanium dioxide (E171)
Red Iron oxide (E172)
Yellow Iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country or origin.

6.4 Special precautions for storage

Do not store above 25ºC

6.5 Nature and contents of container

Cartons of 28 tablets. Each carton contains 2 blister strips of 14 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licensing Ltd.
Ballymurray
Co. Roscommon
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1447/24/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: July 4th 2008.

10 DATE OF REVISION OF THE TEXT

December 2010