Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Simvastatin 10mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg simvastatin.

Excipients:

Each film-coated tablet contains 69.5 mg lactose monohydrate.

Product also contains soya lecithin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Light-pink film-coated tablet, lenticular in shape, smooth and intact surface, spotless.

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 manifested 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 of cardiovascular complications.

Hypercholesterolaemia
The patient should be placed on a standard cholesterol-lowering diet and should continue on this diet during treatment with Simvastatin. The usual starting dose is 10-20 mg/day given as a single dose in the evening. Patients who require a large reduction in LDL-cholesterol (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 simvastatin 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. Simvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Cardiovascular prevention
The usual dose of Simvastatin is 20-40 mg/day given as a single dose in the evening in patients with 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
Simvastatin 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 cyclosporine, danazol, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses (≥ 1 g/day) of niacin concomitantly with Simvastatin, the dose of Simvastatin should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with Simvastatin, the dose of Simvastatin should not exceed 20 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 necessary, implemented cautiously.

Use in elderly
No dosage adjustment is necessary.

Use in children and adolescents

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; the maximum recommended dose is 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 of simvastatin in pre-pubertal children is limited.

Instruction for use
The tablets are not intended as breakable. If instructed by the doctor to break the tablet, than a knife should be used.

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).
- Simgal contains soya lecitin. If you are allergic to soya do not use this medicinal product.

4.4 Special warnings and precautions for use

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.

Myopathy/rhabdomyolysis
Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally cause myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) about ten times the upper limit of normal. Myopathy sometimes takes a 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 41,050 patients were treated with simvastatin, 24,747 (approximately 60%) of whom were enrolled in studies with a median follow−up of 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.

Creatine Kinase measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in 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 upper limit of normal), 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 > 70 years)
- Renal impairment
- Uncontrolled hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on fibrate or a statin, treatment with a different member of the class should be initiated with caution. If CK levels are significantly elevated at baseline (> 5 x upper limit of normal), 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 upper limit of normal), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are < 5 x upper limit of normal, 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.

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 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, fluconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), nefazodone), as well as gemfibrozil and cyclosporine and danazol (see section 4.2).

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of other fibrates, lipid-lowering doses (≥ 1 g/day) of niacin or by concomitant use with amiodarone or verapamil with higher doses of simvastatin (see sections 4.2 and 4.5). The risk is increased 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).

Consequuently, regarding CYP3A4 inhibitors, the use of simvastatin concomitantly with itraconazole, ketoconazole, fluconazole, posaconazole, HIV protease inhibitors (e.g. nelfinavir), erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated (see sections 4.3 and 4.5). If treatment with itraconazole, ketoconazole,fluconazole, posaconazole, 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: cyclosporine, 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 cyclosporine, danazol, gemfibrozil, or lipid-lowering doses (≥ 1 g/day) of niacin. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. The benefits of the combined use of simvastatin 10 mg daily with other fibrates (except fenofibrate), niacin, cyclosporine or danazol should be carefully weighed against the potential risks of these combinations (see sections 4.2 and 4.5).

Caution should be used when prescribing fenofibrate or at lipid-modifying doses (≥1 g/day) of niacin 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 overweigh the increased risk of myopathy (see sections 4.2 a 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, persistent increases (to > 3 x upper limit of normal) 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, a 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 upper limit of normal 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 upper limit of normal) 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.

Diabetes mellitus

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

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.

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

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 and niacin (nicotinic acid) (≥ 1 g/day). 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.

Pharmacokinetic interactions

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

Drug interactions associated with increased risk of myopathy/rhabdomyolysis.	
Interacting agents	Prescription recommendations
Potent CYP3A4 Inhibitors: Itraconazole Ketoconazole Posaconazole Fluconazole Erythromycin Clarithromycin	Contraindicated with simvastatin.

Telithromycin HIV protease inhibitors (*e.g.* nelfinavir) Nefazodone	
Gemfibrozil	Avoid but if necessary, do not exceed 10 mg simvastatin daily
Ciclosporin Danazol Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily
Amiodarone Verapamil	Do not exceed 20 mg simvastatin daily
Diltiazem Amlodipine	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.

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, fluconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), and nefazodone. Concomitant administration of intraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin cause an 11-fold increase in exposure to simvastatin acid.

Therefore, combination with itraconazole, ketoconazole, fluconazole, posaconazole, HIV protease inhibitors (e.g. nelfinavir), 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: cyclosporine, verapamil, diltiazem (see sections 4.2 and 4.4).

Cyclosporine
The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine 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 cyclosporine. Although the mechanism is not fully understood, cyclosporine increases the AUC of simvastatin acid presumably due, in part, to inhibition of CYP3A4.

Danazol
The risk of myopathy and rhabdomyolisis 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 glucuronidation pathway (see sections 4.2 and 4.4).

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.

Amiodarone and verapamil
The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see section 4.4). In an ongoing clinical trial, myopathy has been reported in 6 % of patients receiving simvastatin 80 mg and amiodarone.

An analysis of the available clinical trials showed an approximately 1 % incidence of myopathy in patients receiving simvastatin 40 mg or 80 mg and verapamil. 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 overweigh the increased risk of myopathy and rhabdomyolysis.

Diltiazem
An analysis of available clinical trials showed an approximately 1 % incidence of myopathy in patients receiving simvastatin 80 mg and diltiazem. 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 cause 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 overweigh the increased risk of myopathy and rhabdomyolysis.

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.

Colchicine
There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal insufficiency. Close clinical monitoring of such patients taking this combination is advised.

Rifampicin
Because rifampicin is a potent CYP 3A4 inducer, patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis) may experience loss of efficacy of simvastatin. In a pharmacokinetic study in normal volunteers, the area under the plasma concentration curve (AUC) for simvastatin acid was decreased by 93% with concomitant administration of rifampicin.

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 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.

Digoxin
Simvastatin may increase the plasma concentration of digoxin due to inhibition of P-glycoprotein.

Effect 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.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in males and females

See section Pregnancy.

Pregnancy
Simgal 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 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 simvastatin may reduce the foetal levels of mevalonate which is 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, Simgal should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Simgal must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

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 Simgal must not breast-feed their infants (see section 4.3).

Fertility
No information is available.

4.7 Effects on ability to drive and use machines

Simvastatin has no or negligible influence on the ability to drive or 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 the 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 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 simvastatin (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with simvastatin 40 mg and patient 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 simvastatin 40 mg compared with 5.1 % in patients treated with placebo). The incidence of myopathy was < 0.1 % in patients treated with simvastatin 40 mg. Elevated transaminases (> 3 x upper limit of normal confirmed by repeat test) occurred in 0.21 % (n = 21) of patients treated with simvastatin 40 mg compared with 0.09 % (n = 9) of patients treated with placebo.

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 simvastatin 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.).

The frequencies of adverse events are ranked according to the following: very common (> 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10 000, < 1/1000), very rare (< 1/10, 000) including isolated reports.

Blood and lymphatic system disorders:
Rare: anaemia

Nervous system disorders:
Uncommon: sleep disturbances including nightmares, depression, memory loss
Rare: headache, paresthesia, dizziness, peripheral neuropathy, peripheral polyneuropathy

Respiratory, thoracic and mediastinal disorders:
Exceptional cases of interstitial lung disease, especially with long term therapy.

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

Hepato-biliary disorders:
Rare: hepatitis/jaundice
Very rare: hepatic failure

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

Musculoskeletal, connective tissue and bone disorders:
Rare: myopathy, rhabdomyolysis with or without acute renal failure (see section 4.4), myalgia, muscle cramps, myositis, polymyositis

General disorders and administration site conditions:
Rare: asthenia, sexual dysfunction.

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

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

Class effects:
- Sleep disturbances, including nightmares
- Memory loss
- Sexual dysfunction
- Diabetes mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30 kg/m2, raised triglycerides, history of hypertension).

4.9 Overdose

To date, a few cases of overdosage have been reported; 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: C10AA01

After oral ingestion, simvastatin, which is inactive lactone, is hydrolyzed 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 rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-cholesterol 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 simvastatin may involve both reduction of VLDL-cholesterol concentration and induction of LDL receptor, leading to reduced production and increased catabolism of LDL-cholesterol. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases HDL-cholesterol and reduces plasma triglycerides. As a result of these changes the ratios of total-C to HDL-C and LDL-C to HDL-C are reduced.

High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease

In the Heart Protection Study (HPS), the effects of therapy with simvastatin 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 simvastatin 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 LDL-cholesterol below 116 mg/dl; 5,063 patients (25 %) had levels between 116 and 135 mg/dl; and 8,680 patients (42 %) had levels greater than 135 mg/dl.

Treatment with simvastatin 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 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. Simvastatin also decreased the risk of major coronary events (a composite endpoint comprised of non-fatal MI or CHD death) by 27 % ($p < 0.0001$). 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 % ($p < 0.0001$) and 16 % (p=0.006), respectively. Simvastatin 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, simvastatin 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 simvastatin 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 simvastatin 20-40 mg/day (n = 2,221) or placebo (n = 2 223) for a median duration of 5.4 years. Simvastatin 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%). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent non-fatal MI) by 34 %. Furthermore, simvastatin significantly reduced the risk of fatal plus non-fatal cerebrovascular events (stroke and transient ischemic attacks) by 28 %. There was no statistically significant difference between groups in non-cardiovascular mortality.

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-cholesterol 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-cholesterol 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.

Simvastatin 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: 64.0289.0 mg/dL) in the Simvastatin 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), Simvastatin 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 Simvastatin 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 beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; hydrolysis in human plasma is very slow.

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 beta-hydroxyacid 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 % 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 i.v. dose was excreted in urine as inhibitors.

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

5.3 Preclinical safety data

Based on conventional animal studies regarding pharmacodynamics, repeated dose toxicity, genotoxicity and cancerogenicity, there are no other risks for 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

Core:
Ascorbic acid
Butylhydroxyanisole
Citric acid monohydrate
Microcrystalline cellulose
Pregelatinised maize starch 1500
Magnesium stearate
Lactose monohydrate

Coating:
Opadry OY-B-34915 pink containing:
Polyvinyl alcohol
Titanium dioxide (E171)
Talc
Soya Lecithin
Xanthan gum (E415)
Iron oxide red (E172)
Iron oxide yellow (E172)
Indigo carmine lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25 °C in the original container in order to protect from light and moisture.

6.5 Nature and contents of container

Al/PVC/PVDC blister
Pack size: 28 tablets, 84 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Norton Waterford
T/A IVAX Pharmaceuticals Ireland
Unit 301
IDA Industrial Park
Cork Road
Waterford
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 436/43/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 14 April 2010

10 DATE OF REVISION OF THE TEXT

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