SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Simvastatin 10mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg of Simvastatin.

Also contains Lactose anhydrous 74.50 mg

For the full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

White, oblong, biconvex tablets, scored on one side, embossed with “10” on the scored side and with “SVT” on the opposite side.

OR

White oblong, biconvex tablets, scored on both sides, embossed with “SVT” and “10” on one side.

OR

White, oblong, biconvex, film-coated tablets, embossing “10”, split by breakline on one side, embossing “SVT” on 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

Simvastatin is given as a single 10mg dose in the evening.

Simvastatin treatment can be initiated simultaneously with diet, exercise and smoking cessation.
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 Simvastatin concomitantly with fibrates, other than gemfibrozil (see section 4.3) or fenofibrate, the dose of Simvastatin should not exceed 10 mg/day. In patients taking amiodarone, amlodipine, verapamil, or diltiazem, or products containing elbasvir or grazoprevir concomitantly with Simvastatin, the dose of Simvastatin should not exceed 20 mg/day. (See sections 4.4 and 4.5.)
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; 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.

Method of administration
For oral administration

4.3 Contraindications

- Hypersensitivity to simvastatin or any of the excipients;
- 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

Simvastatin 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 Simvastatin 10 mg Tablets.

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.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

1. General measures
All individuals starting therapy with Simvastatin must be advised of the risk of myopathy and told to immediately stop taking Simvastatin 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 longstanding 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 Simvastatin 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, 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.

Reduced function of transport proteins

Reduced function of hepatic OATP transport proteins can increase the systemic exposure of simvastatin and increase the risk of myopathy and rhabdomyolysis. Reduced function can occur as the result of inhibition by interacting medicines (eg ciclosporin) or in patients who are carriers of the SLCO1B1 c.521T>C genotype.

Patients carrying the SLCO1B1 gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin and increased risk of myopathy. The risk of high dose (80 mg) simvastatin related myopathy is about 1 % in general, without genetic testing. Based on the results of the SEARCH trial, homozygote C allele carriers (also called CC) treated with 80 mg have a 15% risk of myopathy within one year, while the risk in heterozygote C allele carriers (CT) is 1.5%. The corresponding risk is 0.3% in patients having the most common genotype (TT) (See section 5.2). Where available, genotyping for the presence of the C allele should be considered as part of the benefit-risk assessment prior to prescribing 80 mg simvastatin for individual patients and high doses avoided in those found to carry the CC genotype. However, absence of this gene upon genotyping does not exclude that myopathy can still occur.

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 Simvastatin without medical supervision. Active liver diseases or unexplained 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 Simvastatin 10 mg Tablets the drug should be discontinued immediately and medical advice should be sought.

Patients with rare hereditary problems of fructose or galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 dypsnoea, 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.

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>30kg/m2, 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.

Myopathy/Rhabdomyolysis
Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)
Patients taking other medicines labeled as having a moderate inhibitory effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy. When coadministering simvastatin with a moderate inhibitor of CYP3A4 (agents that increase AUC approximately 2-5 fold), a dose adjustment of simvastatin may be necessary. For certain moderate CYP3A4 inhibitors e.g. diltiazem, a maximum dose of 20mg simvastatin is recommended (see section 4.2).

Simvastatin is a substrate of the Breast Cancer Resistant Protein (BCRP) efflux transporter. Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of simvastatin should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with simvastatin has not been studied; however, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir (see section 4.5).

Patients with rare hereditary problems of galactose intolerance, total 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 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
Grapefruit juice	Avoid grapefruit juice when taking simvastatin
Fusidic acid	Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.
Amiodarone Amlodipine Verapamil Diltiazem Elbasvir Grazoprevir	Do not exceed 20 mg simvastatin daily

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).

Ticagrelor

Co-administration of ticagrelor with simvastatin increased simvastatin Cmax by 81% and AUC by 56% and increased simvastatin acid Cmax by 64% and AUC by 52% with some individual increases equal to 2- to 3-fold.
Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg daily could cause adverse reactions of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. Ticagrelor may have similar effect on lovastatin. The concomitant use of ticagrelor with doses of simvastatin or lovastatin greater than 40 mg is not recommended.

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 of 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 maybe 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.

Inhibitors of the Transport Protein OATP1B1
Simvastatin acid is a substrate of the transport protein OATP1B1. Concomitant administration of medicinal products that are inhibitors of the transport protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and an increased risk of myopathy (see sections 4.3 and 4.4).

Inhibitors of Breast Cancer Resistant Protein (BCRP)
Concomitant administration of medicinal products that are inhibitors of BCRP, including products containing elbasvir or grazoprevir, may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy (see sections 4.2 and 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Simvastatin 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 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 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, Simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Simvastatin 10 mg Tablets 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:

Blood and lymphatic system disorders:
Anaemia

Immune system disorders:
Very rare: anaphylaxis

Nervous system disorders:
Headache, paraesthesia, dizziness, peripheral neuropathy

Eye disorders:
Rare: Vision blurred, visual impairment

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

Hepato-biliary disorders:
Hepatitis/jaundice

Skin and subcutaneous tissue disorders:
Rash, pruritus, alopecia
Very rare: Lichenoid drug eruptions

Musculoskeletal, connective tissue and bone disorders:
Myopathy, rhabdomyolysis (see section 4.4), myalgia, muscle cramps
Very rare: muscle rupture
Not known: Immune-mediated necrotizing myopathy (see section 4.4)

Reproductive system and breast disorders:
Very rare: Gynecomastia

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).
The following adverse events have been reported with Simvastatin:

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

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.).

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system via the internet at Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: HMG-CoA reductase inhibitor
ATC-Code: C10A A01

After oral ingestion, simvastatin, which is an active 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 methylglutaryly CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin 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 'Simvastatin tablets' may involve both reduction of VLDL-chlolestrol (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 'Simvastatin tablets'. In addition, 'Simvastatin tablets' 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 Simvastatin tablets were assessed in 20,536 patients (age 40-48 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 tablets 40mg/day and 10,267 patients were treated with placebo for a mean duration of 5 years. At baseline, 6,793 patients (33 %) had LDL-C levels below 116 mg/dL; 5,063 patients (25 %) had levels between 116 mg/dL and 135mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

Treatment with Simvastatin tablets 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. 'Simvastatin tablets' 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 tablets 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 tablets 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 tablets 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 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 tablets 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 nonfatal MI) by 34 %. Furthermore, simvastatin 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.

Primary Hypercholesterolaemia and Combined Hyperlipidaemia

In studies comparing the efficacy and safety of simvastatin 10, 20, 40 and 80 mg daily in patients with hypercholesterolaemia, 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.

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.

Elimination

Simvastatin is taken up actively into the hepatocytes by the transporter OATP1B1.

Simvastatin is a substrate of the efflux transporter BCRP.

Special populations

Carriers of the SLCO1B1 gene c.521T>C allele have lower OATP1B1 activity. The mean exposure (AUC) of the main active metabolite, simvastatin acid is 120% in heterozygote carriers (CT) of the C allele and 221% in homozygote (CC) carriers relative to that of patients who have the most common genotype (TT). The C allele has a frequency of 18% in the European population. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of simvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4).

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

Lactose, anhydrous

Cellulose, microcrystalline

Maize starch, pregelatinised

Butylhydroxyanisole (E320)

Magnesium stearate

Talc

Hyprolose

Hypromellose

Titanium dioxide (E 171)

6.2 Incompatibilities

None

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package

6.5 Nature and contents of container

PVC/PE/PVDC/aluminium blisters- Each blister contains 14 tablets to give pack sizes of 28 tablets,

PVC/PE/PVDC/aluminium blisters in polyester/aluminium/PE sachets, - Each blister contains 14 tablets. 2 blisters will be enclosed in a sachet to give pack size of 28 tablets. This sachet will then be placed in an outer carton.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

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