Safeguarding public health

MHRA

Public Assessment Report

Simvastatin 10mg Tablets

PL 17745/0001

Medicines and Healthcare products Regulatory Agency

SIMVASTATIN 10MG TABLETS

PL 17745/0001

UKPAR

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SIMVASTATIN 10MG TABLETS

PL 17745/0001

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Wainwright Associates Limited a Marketing Authorisation (licence) for the medicinal product Simvastatin 10mg Tablets (PL 17745/0001). This is a prescription only medicine [POM] for treating high levels of blood cholesterol and preventing cardiovascular disease.

Simvastatin belongs to a class of medicines known as HMG-CoA reductase inhibitors and works by reducing the amount of cholesterol made in the body.

This is a simple abridged application that cross-refers to a previously granted licence for Simvastatin 10mg Tablets (PL 04012/0059).

No new or unexpected safety concerns arose from this simple application and it was therefore judged that the benefits of using Simvastatin 10mg Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

SIMVASTATIN 10MG TABLETS

PL 17745/0001

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Simvastatin 10mg Tablets (PL 17745/0001) to Wainwright Associates Limited on 30 June 2006. The product is a prescription only medicine [POM].

This application was submitted as a simple abridged application according to Article 10.1(a)i of Directive 2001/83/EC, cross-referring to Simvastatin 10mg Tablets (PL 04012/0059, approved in the UK on 16 January 2002).

The product contains simvastatin. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active beta-hydroxyacid form which has 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.

No new data were submitted for this simple application, nor were any necessary, as the data are identical to that of the previously granted cross-referenced product. As the cross-referenced product was granted prior to the introduction of current legislation, no public assessment report was generated for it.

Simvastatin 10mg Tablets is used in the treatment of hypercholesterolaemia and for the prevention of cardiovascular disease.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: **PL 17745/0001**
PROPRIETARY NAME: **Simvastatin 10mg Tablets**
ACTIVE(S): **Simvastatin**
COMPANY NAME: **Wainwright Associates Limited**
E.C. ARTICLE: **10.1(a)(i)**
LEGAL STATUS: **POM**

INTRODUCTION AND BACKGROUND

This is an "informed consent" application which piggy-backs to PL 04012/0059 (held by Hexal A/S).

EXPERT STATEMENT

Satisfactory statements have been provided.

MARKETING AUTHORISATION APPLICATION (MAA)

A letter stating that the applicant has access to all preclinical and clinical data supporting the application has been supplied. A declaration that the applicant is in possession of the quality documentation is also provided.

MANUFACTURER

Batch release for the formulation will be at:

- Hexal A/S (Denmark)
- Salutas Pharma GmbH (Germany)

A letter of consent from the reference product manufacturer indicating willingness to manufacture the final product on behalf of the applicant has been included.

STORAGE DETAILS

These are satisfactory.

TSE COMPLIANCE

Evidence that magnesium stearate is obtained from plant sources and that lactose monohydrate is derived from milk sourced from healthy animals under the same conditions as milk collected for human consumption has been provided.

PRODUCT PARTICULARS

Satisfactory.

CONCLUSION

A marketing authorisation may be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The data for this application are consistent with those previously assessed for the cross-referenced product and as such have been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

This application is identical to a previously granted application for Simvastatin 10mg Tablets.

No new or unexpected safety concerns arose from this application.

The SPC, PIL and labelling are satisfactory and consistent with those of the cross-referenced product.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-referenced product. Extensive clinical experience with the active ingredient simvastatin is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.

SIMVASTATIN 10MG TABLETS

PL 17745/0001

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application for Simvastatin 10mg Tablets on 9 February 2005.
2	The MHRA's assessment of the submitted data was completed on 15 March 2005.
3	Further information was requested from the company on 14 April 2005.
4	The applicant submitted its response to further information request in a letter dated 29 September 2005.
5	Further information was requested from the company on 23 November 2005.
6	The applicant submitted its response to further information request on 13 December 2005.
7	Further information was requested from the company on 3 March 2006.
8	The applicant responded to further information request on 16 March 2006.
9	Additional information was requested from the applicant on 14 June 2006.
10	The applicant responded to additional information request on 14 and 16 June 2006.
11	The MHRA completed its assessment of the application on 29 June 2006.
12	The application was determined on 30 June 2006.

SIMVASTATIN 10MG TABLETS

PL 17745/0001

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Simvastatin 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg simvastatin.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Light red, coated, oval, scored, convex tablet coded SIM 10 on one 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) are 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 disease prevention

Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, in patients 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 at high risk for cardiovascular complications.

Hypercholesterolaemia

The patient should be placed on a standard cholesterol-lowering diet, and 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-C (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 of simvastatin is 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 normally be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Cardiovascular disease prevention

The usual dose of simvastatin 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

If simvastatin is to be prescribed in combination with bile acid sequestrants, dosing or simvastatin 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) 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).

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/day), dosages above 10 mg/day should be implemented cautiously.

Elderly people

No dosage adjustment is necessary.

Children and adolescents (< 18 years)

Efficacy and safety of use in children have not been established. Therefore simvastatin is not recommended for paediatric use.

4.3 Contraindications

- Hypersensitivity to simvastatin or to any of the excipients.
- Active liver disease or unexplained persistent elevation 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 special 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.

The risk of myopathy/rhabdomyolysis is dose related. The incidence in clinical trials, in which patients were carefully monitored and some interacting medicinal products were excluded, has been approximately 0.03% at 20 mg, 0.08% at 40 mg and 0.4% at 80 mg.

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 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 and 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 myopathy 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 simvastatin or 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 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, lipid-lowering doses (≥ 1 g/day) of niacin, or by concomitant use of amiodarone or verapamil with higher doses of simvastatin (see sections 4.2 and 4.5). There is also a slight increase in risk when diltiazem is used with simvastatin 80 mg.

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, 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 or ciclosporin should be carefully weighed against the potential risks of these combinations (see sections 4.2 and section 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).

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.

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 medical 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

Effects of other medicinal products on simvastatin

Interactions involving Cytochrome P450 3A4

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of CYP450 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 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, 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 increases the AUC of simvastatin acid, presumably due, in part, to inhibition of CYP3A4.

Danazol

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

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 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 one ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

A meta-analysis of all 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 outweigh the increased risk of myopathy and rhabdomyolysis.

Diltiazem

A meta-analysis of all available clinical trials showed a 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 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.

Grapefruit juice

Grapefruit juice inhibits CYP 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.

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 the International Normalised Ratio (INR), was 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 a coumarin anticoagulant, 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.

Effects of simvastatin on the pharmacokinetics of other medicinal products

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

4.6 Pregnancy and lactation

Pregnancy

Simvastatin is contraindicated in 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, found 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 should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3).

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 simvastatin should not breast-feed their infants (see section 4.3).

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-authorisation use.

4.8 Undesirable effects

The frequencies of the following adverse events, which have been reported during clinical studies and/or post-marketing use, are categorised based on an assessment of their incidence rates in large, long-term, placebo-controlled, clinical trials including Heart Protection Study (HPS) and Scandinavian Simvastatin Survival Study (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, with increases in serum transaminases and CK. For 4S, all the adverse events listed below were recorded. If the incidence rates on simvastatin

were lower than or similar to that of placebo in these trials, and there were similar reasonably causally related spontaneous report events, these adverse events are categorised 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 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 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 ULN 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.

Body system	**Adverse Event (RARE = >1/10,000, <1/1,000)**
Blood and the lymphatic system disorders	Anaemia
Nervous system disorders	Headache Paresthesia Peripheral neuropathy Dizziness
Gastrointestinal disorders	Constipation Abdominal pain Flatulence Dyspepsia Diarrhoea Nausea Vomiting Pancreatitis
Hepato-biliary disorders	Jaundice Hepatitis
Skin and subcutaneous tissue disorders	Skin rash Pruritus Alopecia
Musculoskeletal, connective tissue and bone disorders	Myopathy Rhabdomyolysis (see section 4.4 Special warnings and special precautions). Myalgia Muscular cramps
General disorders and administration site conditions	Asthenia
Investigations	Increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase) (see section 4.4 Special warnings and special precautions for use). Elevated alkaline phosphatase Increase in serum CK levels (see section 4.4 Special warnings and special precautions).

An apparent hypersensitivity syndrome has been reported in rare instances. It has been associated with some of the following symptoms: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, elevation of ESR, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise

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 inhibitors

ATC-Code: C10A A01

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active beta-hydroxyacid form which has 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.

Simvastatin has been shown to reduce both normal and elevated low density lipoprotein cholesterol (LDL-C) concentrations. LDL (low density lipoprotein) is formed from very-low-density lipoprotein (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 (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. In addition, simvastatin moderately increases high density lipoprotein cholesterol (HDL-C) and reduces plasma triglycerides. 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 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-C 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 simvastatin 40 mg/day compared 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, and this was 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 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 revascularisation procedures (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) and peripheral and other non-coronary revascularisation 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 revascularisation 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 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 multicentre, 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 nonfatal MI) by 34%. Furthermore simvastatin significantly reduced the risk of fatal plus non-fatal cerebrovascular events (stroke and transient ischaemic 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 beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

Absorption

In man, simvastatin is well absorbed and undergoes extensive hepatic first-pass metabolism. The metabolism 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 metabolites 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 radiolabelled 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, repeat 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: Pregelatinised starch, lactose monohydrate, microcrystalline cellulose, butylated hydroxyanisole (E320), ascorbic acid (E300), citric acid monohydrate (E330) and magnesium stearate.

Film-coating: Hypromellose (E464), talc (E553b), titanium dioxide (E171), yellow ferric oxide (E172) and red ferric oxide(E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Blisters
Do not store above 30°C.
Store in original packaging. Keep blisters in outer carton.
Tablet container
Do not store above 30°C.
Store in the original container.

6.5 Nature and contents of container

Blister packs of PVC foil lidded with aluminium foil
Pack sizes: 10, 20, 28, 30, 40, 49, 50, 98 and 100 film-coated tablets.

High density polyethylene bottle with tamper evident screw cap closure
Pack sizes: 10, 20, 28, 30, 40, 50, 100 and 250 film-coated tablets.

Not all packs sizes or pack types may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Wainwright Associates Limited
Wessex House
Marlow Road
Bourne End
Buckinghamshire
SL8 5SP

8. MARKETING AUTHORISATION NUMBER

PL 17745/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/06/2006

10 DATE OF REVISION OF THE TEXT

30/06/2006

Patient Information Leaflet

SIMVASTATIN 10MG TABLETS

PL 17745/0001

Patient Information Leaflet

SIMVASTATIN 10mg TABLETS

This is important information which you should know before taking Simvastatin Tablets. If after reading this leaflet, you have any questions, please discuss these with your doctor or pharmacist.

Remember:
This medicine is for you. Only a doctor can prescribe it for you. Never give this medicine to anyone else. It may harm them even if they have the same symptoms as you.

What is your medicine made of?
One film-coated tablet contains 10mg of the active ingredient simvastatin. The other ingredients are pregelatinised starch, lactose, microcrystalline cellulose, butylhydroxyanisole (E320), ascorbic acid (E300), citric acid (E330), magnesium stearate, hypromellose (E464), talc (E553b) and titanium dioxide (E171), red ferric oxide (E172) and yellow ferric oxide (E172).

Simvastatin 10mg Tablets are available in packs of 28 tablets.

Who supplies Simvastatin Tablets?
(Marketing Authorisation Holder)
Wainwright Associates Limited, Wessex House, Marlow Road, Bourne End, Bucks, SL8 5SP

(Manufacture)
Salutas Pharma GmbH, Otto-von-Guericke-Allee 1
39179 Barleben, Germany

Distributor:
Tillomed Laboratories Ltd, 3 Howard Road, Eaton Socon, St Neots, Cambridgeshire, PE19 3ET, UK.

What is your medicine used for?
Simvastatin is a cholesterol-lowering drug. It belongs to a class of medicines known as HMG-CoA reductase inhibitors. Cholesterol is vital to the normal functioning of the body. It works by reducing the amount of cholesterol your body makes. High cholesterol in your blood may be caused by many factors, including diet high in saturated fatty acids, certain existing diseases, hereditary disposition, high blood sugar (diabetes) and lack of exercise. Normally you will be treated with a combination of a low cholesterol diet and Simvastatin Tablets, thereby controlling the intake of cholesterol and the amount of cholesterol that the liver makes.

Simvastatin Tablets are used for treatment of high cholesterol levels in your blood. Cholesterol can cause heart disease by clogging the blood vessels that carry oxygen and nutrients. This clogging, or hardening of the arteries, is called atherosclerosis. Atherosclerosis can cause chest pain (angina pectoris) and heart attack. If you have angina or coronary heart disease, your doctor may have prescribed Simvastatin Tablets to help keep your arteries clear, even if your cholesterol levels are normal in order to lessen the risk of a further heart attack and to reduce your risk of needing a surgical procedure to increase the blood flow to your heart. Simvastatin Tablets also slow the progression of atherosclerosis and may reduce the development of new atherosclerosis.

Before taking the medicine
You should not take Simvastatin Tablets if you:
- are allergic to any of the ingredients
- have impaired liver (hepatic) function
- have a muscle disease called myopathy
- are pregnant or planning to become pregnant; if you are a woman of child-bearing age you must take adequate contraceptive precautions
- are breast-feeding
- take the antibiotics erythromycin, clarithromycin or telithromycin
- take the antidepressant nefazodone
- take antifungal medicine by mouth containing itraconazole or ketoconazole
- take HIV-protease inhibitors
- have a rare inherited disease called porphyria

Simvastatin Tablets must not be used in children.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

If any of the above apply, you should seek advice from your doctor.

Precautions and cautions with Simvastatin Tablets
Take special care if you:
- experience any unexplained muscle aches or pains
- have severe renal (kidney) impairment
- have liver problems or if you consume large quantities of alcohol

If any of the above apply to you inform your doctor as it may be necessary to reduce the dose you are taking.

Avoid drinking grapefruit juice as grapefruit juice can influence the effect of Simvastatin Tablets.

If you are pregnant, do not take Simvastatin Tablets. If you become pregnant during treatment with simvastatin you should stop taking the medicine and consult your doctor.

To check that this medication is suitable for you, your doctor may need to take blood samples prior to and/or during your treatment with Simvastatin Tablets.

Do not breast-feed whilst taking simvastatin.

Can you take other medicines?
You should not take other medicines while you are taking Simvastatin Tablets, including those bought without a prescription, unless you have told your doctor.

Certain other medicines may influence the effect of simvastatin and their effect may also be influenced by simvastatin. Some of the medicines in question are listed below:
- medicines for a heart condition (e.g. amiodarone, verapamil or diltiazem)
- medicines for thinning the blood (e.g. warfarin)
- cholesterol-lowering medicines such as fibrates (e.g. bezafibrates, fenofibrate, gemfibrozil) and large doses of niacin (nicotinic acid)
- immunosuppresant medicines (e.g. ciclosporin)

- antifungal medicine taken by mouth containing itraconazole or ketoconazole
- HIV-protease inhibitors
- antibiotics called erythromycin, clarithromycin or telithromycin
- medicines against depression containing nefazodone
- Danazol, a steroid used to treat endometriosis and breast cysts.

Let your doctor know before taking Simvastatin Tablets if you are or think you are taking any of the above medicines.

Can you take alcohol?
Alcohol can affect the action of simvastatin, check with your doctor whether drinking is advisable.

Is it possible to drive while taking Simvastatin?
Simvastatin does not usually affect your ability to drive. Do not drive if you feel light-headed, dizzy or tired. Check with your doctor if you have these symptoms.

How to Take your medicine
Your doctor will decide the dose you should take depending upon your condition.

Adults and elderly: The usual starting dose is 10mg daily for high cholesterol levels and 20mg daily for coronary heart disease, given as a single dose in the evening. Your doctor may adjust your dose to a maximum of 40mg daily, and in exceptional cases 80mg daily. given as a single dose in the evening.

Your doctor may prescribe lower doses, particularly if you take other medicine or if you have severe kidney problems. Your doctor may need to change your dose in order to obtain the best effect. Do not take more or fewer tablets than your doctor has prescribed and keep taking your tablets for as long as your doctor has told you to. Do not stop taking simvastatin without consulting your doctor.

The tablets should be swallowed with a glass of water.

Children: The use of Simvastatin Tablets in children is not recommended.

Do not take more than the dose prescribed by your doctor.

How long should the tablets be taken?
You should continue to take Simvastatin Tablets for as long as your doctor recommends. If you need to stop this medicine, you should discuss it with your doctor.

What if too many tablets are taken or some are accidentally swallowed by a child?
You should contact your doctor immediately or go to the nearest casualty department. Remember to take the pack and any remaining tablets with you.

What if you miss a dose?
Do not worry if you miss a dose. Just carry on taking your normal dose when the next one is due. Do not take a double dose to make up for the one missed.

Can your medicine upset you?
Medicines can upset people and cause unwanted side effects in a few. If you experience any of the following you should contact your doctor immediately:

- muscle cramps
- muscle diseases presenting themselves as pains and aches,
- pins and needles
- constipation
- stomach pain
- wind
- nausea
- indigestion
- diarrhoea
- weakness
- headache
- skin rash
- itching
- eczema
- disturbance of liver function
- vomiting
- anaemia
- loss of hair
- jaundice
- hepatitis
- inflammation of the pancreas
- dizziness

On rare occasions, simvastatin with a wide variety of symptoms based on allergic type reactions have been reported. These symptoms include urticaria, swelling of the face, lupus-like symptoms (an immunosystem disease), muscle and joint pains, severe muscle and blood vessel inflammation, various disorders of blood cells (that may result in anaemia, infection or blood clotting problems), photosensitivity (reaction following exposure to sun or artificial UV light), fever, flushing or difficulty in breathing.

If you experience any unexplained muscle pain, tenderness or weakness you should report this to your doctor immediately, as this can be serious in rare cases.

If you experience any of these, or any other unusual symptoms, you should inform your doctor at once.

Looking after your medicine.

Keep your tablets out of the reach and sight of children.

Do not store Simvastatin Tablets above 30°C. Store in the original packaging. Keep blisters in outer cartons.

Do not use the tablets after the expiry date printed on the carton.

If your doctor decides to end your treatment, return any unused Simvastatin Tablets to your pharmacist.

A reminder.
Remember this medicine is for you. Never give it to anybody else even if they have the same symptoms as yours.

This leaflet does not contain the complete information about Simvastatin Tablets. If you have any questions or are unsure about anything ask your doctor or pharmacist who has access to additional information.

This information applies only to Simvastatin Tablets.

This leaflet was issued in November 2005.

Product Licence Numbers:

Simvastatin 10mg Tablets: PL 17745/0001

Labelling

SIMVASTATIN 10MG TABLETS

PL 17745/0001

Carton

SIMVASTATIN 10MG TABLETS

PL 17745/0001

Tub label

SIMVASTATIN 10MG TABLETS

PL 17745/0001

Blister label