

**SIMVASTATIN 10MG TABLETS (PL 20092/0012)**  
**SIMVASTATIN 20MG TABLETS (PL 20092/0013)**  
**SIMVASTATIN 40MG TABLETS (PL 20092/0014)**  
**SIMVASTATIN 80MG TABLETS (PL 20092/0015)**

**UKPAR**

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**SIMVASTATIN 10MG TABLETS (PL 20092/0012)**

**SIMVASTATIN 20MG TABLETS (PL 20092/0013)**

**SIMVASTATIN 40MG TABLETS (PL 20092/0014)**

**SIMVASTATIN 80MG TABLETS (PL 20092/0015)**

## **LAY SUMMARY**

The MHRA granted Lupin Europe Limited licences for the medicinal products Simvastatin 10mg, 20mg, 40mg and 80mg Tablets (PL 20092/0012-5) on 14<sup>th</sup> December 2007. These are prescription-only medicines (POM) that reduce the amount of cholesterol and fatty substances called triglycerides in the blood.

Simvastatin 10mg, 20mg 40mg and 80mg Tablets contain the active ingredient simvastatin, which belongs to a group of medicines known as “statins”.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Simvastatin 10mg, 20mg 40mg and 80mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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**SCIENTIFIC DISCUSSION**

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## INTRODUCTION

Based on the review of the data on quality, safety and efficacy MHRA granted marketing authorisations for the medicinal products Simvastatin 10mg, 20mg 40mg and 80mg Tablets to Lupin (Europe) Limited (PL 20092/0012-5) on 14<sup>th</sup> December 2007. The products are prescription-only medicines.

The applications were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the reference products Zocor 10mg, 20mg 40mg and 80mg Tablets (PL 00025/0241-3 and PL 00025/0366), which have been authorised to Merck, Sharp and Dohme.

The products contain the active ingredient simvastatin and are indicated for the treatment of hypercholesterolaemia and the reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus.

Simvastatin is derived synthetically from a fermentation product of *Aspergillus terreus*. It is a lipid-lowering agent that reduces concentrations of total cholesterol, low-density lipoprotein, very low-density lipoprotein and plasma triglycerides, while elevating concentrations of high-density lipoprotein. It is an inactive lactone that, after oral ingestion, is hydrolysed to the corresponding  $\beta$ -hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that catalyses the conversion of HMG-CoA to mevalonate – an early, rate-limiting step in the biosynthesis of cholesterol.

## PHARMACEUTICAL ASSESSMENT

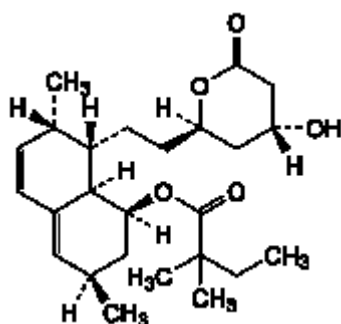
### DRUG SUBSTANCE

INN: Simvastatin

Chemical Name: (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8- $\{2-[(2R,4R)$ -tetra-hydro-4-hydroxy-6-oxo-2H-pyran-2-yl]-ethyl}-1-naphthyl-2,2-dimethylbutyrate

Molecular Formula:  $C_{25}H_{38}O_5$

Chemical Structure:



Molecular Weight: 418.6

Appearance: White to off-white powder

Properties: Simvastatin is a white or almost crystalline white powder. It is soluble in water, very soluble in methylene chloride, free soluble in alcohol.

Simvastatin is the subject of a Drug master file and letter of access has been provided.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance simvastatin.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Simvastatin is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. The data support a retest period of 2 years with storage condition "Protect from light".

## **DRUG PRODUCT**

### **Other Ingredients**

Other ingredients consist of pharmaceutical excipients lactose monohydrate, cellulose microcrystalline, starch pregelatinised, citric acid monohydrate, ascorbic acid, butyl hydroxyl anisole, magnesium stearate, hydroxypropyl cellulose, hypromellose 6cp, titanium dioxide, talc, Iron oxide red, and Iron oxide yellow

All excipients comply with European Pharmacopoeia monographs with the exception of hydroxypropyl cellulose, hypromellose 6cp, titanium dioxide, talc, Iron oxide red, and Iron oxide yellow which are in-house specifications.

Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph.

Lactose monohydrate is the only ingredient that comes from an animal source. The lactose used to produce lactose monohydrate is sourced from healthy animals under the same conditions as milk for human consumption.

The origin of magnesium stearate is vegetable and a declaration from the manufacturer is provided.

### **Pharmaceutical development**

The objective of the pharmaceutical development programme was to produce products with 10mg, 20mg 40mg and 80mg simvastatin that can be considered as generic equivalents to the originator products Zocor 10mg, 20mg 40mg and 80mg Tablets.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative *in vitro* dissolution profiles have been generated for the proposed and reference products with satisfactory results. Comparative impurity studies have also been undertaken.

### **Manufacturing Process**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results are satisfactory.

**Finished Product Specification**

The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container-Closure System**

Product is packaged in opaque blisters composed of aluminium and PVC/PVDC. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

**Stability of the product**

Stability studies were performed on pilot-scale batches of all strengths of finished product and all packaging types, in accordance with current guidelines. All results from stability studies on pilot batches were within specified limits. These data support a shelf-life of 2 years, with storage condition 'Do not store above 25°C'

**Bioequivalence/bioavailability**

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

***SPC, PIL, Labels***

The SPC, PIL and Labels are pharmaceutically acceptable.

**CONCLUSION**

It is recommended that Marketing Authorisations are granted for these applications.

The proposed products are considered to be a generic medicinal product to the reference product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

## **PRECLINICAL ASSESSMENT**

These applications for generic products claims to be a generic medicinal product of Zocor 10mg, 20mg, 40mg and 80mg Tablets (Merck, Sharp and Dohme).

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



## CLINICAL ASSESSMENT

### 1. INTRODUCTION AND BACKGROUND

These are standard abridged national applications for Simvastatin 10mg, 20mg, 40mg and 80mg Tablets submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applications cross-refer to Zocor 10mg, 20mg, 40mg and 80mg Tablets (Merck, Sharp and Dohme), which have been authorised in the EU for more than 10 years.

### 2. 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).

The indications proposed are consistent with those for the originator products and are, therefore, satisfactory.

### 3. DOSE & DOSE SCHEDULE

The dosage range is 5-80 mg/day given orally as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.

#### 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-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 (reference product), the recommended dosage is Simvastatin 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20mg, 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 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

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 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.)

#### Dosage in renal insufficiency

No modification of dosage should be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance < 30 ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

#### Use in the elderly

No dosage adjustment is necessary.

#### Use in children and adolescents

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

The dose and dose schedule proposed are consistent with those for the originator products and are, therefore, satisfactory.

## **4. CLINICAL PHARMACOLOGY**

With the exception of the bioequivalence study comparing the proposed product to Zocor 40mg Tablets, no formal data are provided and none are required for these applications.

### **Bioequivalence**

In support of the application, the applicant has submitted a bioequivalence study comparing the test product Simvastatin 40mg tablets with the reference product Zocor® 40mg tablets. Both are Immediate Release formulations.

The study is a conventional open, randomised, two way crossover design. It compared a single 40mg dose of the test product simvastatin 40mg tablets with a single 40mg dose of the reference product Zocor® 40mg tablets, marketed by Merck, Sharp & Dhome-Chibret, France.

An adequate statistical plan is provided and the planned statistical methods are conventional. Log-transformed data for AUC<sub>t</sub>, AUC<sub>inf</sub> and C<sub>max</sub> were analysed by ANOVA. T<sub>max</sub> is defined as the first time point with this value. This is acceptable.

Of the 24 subjects randomised, 21 subjects completed the study. The results are summarised in the table below.

### RESULTS FOR MAIN PHARMACOKINETIC PARAMETERS

<b>Parent drug -Simvastatin</b>		
Treatment Geometric Means (SD)*		
	<b>Test</b>	<b>Reference</b>
<b>C<sub>max</sub> (ng/mL)</b>	6.546 ± 5.098	6.802 ± 7.274
<b>AUC<sub>t</sub> (ng.h/mL)</b>	30.509 ± 28.891	29.659 ± 24.848
<b>AUC<sub>∞</sub> (ng.h/mL)</b>	36.402 ± 43.612	34.064 ± 25.901
<b>T<sub>max</sub> (h)*</b>	1.61 ± 0.91	1.73 ± 1.57
<b>T<sub>1/2</sub></b>	4.59 ± 3.54	4.12 ± 4.08
Bioequivalence results for log-transformed test/reference ratios. Point estimate (90% Confidence Interval)		
<b>AUC<sub>t</sub></b>	102.70% (93.25% - 113.12%)	
<b>AUC<sub>inf</sub></b>	106.55% (93.92% - 120.87%)	
<b>C<sub>max</sub></b>	96.54% (80.54% - 115.84%)	

<b>Active metabolite – Simvastatin hydroxyacid</b>		
Treatment Geometric Means (SD)*		
	<b>Test</b>	<b>Reference</b>
<b>C<sub>max</sub> (ng/mL)</b>	4.062 ± 3.722	4.242 ± 4.109
<b>AUC<sub>t</sub> (ng.h/mL)</b>	34.444 ± 28.754	34.001 ± 32.205
<b>AUC<sub>∞</sub> (ng.h/mL)</b>	39.686 ± 31.041	38.653 ± 33.792
<b>T<sub>max</sub> (h)*</b>	4.94 ± 1.75	6.05 ± 1.98
<b>T<sub>1/2</sub></b>	4.65 ± 2.72	3.97 ± 2.21
Bioequivalence results for log-transformed test/reference ratios. Point estimate (90% Confidence Interval)		
<b>AUC<sub>t</sub></b>	100.98% (88.73% - 114.93%)	
<b>AUC<sub>inf</sub></b>	102.28% (90.38% - 115.75%)	
<b>C<sub>max</sub></b>	95.38% (81.16 – 112.08%)	

\* SD is for arithmetic means

AUC<sub>0-t</sub> / AUC<sub>∞</sub> is > 0.8, confirming adequate sampling duration.

The 90% confidence intervals for test/reference lie within the acceptance criteria specified by the medical assessor for this active substance and with those pre-specified in the study protocol.

The test/reference 90% confidence interval for AUC and C<sub>max</sub> lies within the acceptance range specified for this active substance as well as for the metabolite.

### ASSESSOR'S CONCLUSIONS

Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria and can be approved.

The multiple dose waiver criteria are met and hence this study is accepted as demonstrating bioequivalence for the other product strengths.

#### **5. EFFICACY**

No new data on the efficacy of simvastatin are submitted and none are required for this type of application.

#### **6. SAFETY**

No new data on the safety of simvastatin are submitted and none are required for this type of application.

#### **7. EXPERT REPORTS**

A clinical expert report is provided, written by an appropriately qualified Doctor. It includes a suitable review of the bioequivalence study.

#### **8. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

The SPCs are consistent with the approved SPCs for the originator products Zocor 10mg, 20mg 40mg and 80mg Tablets and are satisfactory.

#### **9. PATIENT INFORMATION LEAFLET (PIL)**

The PIL has been provided and is consistent the SPC.

#### **10. LABELLING**

Labelling has been provided and these are satisfactory.

#### **11. APPLICATION FORM (MAA)**

The MAA form is satisfactory.

#### **12. DISCUSSION**

Bioequivalence has been satisfactorily demonstrated for the 40mg product in accordance with CPMP criteria. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 40mg strength can be extrapolated to the other strength tablets.

The SPC, PIL and Labelling are consistent with those approved in the UK for the originator product Zocor 10mg, 20mg 40mg and 80mg Tablets and are satisfactory.

#### **13. MEDICAL CONCLUSION**

Marketing authorisations may be granted for these products.

## OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

### QUALITY

The important quality characteristics of Simvastatin 10mg, 20mg 40mg and 80mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### PRECLINICAL

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

### EFFICACY

Bioequivalence has been demonstrated between the applicant's Simvastatin 40mg Tablets and Zocor 40mg Tablets (Merck, Sharp and Dohme). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 40mg strength can be extrapolated to the other strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Zocor Tablets.

### RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with simvastatin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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**STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation applications on 8 <sup>th</sup> November 2005
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 17 <sup>th</sup> January 2006
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 6 <sup>th</sup> April 2006 and 28 <sup>th</sup> August 2007
4	The applicant responded to the MHRA's requests, providing further information on the quality dossiers on 20 <sup>th</sup> March 2007 and 22 <sup>nd</sup> October 2007
5	The applications were determined on 14 <sup>th</sup> December 2007

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**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>

**SUMMARY OF PRODUCT CHARACTERISTICS**

- 1 NAME OF THE MEDICINAL PRODUCT**  
Simvastatin 10 mg Tablets
- 2 QUALITATIVE AND QUANTITATIVE COMPOSITION**  
Each tablet contains 10 mg of simvastatin.  
Excipients: Lactose anhydrous  
For full list of excipients, see section 6.1.
- 3 PHARMACEUTICAL FORM**  
Simvastatin 10 mg tablets, are peach coloured, oval shaped, biconvex, Tablets debossed with '10' on one side and plain on the other side, containing  
Simvastatin 10 mg.
- 4 CLINICAL PARTICULARS**
- 4.1 Therapeutic indications**  
*Hypercholesterolaemia*  
Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.  
Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.  
*Cardiovascular prevention*  
Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy (see section 5.1).
- 4.2 Posology and method of administration**  
The dosage range is 5-80 mg/day given orally as a single dose in the evening.  
Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.  
*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-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 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 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***

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 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.)

#### ***Dosage in renal insufficiency***

No modification of dosage should be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance < 30 ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

#### ***Use in the elderly***

No dosage adjustment is necessary.

#### ***Use in children and adolescents***

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 elevations of serum transaminases.

Pregnancy and lactation (see section 4.6)

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

### **4.4 Special warnings and precautions for use**

#### ***Myopathy/Rhabdomyolysis***

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase

(CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. 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 ( $> 5 \times$  ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

#### ***Before the treatment***

All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

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

- Elderly (age  $> 70$  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 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 ( $> 5 \times$  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 ( $> 5 \times$  ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are  $< 5 \times$  ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued. If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with

close monitoring. 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 and ciclosporin (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, 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 or ciclosporin should be carefully weighed against the potential risks of these combinations. (See sections 4.2 and 4.5.) Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.

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

#### ***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.

Hereditary disorders:

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

Prescribing 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).

<b>Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis</b>	
<b>Interacting agents</b>	<b>Prescribing recommendations</b>
Potent CYP3A4 inhibitors: Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone	<b>Contraindicated with simvastatin</b>

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
Amiodarone Verapamil	Do not exceed 20 mg simvastatin daily
Diltiazem	Do not exceed 40 mg simvastatin daily
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Effects of other medicinal products on simvastatin

#### ***Interactions involving CYP3A4***

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, 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.

#### ***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 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 outweigh the increased risk of myopathy and rhabdomyolysis.

#### ***Diltiazem***

An analysis of the 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.

#### ***Danazol***

Danazol, a synthetic steroid used to treat endometriosis and breast cysts in women. The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with higher doses of simvastatin (see sections 4.2 and 4.4).

#### ***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.

#### ***Oral anticoagulants***

In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. Very rare cases of elevated INR have been reported. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the

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

***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.

#### **4.6 Pregnancy and lactation**

***Pregnancy:*** Simvastatin 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 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-marketing experiences.

#### **4.8 Undesirable effects**

The frequencies of the following adverse events, which have been reported during

clinical studies and/or post-marketing use, are categorized based on an assessment of their incidence rates in large, long-term, placebo-controlled, clinical trials including HPS and 4S with 20,536 and 4,444 patients, respectively (see section 5.1). For HPS, only serious adverse events were recorded as well as myalgia, increases in serum transaminases and CK. For 4S, all the adverse events listed below were recorded. If the incidence rates on simvastatin were less than or similar to that of placebo in these trials, and there were similar reasonably causally related spontaneous report events, these adverse events are categorized as “rare”.

In HPS (see section 5.1) involving 20,536 patients treated with 40 mg/day of 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. 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:***

*Rare:* headache, paresthesia, dizziness, peripheral neuropathy

***Gastrointestinal disorders:***

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

***Hepato-biliary disorders:***

*Rare:* hepatitis/jaundice

***Skin and subcutaneous tissue disorders:***

*Rare:* rash, pruritus, alopecia

***Musculoskeletal, connective tissue and bone disorders:***

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

***General disorders and administration site conditions:***

*Rare:* asthenia

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



dyspnoea and malaise.

**Investigations:**

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

**4.9 Overdose**

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

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: HMG-CoA reductase inhibitor

**ATC-Code: C10A A01**

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active beta-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy – 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

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 may involve both reduction of VLDLcholesterol (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 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.

**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-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 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 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 noncoronary 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 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 hypercholesterolemia, the mean reductions of LDL-C were 30, 38, 41 and 47 %, respectively. In studies of patients with combined (mixed) hyperlipidaemia on simvastatin 40 mg and 80 mg, the median reductions in triglycerides were 28 and 33 % (placebo: 2 %), respectively, and mean increases in

HDL-C were 13 and 16 % (placebo: 3 %), respectively.

## 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; the rate of 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 % 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, repeated 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

Lactose Monohydrate

Cellulose, Microcrystalline

Starch, Pregelatinized  
Citric Acid Monohydrate  
Ascorbic acid  
Butyl hydroxy anisole  
Magnesium Stearate  
Hydroxypropyl Cellulose  
HPMC 2910/Hypromellose 6cP  
Titanium Dioxide  
Talc  
Iron Oxide Red  
Iron Oxide Yellow

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years.

**6.4 Special precautions for storage**

Do not store above 25°C

**6.5 Nature and contents of container**

PVC/ PE/ PVDC/ Aluminium blisters in a cardboard carton. Packs of 28 tablets.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Lupin (Europe) Limited  
Victoria Court, Bexton Road  
Knutsford  
Cheshire WA 16 0PF  
United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20092/0012

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

14/12/2007

**10 DATE OF REVISION OF THE TEXT**

14/12/2007

**SUMMARY OF PRODUCT CHARACTERISTICS****1 NAME OF THE MEDICINAL PRODUCT**

Simvastatin 20 mg Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 20 mg of simvastatin.

Excipients: Lactose anhydrous

For full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Simvastatin 20 mg tablets, are tan coloured, oval shaped, biconvex, tablets debossed with '20' on one side and breakline on the other side, containing Simvastatin 20 mg.

**4 CLINICAL PARTICULARS****4.1 Therapeutic indications*****Hypercholesterolaemia***

Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

***Cardiovascular prevention***

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

**4.2 Posology and method of administration**

The dosage range is 5-80 mg/day given orally as a single dose in the evening.

Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.

***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-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 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 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***

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 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.)

#### ***Dosage in renal insufficiency***

No modification of dosage should be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance < 30 ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

#### ***Use in the elderly***

No dosage adjustment is necessary.

#### ***Use in children and adolescents***

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 elevations of serum transaminases.

Pregnancy and lactation (see section 4.6)

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

### **4.4 Special warnings and precautions for use**

#### ***Myopathy/Rhabdomyolysis***

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes

myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. 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 ( $> 5 \times$  ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

#### ***Before the treatment***

All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

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

a treatment in the following situations:

- Elderly (age  $> 70$  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 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 ( $> 5 \times$  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 ( $> 5 \times$  ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are  $< 5 \times$  ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued. If symptoms

resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring. 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 and ciclosporin (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, 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 or ciclosporin should be carefully weighed against the potential risks of these combinations. (See sections 4.2 and 4.5.)

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

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

#### ***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.

**Hereditary disorders:**

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**

Prescribing 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).

<b>Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis</b>	
<b>Interacting agents</b>	<b>Prescribing recommendations</b>
Potent CYP3A4 inhibitors:	

Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone	<b>Contraindicated with simvastatin</b>
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
Amiodarone Verapamil	Do not exceed 20 mg simvastatin daily
Diltiazem	Do not exceed 40 mg simvastatin daily
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Effects of other medicinal products on simvastatin

#### ***Interactions involving CYP3A4***

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, 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.

#### ***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 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 outweigh the increased risk of myopathy and rhabdomyolysis.

#### ***Diltiazem***

An analysis of the 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.

#### ***Danazol***

Danazol, a synthetic steroid used to treat endometriosis and breast cysts in women. The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with higher doses of simvastatin (see sections 4.2 and 4.4).

#### ***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.

#### ***Oral anticoagulants***

In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. Very rare cases of elevated INR have been reported. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

***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.

**4.6 Pregnancy and lactation**

***Pregnancy:*** Simvastatin 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 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-marketing experiences.

#### 4.8 **Undesirable effects**

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

In HPS (see section 5.1) involving 20,536 patients treated with 40 mg/day of 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. 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:***

*Rare:* headache, paresthesia, dizziness, peripheral neuropathy

##### ***Gastrointestinal disorders:***

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

***Hepato-biliary disorders:***

*Rare:* hepatitis/jaundice

***Skin and subcutaneous tissue disorders:***

*Rare:* rash, pruritus, alopecia

***Musculoskeletal, connective tissue and bone disorders:***

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

***General disorders and administration site conditions:***

*Rare:* asthenia

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

***Investigations:***

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

**4.9 Overdose**

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

**5 PHARMACOLOGICAL PROPERTIES****5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: HMG-CoA reductase inhibitor

**ATC-Code: C10A A01**

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active beta-hydroxyacid form, which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy – 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

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 may involve both reduction of VLDLcholesterol (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 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.

### **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-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 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 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 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 hypercholesterolemia, the mean reductions of LDL-C were 30, 38, 41 and 47 %, respectively. In studies of patients with combined (mixed) hyperlipidaemia on simvastatin 40 mg and 80 mg, the median reductions in triglycerides were 28 and 33 % (placebo: 2 %), respectively, and mean increases in HDL-C were 13 and 16 % (placebo: 3 %), respectively.

### **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; the rate of 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 % 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, repeated 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

Lactose Monohydrate

Cellulose, Microcrystalline

Starch, Pregelatinized

Citric Acid Monohydrate

Ascorbic acid

Butyl hydroxy anisole

Magnesium Stearate

Hydroxypropyl Cellulose

HPMC 2910/Hypromellose 6cP

Titanium Dioxide

Talc

Iron Oxide Red

Iron Oxide Yellow

Iron Oxide Black

### 6.2 Incompatibilities

Not Applicable.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Do not store above 25°C.

### 6.5 Nature and contents of container

PVC/ PE/ PVDC/ Aluminium blisters in a cardboard carton. Packs of 28 tablets.

### 6.6 Special precautions for disposal

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited

Victoria Court, Bexton Road  
Knutsford  
Cheshire WA 16 0PF  
United Kingdom

**8**     **MARKETING AUTHORISATION NUMBER(S)**  
PL 20092/0013

**9**     **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
14/12/2007

**10**    **DATE OF REVISION OF THE TEXT**  
14/12/2007

**1 NAME OF THE MEDICINAL PRODUCT**

Simvastatin 40 mg Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 40 mg of simvastatin.

Excipients: Lactose anhydrous

For full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Simvastatin 40 mg tablets, are brick red coloured, oval shaped, biconvex, tablets, debossed with '40' on one side and plain on the other side, containing Simvastatin 40 mg.

**4 CLINICAL PARTICULARS****4.1 Therapeutic indications*****Hypercholesterolaemia***

Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

***Cardiovascular prevention***

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

**4.2 Posology and method of administration**

The dosage range is 5-80 mg/day given orally as a single dose in the evening.

Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.

***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-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 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 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***

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 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.)

#### ***Dosage in renal insufficiency***

No modification of dosage should be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance < 30 ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

#### ***Use in the elderly***

No dosage adjustment is necessary.

#### ***Use in children and adolescents***

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 elevations of serum transaminases.

Pregnancy and lactation (see section 4.6)

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

### **4.4 Special warnings and precautions for use**

#### ***Myopathy/Rhabdomyolysis***

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase

(CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. 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 ( $> 5 \times$  ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

#### ***Before the treatment***

All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

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

- Elderly (age  $> 70$  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 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 ( $> 5 \times$  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 ( $> 5 \times$  ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are  $< 5 \times$  ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued. If symptoms resolve and CK levels return to normal, then re- introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and

with close monitoring. 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 and ciclosporin (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, 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 or ciclosporin should be carefully weighed against the potential risks of these combinations. (See sections 4.2 and 4.5.)

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

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

#### ***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.

**Hereditary disorders:**

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**

Prescribing 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).

<b>Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis</b>	
<b>Interacting agents</b>	<b>Prescribing recommendations</b>
Potent CYP3A4 inhibitors: Itraconazole Ketoconazole	<b>Contraindicated with simvastatin</b>

Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone	
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
Amiodarone Verapamil	Do not exceed 20 mg simvastatin daily
Diltiazem	Do not exceed 40 mg simvastatin daily
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Effects of other medicinal products on simvastatin

#### ***Interactions involving CYP3A4***

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, 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.

#### ***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 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 outweigh the increased risk of myopathy and rhabdomyolysis.

#### ***Diltiazem***

An analysis of the 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.

#### ***Danazol***

Danazol, a synthetic steroid used to treat endometriosis and breast cysts in women. The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with higher doses of simvastatin (see sections 4.2 and 4.4).

#### ***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.

#### ***Oral anticoagulants***

In two clinical studies, one in normal volunteers and the other in

hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. Very rare cases of elevated INR have been reported. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

***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.

**4.6 Pregnancy and lactation**

***Pregnancy:*** Simvastatin 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 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-marketing experiences.

#### **4.8 Undesirable effects**

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

In HPS (see section 5.1) involving 20,536 patients treated with 40 mg/day of 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. 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:***

*Rare:* headache, paresthesia, dizziness, peripheral neuropathy

##### ***Gastrointestinal disorders:***

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

***Hepato-biliary disorders:***

*Rare:* hepatitis/jaundice

***Skin and subcutaneous tissue disorders:***

*Rare:* rash, pruritus, alopecia

***Musculoskeletal, connective tissue and bone disorders:***

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

***General disorders and administration site conditions:***

*Rare:* asthenia

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

***Investigations:***

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

#### **4.9 Overdose**

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

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: HMG-CoA reductase inhibitor

**ATC-Code: C10A A01**

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active beta-hydroxyacid form, which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy – 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

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 may involve both reduction of VLDLcholesterol (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 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.

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

## **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; the rate of 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 % 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, repeated 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**

Lactose Monohydrate  
Cellulose, Microcrystalline  
Starch, Pregelatinized  
Citric Acid Monohydrate  
Ascorbic acid  
Butyl hydroxy anisole  
Magnesium Stearate  
Hydroxypropyl Cellulose  
HPMC 2910 /Hypromellose 6cP  
Titanium Dioxide  
Talc  
Iron Oxide Red  
Iron Oxide Black

### 6.2 **Incompatibilities**

Not applicable.

### 6.3 **Shelf life**

2 years.

### 6.4 **Special precautions for storage**

Do not store above 25°C.

### 6.5 **Nature and contents of container**

PVC/ PE/ PVDC/ Aluminium blisters in a cardboard carton. Packs of 28 tablets.

### 6.6 **Special precautions for disposal**

No special requirements.

**7      MARKETING AUTHORISATION HOLDER**

Lupin (Europe) Limited

Victoria Court, Bexton Road

Knutsford

Cheshire WA 16 0PF

United Kingdom

**8      MARKETING AUTHORISATION NUMBER(S)**

PL 20092/0014

**9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

14/12/2007

**10     DATE OF REVISION OF THE TEXT**

14/12/2007



**1 NAME OF THE MEDICINAL PRODUCT**

Simvastatin 80 mg Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 80 mg of simvastatin.

Excipients: Lactose anhydrous

For full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Simvastatin 80 mg tablets, are brick red coloured, capsule shaped, biconvex, tablets, debossed with '80' on one side and '123' on the other side, containing Simvastatin 80 mg.

**4 CLINICAL PARTICULARS****4.1 Therapeutic indications*****Hypercholesterolaemia***

Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

***Cardiovascular prevention***

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

**4.2 Posology and method of administration**

The dosage range is 5-80 mg/day given orally as a single dose in the evening.

Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.

***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-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 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 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***

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 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.)

#### ***Dosage in renal insufficiency***

No modification of dosage should be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance < 30 ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

#### ***Use in the elderly***

No dosage adjustment is necessary.

#### ***Use in children and adolescents***

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 elevations of serum transaminases.

Pregnancy and lactation (see section 4.6)

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

### **4.4 Special warnings and precautions for use**

#### ***Myopathy/Rhabdomyolysis***

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and

very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. 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 ( $> 5 \times \text{ULN}$ ), levels should be re-measured within 5 to 7 days later to confirm the results.

#### ***Before the treatment***

All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

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

- Elderly (age  $> 70$  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 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 ( $> 5 \times \text{ULN}$ ), 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 ( $> 5 \times \text{ULN}$ ), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are  $< 5 \times \text{ULN}$ , treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued. If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring. 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 and ciclosporin (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, 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 or ciclosporin should be carefully weighed against the potential risks of these combinations. (See sections 4.2 and 4.5.)

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

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

### ***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.

**Hereditary disorders:**

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**

Prescribing 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).

<b>Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis</b>	
<b>Interacting agents</b>	<b>Prescribing recommendations</b>
Potent CYP3A4 inhibitors: Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone	<b>Contraindicated with simvastatin</b>
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
Amiodarone Verapamil	Do not exceed 20 mg simvastatin daily

Diltiazem	Do not exceed 40 mg simvastatin daily
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Effects of other medicinal products on simvastatin

#### ***Interactions involving CYP3A4***

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, 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.

#### ***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 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 outweigh the increased risk of

myopathy and rhabdomyolysis.

#### ***Diltiazem***

An analysis of the 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.

#### ***Danazol***

Danazol, a synthetic steroid used to treat endometriosis and breast cysts in women. The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with higher doses of simvastatin (see sections 4.2 and 4.4).

#### ***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.

#### ***Oral anticoagulants***

In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. Very rare cases of elevated INR have been reported. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

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.

#### 4.6 **Pregnancy and lactation**

**Pregnancy:** Simvastatin 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 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-marketing experiences.

#### 4.8 **Undesirable effects**

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

In HPS (see section 5.1) involving 20,536 patients treated with 40 mg/day of 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. 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:***

*Rare:* headache, paresthesia, dizziness, peripheral neuropathy

***Gastrointestinal disorders:***

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

***Hepato-biliary disorders:***

*Rare:* hepatitis/jaundice

***Skin and subcutaneous tissue disorders:***

*Rare:* rash, pruritus, alopecia

***Musculoskeletal, connective tissue and bone disorders:***

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

***General disorders and administration site conditions:***

*Rare:* asthenia

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

***Investigations:***

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

#### **4.9 Overdose**

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitor

#### ATC-Code: C10A A01

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active beta-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy – 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

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 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 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.

#### *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-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 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 nonvascular

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

## **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; the rate of 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 % 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, repeated 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**

Lactose Monohydrate  
Cellulose, Microcrystalline  
Starch, Pregelatinized  
Citric Acid Monohydrate  
Ascorbic acid  
Butyl hydroxy anisole  
Magnesium Stearate  
Hydroxypropyl Cellulose  
HPMC 2910/Hypromellose 6cP  
Titanium Dioxide  
Talc  
Iron Oxide Red  
Iron Oxide Yellow  
Iron Oxide Black

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years.

**6.4 Special precautions for storage**

Do not store above 25°C.

**6.5 Nature and contents of container**

PVC/ PE/ PVDC/ Aluminium blisters in a cardboard carton. Packs of 28 tablets.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Lupin (Europe) Limited

Victoria Court, Bexton Road

Knutsford

Cheshire WA 16 0PF

United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20092/0015

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

14/12/2007

**10 DATE OF REVISION OF THE TEXT**

14/12/2007

## PATIENT INFORMATION LEAFLET

### PATIENT INFORMATION LEAFLET SIMVASTATIN 10mg, 20mg, 40mg AND 80mg TABLETS

Read all of this leaflet carefully before you start taking this medicine.

Even if this medicine is a repeat prescription, some of the information may have changed.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for **you**. Do **not** pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed on this leaflet, please tell your doctor or pharmacist

#### In This Leaflet:

- 1 What Simvastatin Tablets are and what they are used for.
- 2 Before you take Simvastatin Tablets.
- 3 How to take Simvastatin Tablets.
- 4 Possible side effects.
- 5 How to store Simvastatin Tablets.
- 6 Further information.

#### 1. WHAT SIMVASTATIN TABLETS ARE AND WHAT THEY ARE USED FOR

The **active** ingredient in Simvastatin Tablets is simvastatin. This belongs to a group of medicines called statins or HMG-CoA reductase inhibitors. These work by reducing the amount of cholesterol and of other fatty substances called triglycerides in your blood. Nearly all of this cholesterol is made by our liver. Our bodies produce most of this cholesterol at night. For this reason it is recommended that you take your Simvastatin Tablets in the evening or at night.

For the **other** ingredients in Simvastatin Tablets, (see section 6.)

Your doctor has prescribed Simvastatin Tablets for you to reduce the health risks linked with coronary heart disease (CHD). If you have or are at risk of developing CHD, these tablets may help keep your arteries clear.

There are two types of cholesterol in our blood. Too much “bad” LDL (Low Density Lipoprotein) cholesterol can clog up our arteries, but “good” HDL (High Density Lipoprotein) cholesterol is thought to remove it. These tablets reduce the level of bad cholesterol and of fatty substances called triglycerides, but raise the level of good cholesterol in our blood.

## 2. BEFORE YOU USE SIMVASTATIN TABLETS

### Do not use Simvastatin Tablets

If you are **allergic** (hypersensitive) to the active substance simvastatin, or to any of the **other** ingredients. (See section 6 for a list of these.)

- if you are pregnant or breastfeeding
- if you have liver problems
- if you are taking antifungal drugs called itraconazole or ketoconazole
- if you are taking the antibiotics erythromycin or clarithromycin or telithromycin
- if you are taking the antidepressant nefazodone
- if you are taking a medicine for the treatment of HIV infections (an HIV protease such as indinavir, nelfinavir, ritonavir or sequinavir).

If you think any of these apply to you, do **not** use any of the tablets. Talk to your doctor **first** and follow the advice given to you.

### Take special care with Simvastatin Tablets

#### Tell your doctor

- if you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
- about all your medical conditions, including allergies.
- if you consume large quantities of alcohol or if you have a past history of liver disease, your doctor may wish to carry out some blood tests to check your liver before and after starting treatment.
- if you have any kidney problems.
- **quickly, if you experience any unexplained muscle pain, muscle weakness or tenderness.** In rare instances (fewer than 1 patient in every thousand) there is a risk of muscle problems which could be serious, including muscle breakdown which could lead to kidney damage. The risk of muscle problems is greater at higher doses of simvastatin and the risk of muscular breakdown is greater in certain kinds of patients,

so

#### Make sure your doctor knows

- if you or close family members have a hereditary muscle disorder.

- if you have thyroid problems.
- if you are more than 70 years old.
- if you have ever had problems with other cholesterol lowering drugs such as atorvastatin, pravastatin, or with cholesterol lowering fibrates such as gemfibrozil and bezafibrate.
- If you are taking any of the following:
  - Amiodarone, a drug used for irregular heartbeat.
  - Ciclosporin, a drug used to suppress the immune system.
  - Danazol, a synthetic steroid used to treat endometriosis and breast cysts in women.
  - Verapamil or diltiazem, drugs used to treat high blood pressure, chest pain associated with heart disease or other heart conditions.
  - Niacin or nicotinic acid in doses equal to, or greater than, 1g per day.
  - Anticoagulants, drugs that prevent blood clots, such as warfarin or fenofibrate. (See also the list of drugs and medicines at the beginning of section 2).

### Using other medicines

Please tell your doctor or pharmacist if you are taking or have taken recently any other medicines, **including** medicines obtained without a prescription.

### Using Simvastatin Tablets with food and drink

You should **not** drink **grapefruit juice** throughout the whole period of time you use Simvastatin Tablets, because grapefruit juice changes the way in which the medicine works.

### Pregnancy and breast-feeding

Do **not** use Simvastatin Tablets if you are pregnant, trying to become pregnant or think you may be pregnant. If you become pregnant while using Simvastatin Tablets, stop taking them **immediately** and contact your doctor.

### Breast-feeding

Do not use Simvastatin Tablets if you are breastfeeding. If you are already breastfeeding, or planning to breastfeed, talk to your doctor before using this medicine.

Ask your doctor or pharmacist for advice before using any medicine.

### The Elderly (65 years of age and over)

No dosage adjustment is necessary.

### Children (under 18)

Simvastatin Tablets are **not** recommended for use by children.



### Driving and using machinery

Simvastatin Tablets are not expected to interfere with your ability to drive or to use machinery. However, whenever you drive or use machinery, you should bear in mind that **dizziness** has been reported in rare instances, (fewer than 1 instance in every 1000.)

(Now please read the rest of this leaflet. It has other important information for your safety.)

## 3. HOW TO TAKE SIMVASTATIN TABLETS

Always take Simvastatin Tablets exactly as your doctor has told you to. If you are not sure, you should check with your doctor.

- The usual starting dose is 20mg or 40mg a day, taken as a single dose in the evening or at night, (the times when our bodies produce most of our cholesterol.)
- Your doctor may adjust your dose to a maximum of 80mg a day, as a single dose, taken in the evening. (This 80mg dose is recommended only for patients with a severely high level of cholesterol in their blood.)
- Your doctor may prescribe lower doses, particularly if you are taking some of the medicines listed above, or have certain kidney conditions. Your doctor may have to change the dosage in order to get the best effect.
- Do not take more or fewer tablets than your doctor has prescribed.
- Keep taking your tablets for as long as your doctor has asked you to.

### If you take more Simvastatin tablets than you should

- If you take an **overdose** by mistake, contact your doctor as soon as possible.

### If you forget to take Simvastatin Tablets

If you miss a dose, just carry on with the next dose at the normal time. Do not take a double dose to make up for the forgotten dose.

### If you stop taking Simvastatin Tablets

If you stop taking your tablets, your cholesterol level may rise again.

If you have any further questions about taking this product, ask your doctor or pharmacist

#### 4. POSSIBLE SIDE EFFECTS

Like all medicines Simvastatin Tablets can cause side effects, although not everybody gets them

**Rare side effects:**

Contact your doctor immediately if you experience muscle aches and pains, tenderness, weakness or cramps. This is because on rare occasions muscle damage can be serious. (See Section 2.)

The following side effects may occur, in fewer than 1 in every 1000 patients. These side effects have been mostly mild and short-lived:

- stomach upsets (such as sickness, constipation, diarrhoea, flatulence, indigestion and abdominal pain);
- weakness, headache, dizziness, numbness or loss of feeling in the arms and legs, hair loss, skin rashes, itchiness;
- liver disease, (the signs of this could be a yellowing of the eyes and/or of the skin, itchiness of the skin, dark coloured urine, pale coloured stools);
- an allergic reaction to Simvastatin Tablets. The allergic reaction could include some of the following signs: swelling of the face, tongue or throat (**contact your doctor immediately**); joint pains, joint and blood vessel inflammation, unusual bruising, skin rashes, nettle rash and weals, skin sensitivity to the sun, high temperature, flushing, breathing difficulties or tiredness.

Please remember: -

- the expected benefits of your medicine will usually be greater than the risk of suffering any harmful side effects.
- if you get any side effects that become serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

#### 5. HOW TO STORE SIMVASTATIN TABLETS

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

Do not store them above 25 °C.

Do not use these tablets after the expiry date which is stated on the pack.

The expiry date refers to the last day of that month.

## Disposal

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Simvastatin Tablets contain

The active substance is simvastatin.

The other ingredients are:

Lactose monohydrate, cellulose microcrystalline (E460), starch pregelatinised, citric acid monohydrate (E330), ascorbic acid (E300), butylhydroxyanisole (E320), isopropyl alcohol and magnesium stearate (E572), hydroxypropyl cellulose (E463), hydroxypropylmethylcellulose (E464), titanium dioxide (E171), talc (E553b).

In addition Simvastatin Tablets 10mg, 20mg, 40mg, 80mg contain iron oxide red (E172), Simvastatin Tablets 10mg, 20mg, 80mg contain iron oxide yellow (E172) and Simvastatin 20mg, 40mg contain iron oxide black (E172).

### What Simvastatin Tablets look like and the contents of the pack

Simvastatin Tablets are available in four strengths.

- The peach-coloured, oval-shaped, film-coated tablets marked "10" on one side and plain on the other side contain 10 mg Simvastatin.
- The tan-coloured, oval-shaped, film-coated tablets marked "20" on one side and with a break line on the other side contain 20mg Simvastatin.
- The brick-red-coloured, oval-shaped, film-coated tablets marked "40" on one side and plain on the other side contain 40mg Simvastatin.
- The brick-red coloured, capsule-shaped, film-coated tablets marked "123" on one side and "80" on the other side contain 80mg Simvastatin.

Simvastatin Tablets are available in blister packs of 28 tablets.

**Marketing Authorisation Holder & Manufacturer**

The Marketing Authorisation Holder is:

Lupin (Europe) Limited,  
Victoria Court,  
Bexton Road,  
Knutsford,  
Cheshire WA16 0PF  
United Kingdom  
Tel.: + 44 (0) 1565 751378.


**This leaflet was last approved in**

**Date of preparation:** October, 2007.

### LABELLING

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SAT FRI THU WED TUE MON SUN

 **Simvastatin 10mg Tablets**  
Code No. GO/DRUGS/654  
Lupin (Europe) Limited **PL 20092/0012**


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SAT FRI THU WED TUE MON SUN

 **Simvastatin 10mg Tablets**  
Code No. GO/DRUGS/654  
Lupin (Europe) Limited **PL 20092/0012**


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PL 20092/0012  
Lupin (Europe) Limited  
Victoria Court, Bexton Road, Knutsford,  
Cheshire, WA16 0PF, UNITED KINGDOM

**Simvastatin 10 mg Tablets**

28 Tablets

**Simvastatin 10 mg Tablets**

 Lupin (Europe) Limited

**Simvastatin 10 mg Tablets**


**Simvastatin 10 mg Tablets**

20757010

**POM**  
Each tablet contains 10 mg of Simvastatin.  
Also contains Lactose Monohydrate  
(see enclosed leaflet)

Batch No. :  
Expiry Date :

Please read the enclosed leaflet:  
It contains important information  
about how and when you take  
your tablet.  
Do not store above 25°C  
To be taken orally as directed by  
the prescriber.  
Keep all medicines out of reach  
of children.  
Code No. GO/DRUGS/654

  
8 901107 000981

Put dispensing label here

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SAT FRI THU WED TUE MON SUN

**Simvastatin 20mg Tablets**  
Code No. GO/DRUGS/654  
Lupin (Europe) Limited

PL 20092/0013

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SAT FRI THU WED TUE MON SUN

**Simvastatin 20mg Tablets**  
Code No. GO/DRUGS/654  
Lupin (Europe) Limited

PL 20092/0013

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SAT FRI THU WED TUE MON SUN

**Simvastatin 20mg Tablets**  
Code No. GO/DRUGS/654  
Lupin (Europe) Limited

PL 20092/0013

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207586Ro

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SAT FRI THU WED TUE MON SUN

**Simvastatin 20mg Tablets**  
Code No. GO/DRUGS/654  
Lupin (Europe) Limited

PL 20092/0013

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XXXXXXXXXXXXXXXXXXXX

SAT FRI THU WED TUE MON SUN

**Simvastatin 20mg Tablets**  
Code No. GO/DRUGS/654  
Lupin (Europe) Limited

PL 20092/0013

XXXXXXXXXXXXXXXXXXXX


207586Ro

PL 20092/0013  
Lupin (Europe) Limited  
Victoria Court, Bexton Road, Knutsford,  
Cheshire, WA16 0PF, UNITED KINGDOM

**Simvastatin 20 mg Tablets**

28 Tablets

**Simvastatin 20 mg Tablets**



Lupin (Europe) Limited

**Simvastatin 20 mg Tablets**

20757180

**POM**

Each tablet contains 20 mg of Simvastatin.  
Also contains Lactose Monohydrate  
(see enclosed leaflet)

Batch No. :  
Expiry Date :


Please read the enclosed leaflet:  
It contains important information  
about how and when you take  
your tablet.

Do not store above 25°C

To be taken orally as directed by  
the prescriber.

Keep all medicines out of reach  
of children.

Code No. GO/DRUGS/654



8 901107 400998

Put dispensing label here




The image displays five identical blister packs of Simvastatin 40mg Tablets, arranged vertically. Each blister pack is a rectangular strip with a dashed border, containing two rows of seven oval-shaped tablets. The tablets in the top row are labeled SAT, FRI, THU, WED, TUE, MON, and SUN from left to right. The tablets in the bottom row are labeled SAT, FRI, THU, WED, TUE, MON, and SUN from left to right. In the center of each blister pack, there is a logo consisting of a stylized 'L' and 'P' inside a square, followed by the text 'Simvastatin 40mg Tablets', 'Code No. GO/DRUGS/654', and 'Lupin (Europe) Limited'. To the right of this text, the product code 'PL 20092/0014' is printed. At the bottom left of each blister pack, the number '2075877b' is printed. On the left and right sides of each blister pack, there are vertical bars with the text 'XXXXXXXXXXXXXXXXXXXX' repeated. A small black tab is visible at the top right and bottom right corners of the blister packs.


PL 20092/0014  
Lupin (Europe) Limited  
Victoria Court, Bexton Road, Knutsford,  
Cheshire, WA16 0PF, UNITED KINGDOM

**Simvastatin 40 mg Tablets**

28 Tablets

**Simvastatin 40 mg Tablets**



 Lupin (Europe) Limited

[POM]


Each tablet contains 40 mg of Simvastatin.  
Also contains Lactose Monohydrate  
(see enclosed leaflet)

**Simvastatin 40 mg Tablets**

2075286

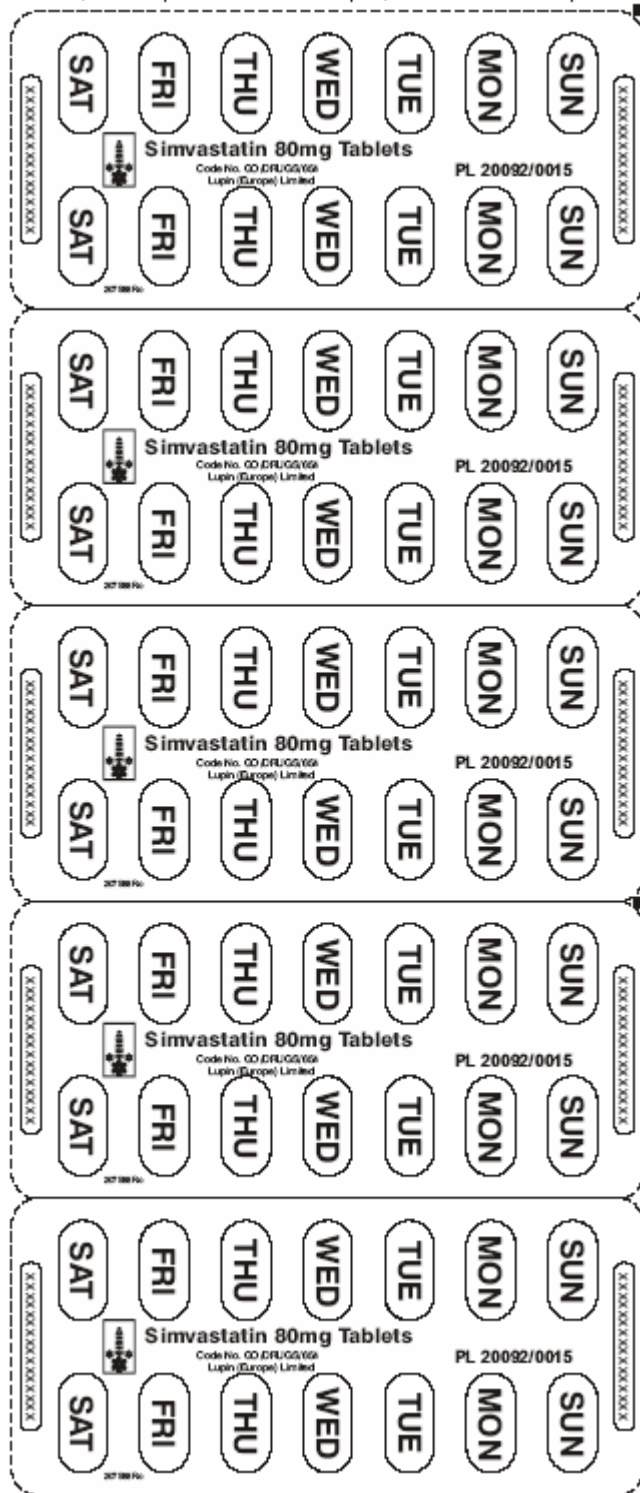
Batch No. :  
Expiry Date :

Please read the enclosed leaflet:  
It contains important information  
about how and when you take  
your tablet.  
Do not store above 25°C  
To be taken orally as directed by  
the prescriber.  
Keep all medicines out of reach  
of children.  
Code No. GO/DRUGS/654



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Put dispensing label here



PL 20092/0015  
Lupin (Europe) Limited  
Victoria Court, Bexton Road, Knutsford,  
Cheshire, WA16 0PF, UNITED KINGDOM

Simvastatin 80 mg Tablets

28 Tablets

**Simvastatin 80 mg Tablets**



Lupin (Europe) Limited

Simvastatin 80 mg Tablets

**POM**

Each tablet contains 80 mg of Simvastatin.  
Also contains Lactose Monohydrate  
(see enclosed leaflet)

Simvastatin 80 mg Tablets

20757986

Batch No. :  
Expiry Date :

Please read the enclosed leaflet:  
It contains important information  
about how and when you take  
your tablet.

Do not store above 25°C

To be taken orally as directed by  
the prescriber.

Keep all medicines out of reach  
of children.

Code No. GO/DRUGS/654



Put dispensing label here