SIMVASTATIN 10MG TABLETS
PL 18866/0050

UKPAR

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SIMVASTATIN 10MG TABLETS
PL 18866/0050

LAY SUMMARY

The MHRA granted Rockspring Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Simvastatin 10mg Tablets (PL 18866/0050) on 20th March 2006. This prescription-only medicine (POM) is indicated for people with coronary heart disease, hyperlipidaemia and homozygous familial hypercholesterolaemia.

Simvastatin 10mg Tablets contain the active ingredient simvastatin which acts by reducing the amount of cholesterol and fatty substance, called triglycerides, in the blood.

This application is a duplicate of a previously granted application, Simvastatin 10mg Tablets (PL 18866/0030), which was initially granted a licence on 27th April 2004.

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

SIMVASTATIN 10MG TABLETS
PL 18866/0050

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Simvastatin 10mg Tablets (PL 18866/0050) to Rockspring Healthcare Limited on 20th March 2006. The product is a prescription-only medicine (POM).

The application was submitted as a simple abridged application according to Article 10c (formerly 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Simvastatin 10mg Tablets (PL 18866/0030), which was initially granted a licence on 27th April 2004.

No new data was submitted nor was it necessary for this simple application, as the data is identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no PAR was generated.

Simvastatin 10mg Tablets contain the active ingredient simvastatin which acts by reducing the amount of cholesterol and triglycerides in the blood. Simvastatin 10mg Tablets is indicated for the treatment of coronary heart disease in patients with a plasma cholesterol level of 5.5mmol or more, hyperlipidaemia and homozygous familial hypercholesterolaemia.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 18866/0050
PROPRIETARY NAME: Simvastatin 10mg Tablets
ACTIVE(S): Simvastatin
COMPANY NAME: Rockspring Healthcare Limited
E.C. ARTICLE: Article 10c (formerly 10.1(a)(i)) of Directive 2001/83/EC
LEGAL STATUS: POM

1. INTRODUCTION

This is a simple, piggy back application for Simvastatin 10mg Tablets submitted under Article 10c (formerly 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Rockspring Healthcare Limited, 38-40 Chamberlayne Road, London, NW10 3JE, UK.

This application cross refers to Simvastatin 10mg Tablets (PL 18866/0030), which is currently registered in the UK. This application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the product is Simvastatin 10mg Tablets. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains simvastatin, equivalent to 10mg. The tablets are to be stored in blister packs (composed of PVC/PVDC with an aluminium foil lid) containing 28 tablets

The proposed shelf-life of 3 years is consistent with the cross-reference product. The storage conditions for the blister packs are "Do not store above 30^{o}C. Store in the original package". This is consistent with the cross-reference product.

2.3 Legal status

On approval, the product will be subject to sale as a prescription-only medicine (POM)

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is Rockspring Healthcare Limited, 38-40 Chamberlayne Road, London, NW10 3JE, UK.

The QP responsible for pharmacovigilance is stated and their CV is included.

2.5 Manufacturers

The proposed manufacturing site is consistent with that registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification for the product is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
The ingredients used are the same as for the cross-referenced product and are obtained from the same sources. A suitable certificate of suitability has been provided for magnesium stearate to show compliance with regulatory guidelines concerning TSE (i.e. showing that this product is TSE free).

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed SmPC is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the application are acceptable. A Marketing Authorisation should be granted.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

As this is a duplicate application to Simvastatin 10mg Tablets (PL 18866/0030), no new clinical data have been supplied and none are required.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

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

EFFICACY
This application is identical to a previously granted application for Simvastatin 10mg Tablets (PL 18866/0030).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. 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.

SIMVASTATIN 10MG TABLETS
PL 18866/0050

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 2nd June 2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 6th July 2005.
3	The application was determined on 20th March 2006

SIMVASTATIN 10MG TABLETS
PL 18866/0050

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

SIMVASTATIN 10MG TABLETS
PL 18866/0050

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Simvastatin 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains Simvastatin,10mg

For excipients see Section 6.1

3 PHARMACEUTICAL FORM
Film coated tablet
Peach-coloured, oval, biconvex film-coated tablets with a scoreline on one side and a "0" imprinted on each half of the scoreline.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Coronary heart disease
In patients with coronary heart disease with a plasma cholesterol level of 5.5 mmol/l or greater, simvastatin is indicated to:
- reduce the risk of mortality;
- reduce the risk of non-fatal myocardial infarction and coronary death;
- reduce the risk for undergoing myocardial revascularisation procedures (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty);
- and slowing the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

Hyperlipidaemia
In patients with primary hypercholesterolaemia, heterozygous and homozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia, Simvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, low density lipoprotein LDL-cholesterol, apolipoprotein B and triglycerides when response to diet and other non-pharmacological measures prove inadequate. Simvastatin also raises HDL-cholesterol and therefore lowers the LDL/HDL and total cholesterol/HDL ratios.

As with any cholesterol-lowering therapy other modifiable risk factors should also be considered when treatment is started.

Homozygous familial hypercholesterolaemia
Simvastatin is indicated as an adjunct to diet and other non dietary measures in reducing elevated total cholesterol, LDL-cholesterol and apolipoprotein B in patients with homozygous familial hypercholesterolaemia when response to these measures is inadequate.

4.2. Posology and method of administration

Oral administration.

The patient should be placed on a standard cholesterol-lowering diet before receiving Simvastatin and should continue on this diet during treatment with Simvastatin.

Coronary heart disease

The starting dose for patients with coronary heart disease can be 20 mg/day, which should be given as a single dose in the evening. Adjustment of dosage, if required, should be made at intervals of not less than four weeks, to a maximum of 80 mg/day given as a single dose in the evening, depending on the patient's individual response.

However, if LDL-cholesterol levels fall below 1.94 mmol/l or total serum cholesterol levels fall below 3.6 mmol/l, consideration should be given to reducing the dose of Simvastatin.

Hyperlipidaemia

For patients with hyperlipideamia the recommended dose is 10 mg once daily taken in the evening. The dose range is 10 mg to 80 mg a day in single doses taken in the evening. A marked response to treatment should be seen within two weeks with maximum therapeutic response reached by four to six weeks which is maintained for the course of therapy. When therapy is ceased the cholesterol levels have been shown to return to pretreatment levels. Adjustment of dosage, if required, should be made as specified above (see 4.2 'Posology and method of administration', *Coronary heart disease).*

Homozygous familial hypercholesterolaemia

Based on the results of a controlled clinical study, the recommended dosage for patients with homozygous familial hypercholesterolaemia is a single dose in the evening of 40 mg/day Simvastatin, or 80 mg/day in three divided doses of 20 mg, 20 mg and a 40 mg dose taken in the evening. 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.

Concomitant therapy

Simvastatin is effective alone or in combination with bile-acid sequestrants.

In patients taking ciclosporin, fibrates or niacin concomitantly with Simvastatin, the maximum recommended dosage is 10 mg/day (see 4.4 'Special warnings and precautions for use', *Muscle effects* and 4.5 'Interaction with other medicinal products and other forms of interaction').

Dosage in renal insufficiency

Because Simvastatin does not undergo significant renal excretion, modification of dosage should not be necessary in patients with moderate renal insufficiency.

However, 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 (see Pharmacokinetic properties*)*

Use in Elderly: Although experience in elderly patients is limited, efficacy using standard doses appears similar to that seen in the population as a whole. There is no apparent increase in the frequency of clinical or laboratory adverse findings.

Children: Studies to show safety and effectiveness in children have not been carried out.

4.3 Contraindications

- Hypersensitivity to the active or any of the excipients of this product;
- Active liver disease or unexplained persistent elevations of serum transaminases; porphyria;
- Concomitant therapy with tetralol class calcium channel blocker mibefradil (see section 4.4)
- Pregnancy and breastfeeding (see also 4.6 'Pregnancy and lactation')

4.4 Special warnings and precautions for use

Muscle Effects

Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine phosphokinase (CPK) (>10X the upper limit of normal [ULN]). Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely. In the Scandinavian Simvastatin Survival Study (4S), one case of myopathy was reported amongst 1,399 patients taking simvastatin 20 mg and no cases amongst 822 patients taking 40 mg daily for a median duration of 5.4 years. In two 6-month controlled clinical studies, there was one case of myopathy among 436 patients taking 40 mg and five cases among 669 patients taking 80 mg. The risk of myopathy is shown to be increased by concomitant therapy with certain drugs, some of which were excluded by the designs of these studies.

Myopathy caused by drug interactions

Concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy increase the incidence and severity.

In addition, the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Simvastatin and other HMG-CoA reductase inhibitors are metabolised by the cytochrome P450 isoform 3A4 (CYP3A4). Certain drugs that have a significant inhibitory effect at therapeutic doses on this metabolic pathway and can substantially raise the plasma levels of HMG-CoA reductase inhibitors and thus increase the risk of myopathy. Such drugs include ciclosporin, the tetralol class calcium channel blocker mibefradil, itraconazole, ketoconazole and anti-fungal azoles, the macrolide antibiotics and erythromycin and clarithromycin and the anti-depressant nefazodone.

Reducing the risk of myopathy

1. General measures

When patients are started on therapy with simvastatin they should be advised of the risk of myopathy and told to report promptly unexplained muscle pain, tenderness or weakness. A CPK level above 10x ULN in a patient with unexplained muscle symptoms indicates myopathy. If myopathy is diagnosed or suspected simvastatin

therapy should be discontinued. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CPK increases resolved.

Many of the patients which presented with rhabdomyolysis, had complicated medical histories. Some had pre-existing renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with simvastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

2. Measures to reduce the risk of myopathy caused by drug interactions (see 4.5)
When contemplating combined therapy of simvastatin with any of the interacting drugs the potential benefits should be weighed up against the risks. Patients on the combined therapy should be carefully monitored for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

The combined use of simvastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of simvastatin have been used without myopathy in small, short-term clinical trials with careful monitoring. Addition of these drugs to HMG-CoA reductase inhibitors typically provides little additional reduction in LDL cholesterol, but further reductions of triglycerides and further increases in HDL cholesterol may be obtained. If one of these drugs must be used with simvastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

Where patients are taking concomitant ciclosporin, fibrates or niacin, the dose of simvastatin should generally not exceed 10 mg/day (see 4.2 'Posology and method of administration'*, Concomitant therapy*), as the risk of myopathy increases substantially at higher doses. Concomitant use of simvastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, or nefazodone is not recommended. Where a short course of treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is required, a brief suspension of simvastatin therapy can be considered as there are no known adverse consequences to brief interruption of long-term cholesterol-lowering therapy. Concomitant use with other medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

Hepatic effects
Minor asymptomatic transient rises in serum transaminase may occur soon after initiation of therapy with simvastatin which do not require the drug to be discontinued. There is no evidence that these changes are due to hypersensitivity to Simvastatin.
In the Scandinavian Simvastatin Survival Study (4S) (see 5.1 'Pharmacodynamic properties') the number of patients with one or more transaminase elevation to>3 times the upper limit of normal, over the course of the study, was not significantly

different between the simvastatin and placebo groups (14 [0.7%] vs 12 [0.6%]), the number of patients with single elevations of SGPT (ALT) to 3 times the upper limit of normal was significantly higher in the simvastatin group in the first year of the study (20 vs 8, p=0.023), but not thereafter.
Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to >3 times the upper limit of normal and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study.

All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In two controlled clinical studies in 1,105 patients, the six month incidence of persistent hepatic transaminase elevations considered drug-related was 0.7% and 1.8% at the 40 and 80 mg dose respectively.

It is recommended that liver-function tests be performed before treatment begins, and periodically thereafter, (e.g. twice a year) for the first year of treatment or until one year after the last elevation in dose in all patients. Patients treated with the 80 mg dose should receive an additional test at three months. 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 three times the upper limit of normal and are persistent, then drug therapy should be discontinued.

Active liver diseases or unexplained transaminase elevations are contra-indications to the use of simvastatin. The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

Hypertriglyceridaemia
Although simvastatin can lower the levels of triglycerides, it is not indicated where hypertriglyceridaemia is the major abnormality (i.e. Types I, IV andV hyperlipidaemia)

Ophthalmic examination
In the absence of any drug therapy, an increase in the prevalence of lens opacities with time is expected as a result of ageing. Current long-term data from clinical trials do not indicate an adverse effect of simvastatin on the human lens.

Use in the elderly
Although experience in elderly patients is limited, efficacy using standard doses appears similar to that seen in the population as a whole. There is no apparent increase in the frequency of clinical or laboratory adverse findings.

Paediatric use
Studies to show safety and effectiveness in children have not been established.

Therefore Simvastatin is not recommended for paediatric use.

4.5 Interaction with other medicinal products and other forms of interaction

Gemfibrozil and other fibrates, lipid-lowering doses (≥ 1g/day) of niacin (nicotinicacid): These drugs have shown to increase the risk of myopathy when given concomitantly with simvastatin, probably because they can produce myopathy when given alone. There is no current evidence to suggest that these agents affect the pharmacokinetics of simvastatin.

CYP3A4 interactions: Simvastatin does not have CYP3A4 inhibitory effect and therefore it is not expected to affect the plasma levels of drugs which are metabolised by CYP3A4. However simvastatin acts as a substrate for CYP3A and therefore potent inhibitors of CYP3A4 may increase the risk of myopathy by increasing the plasma levels of HMG-CoA reductase inhibitory activity during simvastatin therapy. These include ciclosporin, the tetralol-class channel blocker mibefradil, the azole antifungals itraconazole and ketoconazole, the macrolide antibiotics, erythromycin and clarithromycin, HIV protease inhibitors and the antidepressant nefazodone.
It has been found that grapefruit juice contains one or more components that inhibit CYP3A4. The effects of a typical consumption of one 240ml glass per a day is minimal and of no clinical relevance. However, very large quantities (over 1 litre daily) significantly increase the plasma levels of HMG-CoA reductase inhibitory activity during simvastatin therapy and should be avoided.

Propranolol: There was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of Simvastatin and propranolol in normal healthy volunteers.

Digoxin: Concomitant administration of simvastatin and digoxin resulted in a slight elevation (less than 0.3 ng/ml) in drug concentrations (as measured by a digoxin radio-immuno-assay) in plasma compared to concomitant administration of placebo and digoxin.

Coumarin derivatives: In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalised Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. 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, 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.

Other concomitant therapy: In clinical studies, Simvastatin was used concomitantly with ACE inhibitors, beta-blockers, calcium antagonists (except mibefradil),

diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

Pregnancy: Simvastatin is contra-indicated in pregnancy.

As atherosclerosis is a chronic process the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidaemia. Simvastatin and inhibitors of HMG-CoA reductase decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway. Since, cholesterol and these other products are essential components for foetal development, including synthesis of steroids and cell membranes, simvastatin is contra-indicated for use in pregnancy and women of child bearing potential unless such patients are highly unlikely to conceive. An interval of at least one month between the end of therapy with simvastatin and planned conception is advisable. If the patient becomes pregnant while taking simvastatin, treatment should be discontinued immediately and the patient apprised of the potential hazard to the foetus.

A few reports have been received of congenital abnormalities in infants whose mothers were treated during pregnancy with HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and foetal death/stillbirths did not exceed what would be expected in the general population. As safety in pregnant women has not been established and there is no apparent benefit to therapy with simvastatin during pregnancy, treatment should be immediately discontinued as soon as pregnancy is recognised.

Breast-feeding mothers: It is not known whether simvastatin or its metabolites are excreted in human milk. Therefore simvastatin is not recommended during lactation.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Simvastatin is generally well tolerated; for the most part, side effects have been usually mild and transient in nature. Less than 2% of patients were discontinued from controlled clinical studies due to side effects attributable to simvastatin.

In the pre-marketing controlled clinical studies, adverse effects occurring with a frequency of 1% or more and considered by the investigator as possibly, probably or definitely drug-related were: abdominal pain, constipation, and flatulence. Other side effects occurring in 0.5-0.9% of patients were asthenia and headache.

Myopathy has been reported rarely.

In the Scandinavian Simvastatin Survival Study (4S) involving 4,444 patients treated with simvastatin 20-40 mg/day (n=2,221) or placebo (n=2,223), the safety

and tolerability profiles were comparable between groups over the median 5.4 years of the study.

The following additional side effects were reported either in non-clinical trials or in marketed use: nausea, diarrhoea, rash, dyspepsia, pruritus, alopecia, dizziness, muscle cramps, myalgia, pancreatitis, paraesthesia, peripheral neuropathy, vomiting, and anaemia. Rarely, rhabdomyolysis and hepatitis/jaundice occurred. 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, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea, and malaise.

Laboratory test findings
Marked and persistent increases of serum transaminases have been reported infrequently. Liver-function test abnormalities have generally been mild and transient. Elevated alkaline phosphatase and γ-glutamyl transpeptidase have been reported. As have increases in serum creatine phosphokinase (CPK) levels derived from skeletal muscle have been reported (see 4.4 'Special warnings and special precautions for use').

Further side effects as follows have been reported but the causal relationship with therapy has not been proven; depression, erythema multiforme including Stevens-Johnson syndrome, leucopenia and purpura

4.9 Overdose

A few cases of overdosage have been reported; no patient had any specific symptoms, and all patients recovered without sequelae. The maximum dosage taken was 450 mg. General measures should be adopted and liver function should be monitored.

The maximum plasma concentration of inhibitors occurred within 1.3 and 2.4 hours of administration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code C10 A 01 - Serum Lipid Reducing Agents - Cholesterol and Triglyceride Reducers - HMG Co A reductase Reducers

Involvement of LDL cholesterol in atherogenesis has been well documented in both clinical and pathological studies, as well as in many animal experiments. Epidemiological studies show that risk factors for coronary heart disease include raised LDL cholesterol and lowered HDL (high-density lipoprotein) cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-cholesterol concentrations. LDL is formed from VLDL and is catabolised predominantly by the high-affinity LDL receptor. The mechanism of simvastatin lowering LDL may involve both reduction of VLDL-cholesterol concentration and induction of the LDL receptor, leading to both reduced production and increased catabolism of LDL cholesterol. Apolipoprotein B also shown to fall substantially during treatment with simvastatin. One molecule of apoprotein B is found with each LDL particle, and since there is little apolipoprotein B

found in other lipoproteins, this strongly suggests that simvastatin does not merely cause cholesterol to be lost from LDL but also may reduce the concentration of circulating LDL particles. In addition, simvastatin increases HDL cholesterol and reduces plasma triglycerides. As a result of these changes the ratios of total to HDL cholesterol and LDL to HDL cholesterol are reduced.

In controlled clinical study of 12 patients between the ages of 15 and 39 years with homozygous familial hypercholesterolemia, a single daily dose of 40mg or three divided doses or 80mg/day divided into three doses, the mean LDL-cholestrol reduction for the 40mg and 80mg doses were 14% and 25%, respectively. One patient with absent LDL - cholesterol receptor function had an LDL - cholesterol reduction of 41% with an 80mg dose.

In the Scandinavian Simvastatin Survival Study (4S), the effect of simvastatin on total mortality was assessed in 4,444 patients with coronary heart disease (CHD) and baseline total cholesterol of 212 – 309 mg/dl (5.5 to 8.0 mmol/l). In this multicentre, randomised, double-blind, placebo-controlled study, patients with previous angina or myocardial infarction (MI) were treated with standard care, including diet and simvastatin 20 – 40 mg/day or placebo for a median duration 5.4 years. Over the course of the study, treatment with simvastatin led to mean reductions in total cholesterol, LDL cholesterol, LDL cholesterol and triglycerides of 25%, 3% an 10 %, respectively, and a mean increase in HDL cholesterol of 8%. Simvastatin significantly reduced the risk of death by 30%, of CHD death by 42%, and of having a hospital-verified non-fatal myocardial infarction by 37%. Furthermore simvastatin reduced the risk for undergoing myocardial revascularisation procedures (coronary artery by-pass grafting or percutaneous transluminal coronary angioplasty) by 37%.

In a *post hoc* analysis performed on fatal plus non-fatal cerebrovascular events (stroke and transient ischaemic attacks), there were 75 patients with such events in the simvastatin group and 102 in the placebo group (risk reduction 28%, p=0.033).

In a multicentre, placebo-controlled clinical trial in 404 patients using quantitative coronary angiography, simvastatin slowed the progression of coronary atherosclerosis and reduced the development of both new lesions and new total occlusions, whereas coronary atherosclerosis lesions steadily worsened in patients receiving standard care.

The active form is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyses the conversion of HMG-CoA to mevalonate. However, at therapeutic doses, the enzyme is not completely blocked, thereby allowing biologically necessary amounts of mevalonate to be available. Because the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway of cholesterol, therapy with simvastatin would not be expected to cause an accumulation of potentially toxic sterols. In addition, HMG-CoA is metabolised readily back to acetyl CoA, which participates in many biosynthetic processes in the body.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone which is readily hydrolysed *in vivo* to the corresponding ß-hydroxyacid, L-654,969, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the ß-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors). Both are measured in plasma following administration of simvastatin. In a disposition study with ^{14}C-labelled simvastatin, 100 mg (20 uCi) of drug was administered as capsules (5 x 20 mg), and blood, urine, and faeces collected. Thirteen per cent of the radioactivity was recovered in the urine and 60% in faeces. The latter represents absorbed drug equivalents excreted in bile as well as any unabsorbed drug. Less than 0.5%

of the dose was recovered in urine as HMG-CoA reductase inhibitors. In plasma, the inhibitors account for 14% and 28% (active and total inhibitors) of the AUC of total radioactivity, indicating that the majority of chemical species present were inactive or weak inhibitors.

The major metabolites of simvastatin present in human plasma are L-654,969 and four additional active metabolites. Both simvastatin and L-654,969 are highly bound to human plasma proteins >94%). The bioavailability of L-654,969 to the systemic circulation following an oral dose of simvastatin was estimated using an i.v. reference dose of L-654, 969; the value was found to be less than 5% of the dose. By analogy to the dog model, simvastatin is well absorbed and undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. Consequently, availability of active drug to the general circulation is low.

In dose-proportionality studies, utilising doses of simvastatin of 5, 10, 20, 60, 90 and 120 mg, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before a test meal.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of drug occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1.3 to 2.4 hours post-dose.

5.3 Preclinical safety data

The oral LD_{50} of simvastatin in mice is approximately 3.8 g/kg and in rats approximately 5 g/kg.

Administration of high dosage levels of simvastatin and related analogues to a variety of animal species has revealed a spectrum of changes in several tissues. These changes were not unexpected in view of the large doses used, the potency of these drugs in inhibiting mevalonate synthesis, and the essential role of the target enzyme in maintenance of cellular homeostasis. Extensive data generated on several of these changes indicate that they represent an exaggeration of the biochemical effect of these drugs at the high end of the dose-response curve. Thus, morphological changes in the livers of rats, squamous epithelial hyperplasia of the forestomach of rats and mice, and hepatotoxicity in rabbits have all been shown to be directly related to inhibition of HMG-CoA reductase.

Cataracts have been detected at high dosage levels in dog studies with simvastatin, although at a very low incidence. While there is no clear correlation between the magnitude of serum lipid-lowering and the development of cataracts, a consistent relationship has been observed between high serum levels of drug and cataract development with simvastatin and related HMG-CoA reductase inhibitors.

The serum levels in dog receiving a minimal cataratagenic dose of simvastatin of 50mg/kg/day were found to be six times higher than the maximum anticipated therapeutic dose of 1.6mg/kg in a man.

In dogs receiving simvastatin, elevated serum transaminases have been found. They occur as either a chronic low level elevation or as transient enzyme spikes in 10 - 40% of dogs. None of the dogs showing elevated serum transaminases demonstrated any symptoms of illness and none of these transaminase elevations led associated hepatic necrosis, despite

continued drug administration. There were no histopathological changes identified in the liver of any dogs receiving simvastin.

In two dog studies with simvastatin testicular degeneration was identified. However, similar studies to further define the actual nature of these changes has not been successful due to the effects being difficult to reproduce and unrelated to dose, serum cholesterol levels or duration of treatment. A dose of 50mg/kg/day administered to dogs for a period of two years has not shown any testicular effects.

Skeletal muscle necrosis was seen in one study in rats given 90 mg/kg b.d., but this was a lethal dosage in rats.

There are extensive battery of *in vivo* and *in vitro* genetic toxicity tests which have been conducted both with simvastatin and the corresponding open acid L-654,969. These tests include assays for microbial mutagenesis, mammalian cell mutagenesis, single stranded DNA breakage and tests for chromosome aberrations. The results of these tests concluded no evidence of interaction between simvastatin or L-654,969 with genetic material at both the highest soluble non cytotoxic concentrations in *in vitro* assays or maximal tolerated doses in *in vivo* tests.

Initial carcinogenicity studies conducted in rats and mice with simvastatin employed doses ranging from 1 mg/kg/day to 25 mg/kg/day. No evidence of a treatment-related incidence of tumour types was found in mice in any tissue. A statistically significant ($p \leq 0.05$) increase in the incidence of thyroid follicular cell adenomas was observed in female rats receiving 25 mg/kg of simvastatin per day (15.5 times the maximum recommended human dose). This benign tumour type was limited to female rats; no similar changes were seen in male rats or in female rats at lower dosages (up to 5 mg/kg/day). These tumours are a secondary effect reflective of a simvastatin-mediated enhancement of thyroid hormone clearance in the female rat. No other statistically significant increased incidence of tumour types was identified in any tissues in rats receiving simvastatin.

In both these studies there was squamous epithelial hyperplasia in the forestomach of the rodent at all doses. However, these changes are confined to the anatomical structure which is not present in man.

Results from a 73 week carcinogenicity study in mice receiving simvastatin of doses up to 400mg/kg/day (250 times the maximum recommended human dose based on a 50kg person) showed increased hepatocellular adenomas and carcinomas, pulmonary adenomas and Harderian gland adenomas. At 25mg/kg/day no effects were reported which is 15.5 times the maximum therapeutic dose in humans. In an additional 106 week study on rats there was increased incidence of lens opacities and hepatocellular neoplasms at doses 31 - 62.5 times higher than the maximum therapeutic dose in humans. There was also an increase in the thyroid hyperplastic lesions, however, these were consistent with findings that this is species specific response and have no implications in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Lactose Monohydrate
Microcrystalline cellulose
Pregelatinised starch
Butylated hydroxyanisole
Ascorbic acid
Anhydrous citric acid

Colloidal anhydrous silica
Talc
Magnesium Stearate

Film Coating
Hypromellose
Red Iron Oxide E172
Yellow Iron Oxide E172
Triethyl citrate
Titanium Dioxide E171
Talc
Povidone

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 30°C. Store in original package.

6.5 Nature and contents of container
PVC/PVDC/ Aluminum blister pack containing 28 tablets

6.6 Special precautions for disposal
No special instructions

7 MARKETING AUTHORISATION HOLDER
Rockspring Healthcare Limited
38/40 Chamberlayne Road,
London,
England,
NW10 3JE

8 MARKETING AUTHORISATION NUMBER(S)
PL18866/0050

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/03/2006

10 DATE OF REVISION OF THE TEXT
20/03/2006

SIMVASTATIN 10MG TABLETS
PL 18866/0050

PRODUCT INFORMATION LEAFLET

ROCKSPRING HEALTHCARE LTD.

Patient Information Leaflet

Please read this leaflet carefully before you start taking your medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Your medicine is called Simvastatin 10 mg, 20 mg and 40 mg Tablets referred to throughout the leaflet as Simvastatin.

- The active substance in this medicine is simvastatin which is available in 3 strengths. The peach coloured oval shaped film coated tablets with a scoreline on one side contain 10 mg simvastatin, the tan coloured oval film coated tablets contain 20mg simvastatin and the brick red coloured film coated tablets contain 40mg of simvastatin.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, pregelatinised starch, butylated hydroxyanisole (E320), ascorbic acid, anhydrous citric acid, colloidal anhydrous silica, talc, magnesium stearate, hypromellose, red iron oxide (E172), yellow iron oxide (E172), triethylcitrate, titanium dioxide (E171), povidone.
- The 10 mg tablets are supplied in blister packs of 28 tablets. The 20 mg tablets and 40 mg tablets are supplied in blister packs of 14 tablets. Two blister packs per carton.

Simvastatin is manufactured by Laboratorios Belmac S.A., Polígono Industrial Malpica calle C.4, 50016 – Zaragoza, Spain.

The Marketing Authorisation Holder is
Rockspring Healthcare Limited
38/40 Chamberlayne Road,
London,
England,
NW10 3JN

PL 18866/0050

1. WHAT SIMVASTATIN IS AND WHAT IT IS USED FOR

Simvastatin belong to a group of medicines called "HMG-CoA reductase inhibitors". These medicines work by reducing the amount of cholesterol and fatty substances, called triglycerides, in the blood. Cholesterol is vital for the body to function.

Sometimes cholesterol can build up in the blood stream and become deposited in the walls of the blood vessels. There it forms plaques which will eventually block the blood vessels similar to scale furring up of a water pipe.

Your doctor has done some blood tests, which shows that you have high amounts of cholesterol and fatty substances in your blood even though you have been following a low fat diet. Your doctor may have prescribed Simvastatin because you have a high risk of developing heart disease.

It is generally accepted that if you have high amounts of cholesterol in your blood it adds to your risk of heart disease. Other factors such as existing heart disease, high blood pressure, high blood sugar (diabetes), increased weight, lack of exercise, smoking and a diet high in fat increase your risk further to the development of heart disease.

Cholesterol may cause coronary heart disease by obstructing the blood vessels that carry oxygen and nutrients to the heart. This obstruction or hardening of arteries, is called atherosclerosis. Atherosclerosis may cause chest pain (called angina) and heart attack. If you suffer from coronary heart disease, your doctor has prescribed simvastatin to prolong your life. Simvastatin can decrease the risk of heart attack and decrease the risk of having to undergo surgery in order to increase blood flow to the heart. Simvastatin also delays the progression of atherosclerosis and reduces the development of new atherosclerosis.

2. BEFORE YOU TAKE SIMVASTATIN

Make sure it is safe for you to take Simvastatin.

Do not take Simvastatin:
- if you think you may be pregnant
- if you are planning to become pregnant. You should stop taking Simvastatin at least one month before trying to become pregnant
- if you discover you are pregnant while taking Simvastatin you should stop taking Simvastatin immediately
- if you are a woman who could bear children unless you are using a reliable form of contraception other than the pill (you may want to discuss this with your doctor)
- if you are breast feeding
- if you are hypersensitive (allergic) to any of the ingredients
- if you have active liver disease
- if you are taking mibefradil, a drug for the treatment of hypertension and angina
- if you have a rare inherited disease called porphyria

It is important to talk to your doctor if you have any other following conditions:
- persistent muscles aches or pains
- have a history of liver disease. Your doctor may want to do a simple blood test to check your liver is working properly before you take simvastatin.

Tell your doctor of your present and past medical problems, and any allergies you have.

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Simvastatin is not recommended for children.

Taking other medicines:
Please check with your doctor before taking Simvastatin if you are taking or have recently taken any other medicines even if not prescribed. Some medicines may occasionally interfere with Simvastatin including the following:

- immunosuppressants viz. ciclosporin
- antifungal agents (such as itraconazole or ketoconazole)
- other cholesterol lowering agents such as fibric acid derivatives (benzafibrate, phenofibrate and gemfibrozil)
- antibiotics erythromycin and clarithromycin
- the anti-depressant nefazodone
- high doses (> 1 g/day) of niacin (nicotinic acid)
- HIV protease inhibitors used in the treatment of HIV infections (indinavir, nelfinavir, ritonavir or saquinavir
- blood thinning agents such as warfarin
- digoxin used in the treatment of heart conditions
- amiodarone a drug used to treat an irregular heartbeat
- mibefradil, verapamil and diltiazem (drugs used to treat high blood pressure, angina or other heart conditions)

Taking Simvastatin with food and drink:
Grapefruit juice has one or more components that alter the metabolism of some medications including Simvastatin. Large volumes of grapefruit juice (more than 1 litre) may have adverse effects, however typical consumption (one 250 ml glass daily) is unlikely to cause problems. If you are unsure ask your doctor for advice.

Your doctor will have told you to keep alcohol to a minimum. If you are concerned about how much alcohol you can drink you should discuss this with your doctor.

Driving and using machines:
According to current information, Simvastatin does not affect the capacity to drive or use machines.

Important information about some of the ingredients of Simvastatin.
These tablets contains Lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE SIMVASTATIN

Your doctor will decide what is the right dose for you to take and how long you will need to continue taking the medicine. Check the label and if you're not sure ask your doctor or pharmacist.

Usual Dose:
The usual starting dose is 10 mg daily for high cholesterol levels and 20 mg daily for coronary heart disease, taken as a single dose in the evening. Your doctor may adjust the dose to a maximum daily dose of 80 mg, taken as a single dose in the evening. Your doctor may prescribe lower doses, especially if you are taking ciclosporin or suffer from certain kidney disorders. Continue taking Simvastatin until your doctor tells you to stop treatment.

Take your tablet whole with a glass of water.

Your doctor will inform you how long to take Simvastatin. If you stop taking Simvastatin your cholesterol levels may rise again.

While Taking Your Medicine

If you take more Simvastatin than you should:
Contact your doctor or pharmacist immediately or go to your nearest casualty department.

If you forget to take Simvastatin:
If you forget to take a tablet, wait until the next dose is due then continue as before. Do not take a double dose to make up for forgotten individual doses

4. POSSIBLE SIDE EFFECTS

Like all medicines, Simvastatin can have side effects in some people.

The most common side effects are stomach upsets (such as sickness, stomach pain, constipation, diarrhoea and flatulence), rash, itchiness, weakness, headache or indigestion. Other possible but less common side effects include dizziness, hair loss, abdominal pain, abnormal sensations in the arms and legs.

Rarely a few patients have experienced liver disease, muscle disease presenting as pains and aches or an allergic reaction which may include swelling of the face or neck, muscle and joint pains, joint and blood vessel inflammation, urticaria, a high temperature, flushing, difficulty in breathing or tiredness.

If you experience any of these side effects or you have any other unusual symptoms or feelings, stop taking the tablets and consult your doctor immediately.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING SIMVASTATIN

Keep out of the reach and sight of children
Store in the original package
Do not store above 30°C
Do not use after the expiry date stated on the carton.

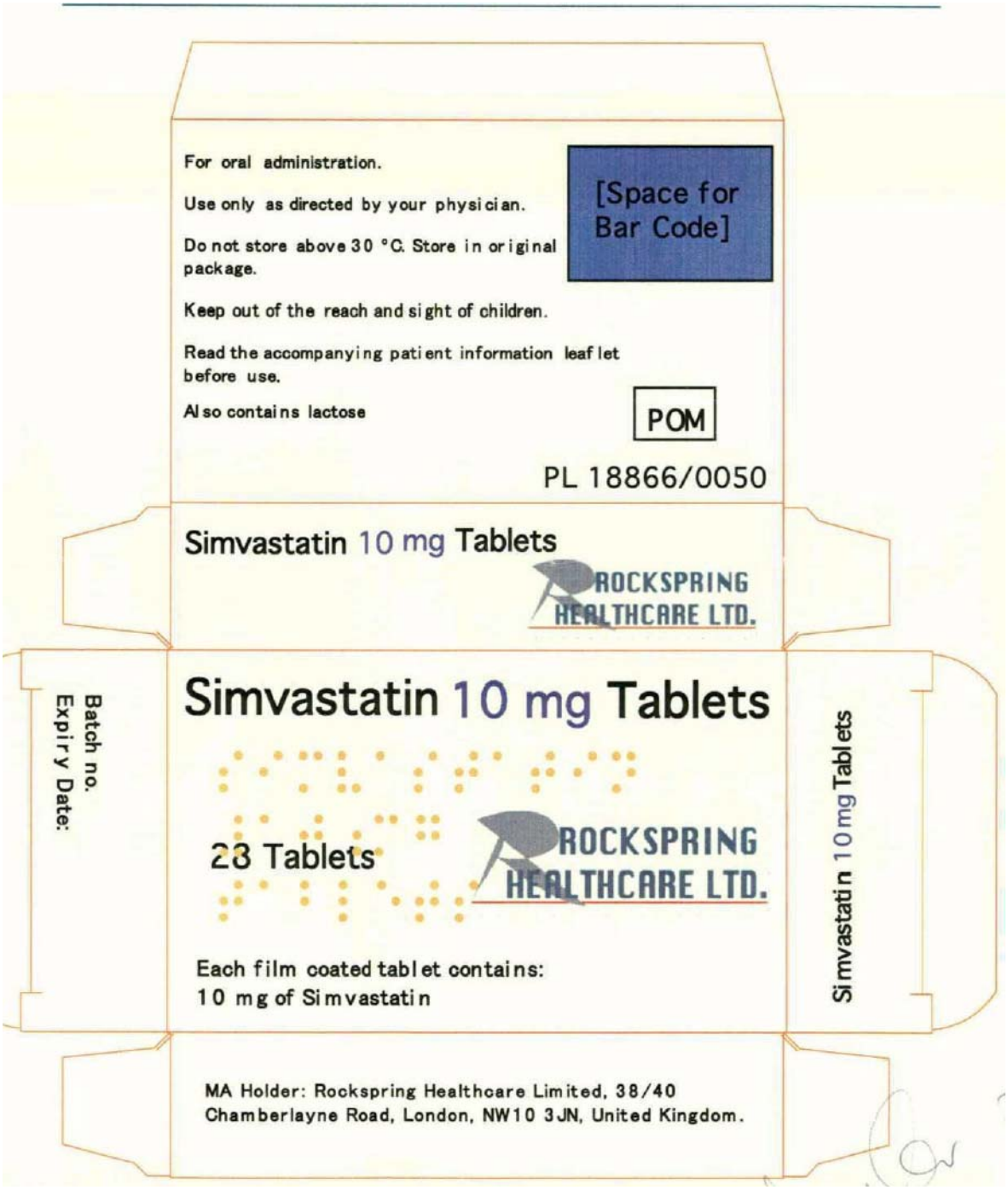
Any unused medicine should be returned to your doctor or pharmacist.

If you notice any visible signs of deterioration in the tablets, take them to your pharmacist for advice before taking it.

This leaflet was last updated in January 2006

SIMVASTATIN 10MG TABLETS
PL 18866/0050

LABELLING


For oral administration.
Use only as directed by your physician.
Do not store above 30 °C. Store in original package.
Keep out of the reach and sight of children.
Read the accompanying patient information leaflet before use.
Also contains lactose
[Space for Bar Code]
POM
PL 18866/0050
Simvastatin 10 mg Tablets
ROCKSPRING HEALTHCARE LTD.
Batch no.
Expiry Date:
Simvastatin 10 mg Tablets
28 Tablets
ROCKSPRING HEALTHCARE LTD.
Each film coated tablet contains:
10 mg of Simvastatin
Simvastatin 10 mg Tablets
MA Holder: Rockspring Healthcare Limited, 38/40 Chamberlayne Road, London, NW10 3JN, United Kingdom.