AUSTRALIAN PRODUCT INFORMATION - NOUMED SIMVASTATIN

(simvastatin film-coated tablets]

1. NAME OF THE MEDICINE

Simvastatin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet for oral administration contains either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin.

Excipients with known effect: sugars (as lactose monohydrate). For the full list of excipients, see **section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

NOUMED SIMVASTATIN 5mg film-coated tablets are yellow coated, oval, scored, convex tablets, coded 'SIM 5' on one side.

NOUMED SIMVASTATIN 10mg film-coated tablets are pale pink coated, oval, scored, convex tablets, coded 'SIM 10' on one side.

NOUMED SIMVASTATIN 20mg film-coated tablets are orange coated, oval, scored, convex tablets, coded 'SIM 20' on one side.

NOUMED SIMVASTATIN 40mg film-coated tablets are pink coated, oval, scored, convex tablets, coded 'SIM 40' on one side.

NOUMED SIMVASTATIN 80mg film-coated tablets are light green coated, oval, scored, convex tablets, coded 'SIM 80' on one side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Adjunct to diet for treatment of hypercholesterolaemia.

  Prior to initiating therapy with NOUMED SIMVASTATIN, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

- NOUMED SIMVASTATIN is indicated in patients at high risk of coronary heart disease (CHD) (with or without hypercholesterolaemia) including patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD to reduce the risk of cardiovascular death, major cardiovascular events including stroke, and hospitalisation due to angina pectoris.

  These effects do not replace the need to independently control known causes of cardiovascular mortality and morbidity such as hypertension, diabetes and smoking.

4.2 DOSE AND METHOD OF ADMINISTRATION

The dosage range for simvastatin is 10 to 80 mg/day, given as a single dose in the evening. Adjustments 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. The 80 mg dose of simvastatin should only be used in patients at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks (see **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***).

Patients at high risk of coronary heart disease (CHD) or with existing CHD

Adults: The usual starting dose of simvastatin is 40 mg/day given as a single dose in the evening in patients at high risk of CHD (with or without hypercholesterolaemia), i.e. patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD. Drug therapy can be initiated simultaneously with diet and exercise.

Hypercholesterolaemia and combined hyperlipidaemia (patients who are not in the risk categories above)

Adults: The patient should be placed on a standard cholesterol lowering diet before receiving NOUMED SIMVASTATIN and should continue on this diet during treatment with NOUMED SIMVASTATIN.

The recommended starting dose is 10 to 20 mg/day given in the evening. Therapy should be individualised according to the patient's response.

Concomitant therapy

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

In patients taking fibrates (except fenofibrate) concomitantly with NOUMED SIMVASTATIN, the dose of simvastatin should not exceed 10 mg/day.

In patients taking amiodarone, verapamil or diltiazem concomitantly with simvastatin, the dose of simvastatin should not exceed 20 mg/day.

In patients taking amlodipine concomitantly with simvastatin, the dose of simvastatin should not exceed 40 mg/day.

In patients taking niacin (nicotinic acid) ≥ 1g/day, the dose of simvastatin should not exceed 40 mg/day.

In patients taking lomitapide concomitantly with simvastatin, the dose of simvastatin should not exceed 40 mg/day.

See **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis*** and **section 4.5 Interactions with other medicines and other forms of interactions**.

Paediatric use

See **section 4.4 Special warnings and precautions for use**.

Use in the elderly

See **section 4.4 Special warnings and precautions for use**.

Dosage in renal insufficiency

Simvastatin does not undergo significant renal excretion. However, because no data is available in patients with impaired renal function, caution should be used in these patients.

In patients with severe renal insufficiency (creatinine clearance < 30 mL/minute), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

4.3 CONTRAINDICATIONS

- Hypersensitivity to any component of this preparation.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and lactation (see **section 4.4 Special warnings and precautions for use**). Women of childbearing potential, unless on an effective contraceptive and highly unlikely to conceive.
- Myopathy secondary to other lipid lowering agents.
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and drugs containing cobicistat (see **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis*** and **section 4.5 Interactions with other medicines and other forms of interactions**).
- Concomitant administration of gemfibrozil, ciclosporin or danazol (see **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis*** and **section 4.5 Interactions with other medicines and other forms of interactions**).
- Concomitant use with fusidic acid (see **section 4.4 Special warnings and precautions for use** and **section 4.5 Interactions with other medicines and other forms of interactions**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Myopathy / rhabdomyolysis

Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10x the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma (i.e., elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting drugs that interfere with simvastatin metabolism and/or transporter pathways (see **section 4.5 Interactions with other medicines and other forms of interactions**). Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

In the Scandinavian Simvastatin Survival Study [4S] (see **section 5.1 Pharmacodynamic properties: Clinical trials**), there was one case of myopathy among 1,399 patients taking simvastatin 20 mg/day and no cases among 822 patients taking 40 mg/day for a median duration of 5.4 years. In two six 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.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related for simvastatin. In a clinical trial database in which 41,413 patients were treated with simvastatin, 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a major, large, long-term clinical trial (SEARCH) in which patients with a history of myocardial infarction were treated with simvastatin 80 mg/day (mean follow up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. This includes rhabdomyolysis for which the incidence was 0.1 to 0.2%, all allocated to simvastatin 80 mg/day. There is no universally accepted definition of rhabdomyolysis. In SEARCH, rhabdomyolysis was defined as a subset of myopathy with CK > 40x ULN plus evidence of end organ damage (e.g. elevated creatinine, dark urine).

Approximately half of all the myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%.

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-base therapies with similar low density lipoprotein cholesterol (LDL-C) lowering efficacy. Therefore the 80 mg dose of simvastatin should only be used in patients at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. In patients taking simvastatin 80 mg for whom an interacting agent is needed, a lower dose of simvastatin or an alternative statin-based regimen with less potential for drug-drug interactions should be used (see **section 4.3 Contraindications** and **section 4.2 Dose and method of administration**).

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. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms and a CK level > 10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved (see **section 4.8 Adverse effects (Undesirable effects)**). Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 80 mg dose. There is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer 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.

An increased risk of myopathy in Chinese subjects has been identified. In a clinical trial in which patients at high risk of cardiovascular disease were treated with simvastatin 40 mg/day (median follow-up 3.9 years), the incidence of myopathy was approximately 0.05% for non-Chinese patients (n = 4 of 7367) compared with 0.24% for Chinese patients (n = 13 of 5468). While the only Asian population assessed in this clinical trial was Chinese, caution should be used when prescribing simvastatin to Asian patients and the lowest dose necessary should be employed.

The risk of myopathy/rhabdomyolysis is increased by concomitant use of simvastatin with the following medicines:

Contraindicated medicines

- ***Potent inhibitors of CYP3A4***: Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses (eg, itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone or drugs containing cobicistat) is contraindicated. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy. If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment (see **section 4.3 Contraindications** and **section 4.5 Interactions with other medicines and other forms of interactions**).
- ***Gemfibrozil, ciclosporin or danazol***: Concomitant use of these drugs with simvastatin is contraindicated (see **section 4.3 Contraindications**).
- ***Fusidic acid***: Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy/rhabdomyolysis (see **section 4.5 Interactions with other medicines and other forms of interactions**). Fusidic acid must not be co-administered with statins (see **section 4.3**

Contraindications). In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Simvastatin therapy may be re-introduced seven days after the last dose of fusidic acid.

Other medicines

- ***Amiodarone***: In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone.

  In the same clinical trial, there were no cases of myopathy reported in patients receiving simvastatin 20 mg and amiodarone (see **Table 1**). The dose of simvastatin should not exceed 20 mg daily in patient receiving concomitant medication with amiodarone (See **section 4.2 Dose and method of administration** and **section 4.5 Interactions with other medicines and other forms of interactions**).

- Calcium Channel Blockers

  Verapamil and diltiazem: The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem (see **Table 1**, **section 4.2 Dose and method of administration** and **section 4.5 Interactions with other medicines and other forms of interactions**).

  Co-administration of verapamil increased the incidence of myopathy to 0.7% (with simvastatin 40 mg) or 1% (with simvastatin 80 mg).

  Co-administration of diltiazem and simvastatin 80 mg led to a mean 70% increase in systemic exposure to simvastatin derived HMG-CoA reductase inhibitory activity, with individual increases ranging up to 200%. In a clinical trial, patients on diltiazem treated concomitantly with simvastatin 80 mg had an approximately 3-fold increased risk of myopathy.

  Amlodipine: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80mg had a slightly increased risk of myopathy. The risk of myopathy in patients taking simvastatin 40mg was not increased by concomitant amlodipine. The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine (see **Table 1**, **section 4.2 Dose and method of administration** and **section 4.5 Interactions with other medicines and other forms of interactions**).

- ***Lomitapide***: The dose of simvastatin should not exceed 40 mg daily in patients with homozygous familial hypercholesterolemia (HoFH) receiving concomitant medication with lomitapide (see **section 4.5 Interactions with other medicines and other forms of interactions**).

- ***Moderate inhibitors of CYP3A4***: Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy. When co-administering simvastatin with a moderate inhibitor of CYP3A4, a dose adjustment of simvastatin may be necessary.

- ***Other fibrates***: **The dose of simvastatin should not exceed 10mg daily in patients receiving concomitant medication with other fibrates (except fenofibrate)**. 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. Caution should be used when prescribing fenofibrate with simvastatin as either agent can cause myopathy when given alone. Addition of fibrates to simvastatin typically provides little additional reduction in LDL-C, but further reductions of triglycerides (TG) and further increases in high density lipoprotein cholesterol (HDL-C) may be obtained. Combinations of fibrates with simvastatin have been used without myopathy in small, short-term clinical studies with careful monitoring.

- ***Inhibitors of breast cancer resistance protein (BCRP)***: Concomitant administration of products that are inhibitors of BCRP (e.g. elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of simvastatin may be necessary (see **section 4.5 Interactions with other medicines and other forms of interactions**).
- ***Niacin (≥ 1 g/day)***: **The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥ 1g/day.** Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin. In a clinical trial (median follow-up 3.9 years) involving patients at high risk of cardiovascular disease and with well-controlled LDL-C levels on simvastatin 40 mg/day with or without ezetimibe 10 mg, there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses (≥ 1 g/day) of niacin. Therefore, the benefit of the combined used of simvastatin with niacin should be carefully weighed against the potential risks of the combination. In addition, in this trial, the incidence of myopathy was approximately 0.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 1.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg co-administered with extended-release niacin/laropiprant 2 g/40 mg. In comparison, in European/Non-Chinese patients the incidence of myopathy was approximately 0.05% for patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 0.09% for patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg co-administered with extended-release niacin/laropiprant 2 g/40 mg. **While the only Asian population assessed in this clinical trial was Chinese, because the incidence of myopathy is higher in Chinese than in European/Non-Chinese patients, coadministration of simvastatin with lipid-modifying doses (≥ 1 g/day) of niacin is not recommended in Asian patients.**
- ***Daptomycin***: Reports of myopathy and/or rhabdomyolysis have been observed with HMG-CoA reductase inhibitors co-administered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either agent can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to suspending simvastatin temporarily in patients taking daptomycin (see **section 4.5 Interactions with other medicines and other forms of interactions: Other drug interactions**).

Prescribing recommendations for interacting agents are summarised in **Table 1**, further details are provided in the text (see also **section 4.5 Interactions with other medicines and other forms of interactions** and **section 5. Pharmacological Properties**).

Table 1: Drug interactions associated with increased risk of myopathy / rhabdomyolysis

Interacting agents	Prescribing recommendations
Potent CYP3A4 inhibitors, e.g. Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone Cobicistat Gemfibrozil Ciclosporin Danazol Fusidic acid	CONTRAINDICATED with simvastatin

Interacting agents	Prescribing recommendations
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily
Niacin (≥ 1 g/day)	For Asian patients, not recommended with simvastatin For other patients, do not exceed 40 mg simvastatin daily
Amiodarone Verapamil Diltiazem	Do not exceed 20 mg simvastatin daily
Lomitapide	For patients with HoFH, do not exceed 40mg simvastatin daily
Amlodipine	Do not exceed 40 mg simvastatin daily
Daptomycin	Is not recommended with simvastatin
Grapefruit juice	Avoid grapefruit juice

Hepatic effects

In clinical studies, persistent increases (to more than three times the ULN) in serum transaminases have occurred in 1% of adult patients who received simvastatin. When the drug was interrupted or discontinued in these patients, transaminases usually fell slowly to pre-treatment concentrations. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. Some of these patients had abnormal liver function tests prior to therapy with simvastatin and/or consumed substantial quantities of alcohol.

In the 4S study (see **section 5.1 Pharmacodynamic properties: Clinical trials**), the number of patients with more than one ALT elevation of more than three times the ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 (0.7%) versus 12 (0.6%)). The incidence of ALT elevations in simvastatin subjects was greater than the incidence of AST elevations, and the number of subjects with at least one elevation of ALT greater than three times the ULN was 46 (2.2%) in the simvastatin group and 32 (1.4%) in the placebo group, the difference not being statistically significant. The frequency of single elevations of ALT to three times the ULN was significantly higher in the simvastatin group in the first year of the study (20 versus 8, p = 0.023), but not thereafter. Elevated transaminases resulted in the discontinuation of eight patients from therapy in the simvastatin group (n = 2,221) and five in the placebo group (n = 2,223). Of the 1,986 simvastatin treated patients in 4S with normal liver function tests at baseline, only eight (0.4%) developed consecutive liver function test elevations to greater than three times the ULN 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 simvastatin 20 mg; 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.

In the Heart Protection Study [HPS] (see **section 5.1 Pharmacodynamic properties: Clinical trials**), in which 20,536 patients were randomised to receive simvastatin 40mg/day or placebo, the incidences of elevated transaminases (greater than three times the ULN confirmed by repeat test) were 0.21% (n = 21) for patients treated with simvastatin and 0.09% (n = 9) for patients treated with placebo.

Liver function tests should be performed before the initiation of treatment and thereafter when clinically indicated. Patients titrated to the 80 mg dose should receive an additional test at three months. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***).

There have been rare post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or

jaundice occurs during treatment with simvastatin, promptly interrupt therapy. If an alternate aetiology is not found do not restart simvastatin.

Patients who develop increased transaminase levels should have the finding confirmed and be followed up thereafter with frequent liver function tests until any abnormality(ies) return to normal. Should an increase in AST or ALT of three times the ULN persist, withdrawal of simvastatin therapy is recommended. Liver biopsy should be considered if elevations persist despite discontinuation of the drug. Unconfirmed reports of drug induced hepatitis have been reported with 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. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid lowering agents, moderate (less than three times the ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes were not specific to simvastatin and were also observed with comparable lipid lowering agents. They generally appeared within the first three months after initiation of therapy with simvastatin, were often transient and were not accompanied by any symptoms, and interruption of treatment was not required.

Diabetes mellitus

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

Immune mediated necrotizing myopathy

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

Interstitial lung disease

Cases of interstitial lung disease have been reported with some statins, including simvastatin especially with long term therapy (see **section 4.8 Adverse effects (Undesirable effects)**). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Reduced function of transport proteins

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

Patients carrying the SLCO1B1 gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin and increased risk of myopathy. Where available, genotyping for the presence of the C allele should be considered as part of the benefit-risk assessment prior to prescribing 80 mg simvastatin for individual patients and high doses avoided in those found to carry the CC genotype. However, absence of this gene upon genotyping does not exclude that myopathy can still occur.

Ophthalmological evaluations

Current long-term data from clinical trials, e.g. 4S, do not indicate an adverse effect of simvastatin on the human lens. However, the very long-term effects are not yet established and therefore periodic ophthalmological examinations are recommended after five years of treatment, taking into consideration that in the absence of any drug therapy, an increase in the prevalence of lens opacities with time is expected as a result of ageing.

Animal studies

Cataracts have been detected in two year studies in rats and dogs at dose levels greater than 25 and 10 mg/kg/day, respectively, 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.

Serum levels (expressed as total inhibitors) in rats at the no effect dose level were three to eleven times higher than those in humans receiving the maximum daily dose of 80 mg, whereas serum levels at the no effect level in dogs were approximately two-fold higher than those in humans receiving the maximum daily dose of 80 mg.

Thyroid function

The concentration of serum thyroxine has been measured at baseline and at the end of simvastatin treatment in 785 patients enrolled in multicentre studies. The results of this analysis indicate that simvastatin has little, if any, effect upon thyroxine activity.

In one study involving 183 patients treated with simvastatin, four patients had thyroid stimulating hormone (TSH) levels within the normal range before commencing simvastatin, but had an elevated TSH after two years of simvastatin therapy.

Transient hypotension

Three cases of symptomatic hypotension in the first few days following the start of simvastatin therapy have been reported. Two of the patients were on antihypertensive medication. The hypotension resolved with continued therapy with simvastatin.

Neurological effects

The neurological adverse effects reported to date include cases of peripheral neuropathy and paraesthesia possibly due to simvastatin.

Use in the elderly

In controlled clinical trials, the efficacy of simvastatin for patients over the age of 65 years, as assessed by reduction in total cholesterol and LDL-C levels, was similar to that seen in the population as a whole. There was no apparent increase in the frequency of clinical or laboratory adverse findings.

However, in a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥ 65 years of age had an increased risk of myopathy compared to patients < 65 years of age.

Paediatric use

No data available.

Effects on laboratory tests

See **section 4.8 Adverse effects (Undesirable effects): Effects on laboratory tests**.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Multiple mechanisms may contribute to potential interactions with HMG-CoA reductase inhibitors. Drugs or herbal products that inhibit certain enzymes (e.g. CYP3A4) and/or transporter (e.g. OATP1B) pathways may increase simvastatin and simvastatin acid plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

Consult the prescribing information of all concomitantly used drugs to obtain further information about their potential interactions with simvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

CYP3A4 interactions: Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolised by CYP3A4.

Contraindicated medicines

Concomitant use of the following medicines is contraindicated:

- ***Potent inhibitors of CYP3A4***: Potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of simvastatin.

  Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, drugs containing cobicistat) is contraindicated (see **section 4.3 Contraindications**, **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis*** and **section 5.2 Pharmacokinetic properties**).

  Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite).

- ***Gemfibrozil, ciclosporin or danazol***: (see **section 4.3 Contraindications** and **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***).

- ***Fusidic acid***: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of simvastatin with fusidic acid. Coadministration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown.

  Although interaction studies with statins and fusidic acid have not been conducted, there have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, statin treatment should be discontinued throughout the duration of the fusidic acid treatment (see **section 4.3 Contraindications** and **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***).

Other drug interactions

- ***Amiodarone***: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with simvastatin (see **section 4.2 Dose and method of administration** and **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***).

- ***Calcium Channel Blockers***: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine (see **section 4.2 Dose and method of administration** and **section 4.4 Special warnings and precautions for use: *Myopathy/ rhabdomyolysis***).

- ***Lomitapide***: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide (see **section 4.2 Dose and method of administration** and **section 4.4 Special warnings and precautions for use: *Myopathy/ rhabdomyolysis***).

- ***Moderate inhibitors of CYP3A4***: Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy. (see **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***).
- ***Inhibitors of the Transport Protein OATP1B1***: Simvastatin acid is a substrate of the transport protein OATP1B1. Concomitant administration of medicinal products that are inhibitors of the transport protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and an increased risk of myopathy (see **section 4.3 Contraindications** and **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***).
- ***Inhibitors of breast cancer resistance protein (BCRP)***: Simvastatin is a substrate of the efflux transporter BCRP. Concomitant administration of products that are inhibitors of BCRP (e.g. elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy. When co-administering simvastatin with an inhibitor of BCRP, a dose adjustment of simvastatin may be necessary (see **section 4.2 Dose and method of administration** and **section 4.4 Special warnings and precautions for use: *Myopathy/ rhabdomyolysis***).
- ***Niacin (nicotinic acid) (≥ 1 g/day)***: Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (see **section 4.4 Special warnings and precautions for use: *Myopathy/ rhabdomyolysis***).
- ***Colchicine***: There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal insufficiency. Close clinical monitoring of patients taking this combination is advised.
- ***Daptomycin***: The risk of myopathy and/or rhabdomyolysis may be increased by coadministration of HMG-CoA reductase inhibitors and daptomycin (see **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***).
- ***Other fibrates***: The risk of myopathy is increased by gemfibrozil (see **section 4.3 Contraindications**) and other fibrates (except fenofibrate); these lipid-lowering drugs can cause myopathy when given alone. 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 (see **section 4.3 Contraindications** and **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***).
- ***Grapefruit juice***: Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of drugs metabolised by CYP3A4. The effect of typical consumption (one 250 mL glass daily) is minimal (13% increase in active plasma HMG CoA reductase inhibitory activity as measured by the area under the concentration time curve) and of no clinical relevance. However, because larger quantities significantly increase the plasma levels of HMG CoA reductase inhibitory activity, grapefruit juice should be avoided during simvastatin therapy (see **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***).
- ***Coumarin derivatives***: In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20 to 40 mg/day modestly potentiated the effect of warfarin. 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 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.

- ***Propranolol***: In normal volunteers, concomitant administration of single doses of simvastatin with propranolol produced no clinically significant pharmacokinetic or pharmacodynamic interaction.
- ***Antipyrine***: Simvastatin had no effect on the pharmacokinetics of antipyrine. However, since simvastatin is metabolised by the CYP3A4, this does not preclude an interaction with other drugs metabolised by the same isoform.
- ***Digoxin***: Concomitant administration of simvastatin and digoxin in normal volunteers resulted in a slight elevation (less than 0.3 nanogram/mL) in plasma drug concentrations (as measured by a digoxin radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.
- ***Other concomitant therapy***: In clinical studies, simvastatin was used concomitantly with beta-blockers, diuretics and nonsteroidal anti-inflammatory drugs without evidence of clinically significant adverse interactions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Effects on spermatogenesis and testosterone

In several studies of over 800 men with hypercholesterolaemia treated with simvastatin 20 to 80 mg/day for 12 to 48 weeks, basal testosterone levels were mildly decreased during simvastatin therapy, but there were no consistent changes in luteinising hormone and follicle stimulating hormone. In 86 men treated with simvastatin 20 to 80 mg/day, there was no impairment of hCG-stimulated testosterone secretion.

Testicular degeneration has been seen in two dog safety studies with simvastatin. Special studies designed to further define the nature of these changes have not met with success since the effects are poorly reproducible and unrelated to dose, serum cholesterol levels or duration of treatment. Simvastatin has been administered for up to two years to dogs at a dose of 50 mg/kg/day without any testicular effects.

Fertility of male and female rats was unaffected at oral doses up to 25 mg/kg/day.

Use in pregnancy

Category D[1]

HMG-CoA reductase inhibitors, including simvastatin, are contraindicated during pregnancy. The risk of foetal injury outweighs the benefits of HMG-CoA reductase inhibitor therapy during pregnancy.

Atherosclerosis is a chronic process and the discontinuation of lipid lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolaemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for foetal development, including synthesis of steroids and cell membranes.

In two series of 178 and 134 cases where pregnant women took a HMG-CoA reductase inhibitor (statin) during the first trimester of pregnancy, serious foetal abnormalities occurred in several cases. These included limb and neurological defects, spontaneous abortions and foetal deaths. The exact risk of injury to the foetus occurring after a pregnant women is exposed to a HMG-CoA reductase inhibitor has not been determined. The current data do not indicate that the risk of foetal injury in women exposed to HMG-CoA reductase inhibitors is high. If a pregnant woman is exposed to a HMG-CoA reductase inhibitor,

[1] Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

she should be informed of the possibility of foetal injury and discuss the implications with her pregnancy specialist.

Because of the ability of inhibitors of HMG-CoA reductase such as simvastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, simvastatin is contraindicated during pregnancy. Simvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, simvastatin should be discontinued and the patient informed of the potential hazard to the foetus.

Animal studies showed increased incidences of foetal resorption at dosages of 50 mg/kg/day in rats and 15 mg/kg/day in rabbits. In another study, an increased incidence of skeletal malformations was observed in foetuses of rats dosed with the active metabolite of simvastatin, L-654,969, at a dose level of 60 mg/kg/day. The no effect dose level of this teratogenic activity has not been established. Other inhibitors of HMG-CoA reductase have also been shown to induce skeletal malformations in rats, and the teratogenic effects may be due to the enzyme inhibitory activity of such drugs. The relevance of these findings to humans is not known.

Use in lactation

Animal studies have shown that weight gain during lactation is reduced in the offspring of rats dosed with simvastatin at dosages of 12.5 to 25 mg/kg/day. There is no information from animal studies on whether simvastatin or its metabolites are excreted in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions, women taking NOUMED SIMVASTATIN should not breastfeed their infants (see **section 4.3 Contraindications**).

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

The clinical adverse events occurring at an incidence of greater than 0.5% in controlled clinical trials and considered to be definitely, probably or possibly due to simvastatin may be grouped as shown in **Table 2**.

Table 2: Clinical adverse events definitely, probably or possibly due to simvastatin therapy occurring with an incidence > 0.5% in controlled clinical trials

Adverse events	Simvastatin tablets % (N=2423)	Placebo % (N=167)
Body as a whole		
Abdominal pain	2.5	0.6
Asthenia	0.9	0.6
Gastrointestinal		
Constipation	2.5	1.2
Flatulence	2.0	0.6
Nausea	1.2	0.6
Acid regurgitation	0.6	0
Diarrhoea	0.8	0

Adverse events	Simvastatin tablets % (N=2423)	Placebo % (N=167)
Dyspepsia	0.7	0
Nervous system		
Headache	1.0	1.2
Insomnia	0.5	0
Dermatological		
Rash	0.7	0

Myopathy has been reported rarely.

In HPS (see **section 5.1 Pharmacodynamic properties: Clinical trials**) involving 20,536 patients treated with simvastatin 40 mg/day (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with simvastatin and patients treated with placebo over the mean 5.3 years of the study. In this trial, only serious adverse effects and discontinuations due to any adverse effects were recorded. Discontinuation rates due to side effects were comparable (4.2% in patients treated with simvastatin compared with 4.3% in patients treated with placebo). The incidence of myopathy was 0.07% in patients treated with simvastatin compared with 0.03% in patients treated with placebo. This includes rhabdomyolysis for which incidences were 0.04% in patients treated with simvastatin compared with 0.01% in patients treated with placebo. Some of these patients were taking simvastatin concomitantly with medications which are known to increase the risk of myopathy (see **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***). Elevated transaminases (greater than three times the ULN confirmed by repeat test) occurred in 0.21% of patients treated with simvastatin compared with 0.09% of patients treated with placebo.

In 4S (see **section 5.1 Pharmacodynamic properties: Clinical trials**) involving 4,444 patients treated with simvastatin tablets 20 to 40 mg/day (n = 2,221) or placebo (n = 2,223), the safety and tolerability profiles were comparable between treatment groups over the median 5.4 years of the study.

The following rare (≥ 1/10,000, < 1/1000) or very rare (< 1/10,000) adverse events were reported in patients taking simvastatin:

Eye disorders

Rare: vision blurred, visual impairment

Skin and subcutaneous tissue disorders

Very rare: lichenoid drug eruptions

Musculoskeletal and connective tissue disorders

Very rare: muscle rupture

Reproductive system and breast disorders

Very rare: gynaecomastia

The following additional adverse effects were reported either in uncontrolled clinical trials or in marketed use: nightmare, memory loss, sexual dysfunction occurred uncommonly. Pruritus, alopecia, dizziness, muscle cramps, myalgia, depression, pancreatitis, paraesthesia, peripheral neuropathy, peripheral polyneuropathy, memory impairment, insomnia, vomiting, gynaecomastia, anaemia, interstitial lung disease and hepatic failure occurred very rarely.

There have been very rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterised by: persistent proximal muscle weakness

and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents (see **section 4.4 Special warnings and precautions for use: *Myopathy/ rhabdomyolysis***).

Rhabdomyolysis with or without acute renal failure, hepatitis/jaundice, myositis and polymyositis occurred rarely. Non-fatal hepatic failure occurred very rarely. An apparent hypersensitivity syndrome that included some of the following features has been reported rarely: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, increased erythrocyte sedimentation rate (ESR), arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Diabetes mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30 kg/m^2, raised triglycerides, history of hypertension (see **section 4.4 Special warnings and precautions for use**).

Effects on laboratory tests

Marked and persistent increases of serum transaminases have been reported infrequently. Elevated alkaline phosphatase and gamma-glutamyl transpeptidase have been reported. Liver function test abnormalities have generally been mild and transient. Increases in serum creatine kinase (CK) levels derived from skeletal muscle have been reported (see **section 4.4 Special warnings and precautions for use: *Hepatic effects***).

Increases in HBA1c and fasting serum glucose levels have been reported with statins, including simvastatin tablet.

Adverse effects – causal relationship unknown

The following adverse effects have been reported, however a causal relationship to therapy with simvastatin has not been established: erythema multiforme including Stevens-Johnson syndrome, leucopoenia, impotence, proteinuria and purpura.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Symptoms

A few cases of overdosage have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

Treatment

General measures should be adopted, and liver function should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The involvement of LDL-C in atherogenesis has been well documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that high LDL-C and low HDL-C are both risk factors for coronary heart disease (CHD).

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed to the corresponding beta-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme which catalyses an early and rate limiting step in the biosynthesis of cholesterol. As a result, in clinical studies simvastatin reduced total plasma cholesterol (total-C), LDL-C and very low density lipoprotein cholesterol (VLDL-C) concentrations. In addition, simvastatin increases HDL-C and reduces plasma triglycerides (TG).

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from 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-C concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B (Apo B) also falls substantially during treatment with simvastatin. Since each LDL particle contains one molecule of Apo B, and since little Apo B is found in other lipoproteins, this strongly suggests that simvastatin does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. As a result of these changes the ratios of total-C to HDL-C and LDL-C to HDL-C are reduced.

Even though simvastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyses the conversion of HMG-CoA to mevalonate is not completely blocked at therapeutic doses, therefore it allows the necessary amounts of mevalonate to be available for biological functions. 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.

Clinical trials

Simvastatin tablets have been studied in the treatment of primary hypercholesterolaemia where diet alone has been insufficient. Simvastatin was highly effective in reducing total-C and LDL-C in heterozygous familial (Fredrickson type IIa) and nonfamilial forms of hypercholesterolaemia, and in mixed hyperlipidaemia (Fredrickson type IIb) when elevated cholesterol was a cause of concern. A marked response was seen within two weeks and the maximum therapeutic response occurred within four to six weeks. The response has been maintained during continuation of therapy. In six controlled clinical studies involving approximately 1,700 patients with normal or slightly raised TGs (mean 1.9 mmol/L), plasma TGs, VLDL-C and Apo B decreased in all studies in a dose dependent manner. In two of these studies in patients with hypercholesterolaemia receiving simvastatin tablets 20 or 40mg daily for twelve weeks, the results reported in **Table 3** were observed.

Table 3: Effect of simvastatin in patients with hypercholesterolaemia

	Mean baseline	Mean change (% in each of 2 studies)	
		20 mg once daily (n=166)	40 mg once daily (n=161)
Total cholesterol (total-C)	8.3 mmol/L	-27: -27	-30: -33
LDL-C	6.4 mmol/L	-32: -34	-40: -41

HDL-C	1.2 mmol/L	+10: +10	+10: +13
Triglycerides (TG)	1.9 mmol/L	-13: -17	-19: -27
VLDL-C	0.8 mmol/L	-8 (n=84)*	-28 (n=81)*
Apolipoprotein B (Apo B)	2,000 mg/L	-28: -33	-36: -38

** only measured in one study*

In a separate study involving 180 patients with combined hyperlipidaemia, simvastatin tablets 10 mg daily for 17 weeks was also shown to be effective in lowering total-C, LDL-C, VLDL-C, TGs and Apo B (see **Table 4**).

Table 4: Effect of simvastatin in patients with combined hyperlipidaemia

	Mean baseline	Mean change (%) 10 mg once daily (n=56)
Total cholesterol (total-C)	7.0 mmol/L	-23
LDL-C	4.5 mmol/L	-27
HDL-C	1.0 mmol/L	+13
Triglycerides (TG)[1]	2.6 mmol/L	-26
VLDL-C	1.3 mmol/L	-28
Apolipoprotein B (Apo B)	1,710 mg/L	-21

[1] *median*

The data from these studies demonstrate that in patients with hypercholesterolaemia and normal or slightly raised TGs, simvastatin consistently reduce total-C, LDL-C, TGs, VLDL-C and Apo B in a dose dependent manner.

The results of four separate studies depicting the dose response to simvastatin in patients with primary hypercholesterolaemia are presented in **Table 5**.

Table 5: Dose response in patients with primary hypercholesterolaemia (mean percent change from baseline after 6 to 24 weeks)

Treatment	No. of patients	Total-C	LDL-C	HDL-C	TG*
Lower dose comparative study					
Simvastatin tablets 5 mg**	109	-19	-26	10	-12
Simvastatin tablets 10 mg**	110	-23	-30	12	-15
Scandinavian simvastatin survival study (4S)					
Placebo	2223	-1	-1	0	-2
Simvastatin tablets 20 mg**	2221	-28	-38	8	-19
Upper dose comparative study					
Simvastatin tablets 40 mg**	433	-31	-41	9	-18
Simvastatin tablets 80 mg**	664	-36	-47	8	-24
Multicentre combined hyperlipidaemia study					
Placebo	122 †	1	2	3	-4
Simvastatin tablets 40 mg**	122	-25	-29	13	-28
Simvastatin tablets 80 mg**	123 †	-31	-36	16	-33

* *Median percent change*

** *In the evening*

† *except LDL-C where n=121*

In the upper dose comparative study, one-third of patients obtained a reduction in LDL-C of 53% or more at the 80mg dose. The percent reduction in LDL-C was essentially independent of the baseline level. In contrast, the percent reduction in TG was related to the baseline level of TG. Of the 664 patients randomised to 80 mg, 475 patients with plasma TG less than or equal to 2.25 mmol/L had a median reduction in TG of 21%, while in 189 patients with hypertriglyceridaemia (> 2.25 mmol/L), the median reduction in TG was 36%. In these studies, patients with TG > 4.0 mmol/L were excluded.

In a controlled clinical study, twelve patients 15 to 39 years of age with homozygous familial hypercholesterolaemia received simvastatin 40 mg/day in a single dose or in three divided doses, or 80 mg/day in three divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. The mean LDL-C reductions for the 40 mg and 80 mg doses were 14 and 25%, respectively. One of the twelve patients in this study had complete absence of LDL receptor function (receptor 'deficient'). In this patient, LDL-C reduction of 41% occurred with the 80 mg dose. The magnitude of response to therapy with simvastatin was not predictable by the LDL-receptor gene defects as patients with some LDL-receptor mutations responded differently to the same dose of simvastatin therapy. Five of the twelve patients were also receiving probucol.

The value of drug and/or diet induced reduction in plasma cholesterol is no longer controversial. The benefits of reducing LDL-C on morbidity and mortality due to coronary heart disease (CHD) have been established. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) demonstrated in a seven-year, double blind, placebo-controlled study that lowering LDL-C with diet and cholestyramine decreased the combined incidence of CHD death plus nonfatal myocardial infarction (MI).

In a randomised, double blind, three period crossover study, 130 patients with combined hyperlipidaemia (LDL-C > 3.4 mmol/L and TG 3.4 to 7.9 mmol/L) were treated with placebo, simvastatin 40 and 80 mg/day for six weeks. In a dose dependent manner simvastatin 40 and 80 mg/day, respectively, decreased mean LDL-C by 29 and 36% (placebo 2%) and median TG levels by 28 and 33% (placebo 4%), and increased mean HDL-C by 13 and 16% (placebo 3%) and apolipoprotein A-1 by 8 and 11% (placebo 4%).

In the Scandinavian Simvastatin Survival Study (4S), simvastatin reduced the risk of death, coronary death, nonfatal MI and undergoing myocardial revascularisation procedures (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty) in patients with CHD and hypercholesterolaemia.

In 4S, the effect of therapy with simvastatin on total mortality was assessed in 4,444 patients with CHD and a baseline total cholesterol of 5.5 to 8.0 mmol/L. In this multicentre, randomised, double blind, placebo-controlled study, patients with angina or a previous MI were treated with diet and standard care and either with simvastatin 20 to 40 mg daily (n = 2,221) or placebo (n = 2,223) for a median duration of 5.4 years. 82% of the subjects were male. Over the course of the study, treatment with simvastatin led to mean reductions in total-C, LDL-C and TGs of 25, 35 and 10% respectively, and a mean increase in HDL-C of 8%. Simvastatin reduced the risk of death by 30% (95% confidence interval 15 to 42%; p = 0.0003 (182 deaths in the simvastatin group versus 256 deaths in the placebo group)). The risk of CHD death was reduced by 42% [95% confidence interval 27 to 54%; p = 0.00001 (111 versus 189)]. Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital verified and silent nonfatal MI) by 34% (95% confidence interval 25 to 41%; p < 0.00001 (431 patients versus 622 patients with one or more events)]. The risk of having a hospital verified nonfatal MI was reduced by 37%. Simvastatin reduced the risk for undergoing myocardial revascularisation procedures [coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (95% confidence interval 26 to 46%; p < 0.00001 (252 patients versus 383 patients)].

Furthermore, simvastatin significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischaemic attacks) by 28% [95% confidence interval 3 to 46% (p = 0.033, 75 patients versus 102 patients)]. There was no statistically significant difference between groups in non-

cardiovascular mortality. Simvastatin reduced the risk of major coronary events to a similar extent across the range of baseline total-C and LDL-C levels.

The risk of death in patients greater than or equal to 60 years of age was decreased by 27% and in patients < 60 years of age by 37% (95% confidence interval 12 to 55%; $p < 0.01$ in both age groups). Because there were only 53 female deaths, the effect of simvastatin on mortality in women could not be adequately assessed. However, simvastatin lessened the risk of having major coronary events by 34% (95% confidence interval 9 to 52%; $p = 0.012$ (60 versus 91 women with one or more event)). In a post hoc analysis in patients with diabetes mellitus and CHD, the risk of major coronary events was reduced by 55% (95% confidence interval 24 to 73%; $p = 0.002$ (24 patients versus 44 patients)). Since there were only 39 deaths among diabetic patients (15 among simvastatin treated patients and 24 among placebo treated patients), the effect of simvastatin on mortality in diabetic patients could not be adequately assessed. It should be noted that 4S excluded patients with triglycerides > 2.5 mmol/L or with severe cardiac or renal disease.

In the Multicenter Anti-Atheroma Study (MAAS), the effect of therapy with simvastatin on coronary atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolaemic men and women with coronary heart disease. In this randomised, double blind, controlled clinical trial, 404 patients with total-C values of 5.5 to 8.0 mmol/L and a mean baseline LDL-C value of 4.4 mmol/L were treated with conventional measures and with simvastatin 20 mg/day or placebo. 89% of the subjects were male. Angiograms were evaluated at baseline, two and four years. A total of 347 patients had a baseline angiogram and at least one follow-up angiogram. In the patients who received placebo, coronary atherosclerotic lesions worsened in a near linear manner.

In contrast, simvastatin significantly slowed the progression of lesions as measured in the final angiogram by the mean change per patient in minimum ($p = 0.005$) and mean ($p = 0.026$) lumen diameters (co-primary endpoints, indicating focal and diffuse disease, respectively), as well as in percent diameter stenosis ($p = 0.003$). Simvastatin also significantly decreased the proportion of patients with new lesions (13% simvastatin versus 24% placebo, $p = 0.009$) and with new total occlusions (5 versus 11%, $p = 0.04$). In interpreting these results, it is important to be aware of the limitations of angiography, which may underestimate the extent and severity of atherosclerosis. In addition, angiography cannot be used to predict the site of future coronary occlusion. Acute ischaemic events tend to occur not at the site of severe stenoses but at lesser stenoses which are lipid rich, soft and more prone to rupture.

In MAAS, simvastatin slowed the progression of coronary atherosclerosis and reduced the development of both new lesions and new total occlusions, whereas coronary atherosclerotic lesions steadily worsened over four years in patients receiving standard care.

High risk of coronary heart disease (CHD) or existing coronary heart disease

The Heart Protection Study (HPS) was a large, multicenter, randomised, placebo controlled, double blind study with a mean duration of 5.3 years conducted in 20,536 patients (10,269 on simvastatin 40 mg and 10,267 on placebo). Patients were 40 to 80 years of age and at high risk of developing a major coronary event based on three main categories of past medical history:

1. *Coronary disease* [definite or probable clinical diagnosis of myocardial infarction (MI), unstable angina, stable angina, percutaneous transluminal coronary arterioplasty (PTCA) or coronary artery bypass graft (CABG)];
2. *Occlusive disease of non-coronary arteries* (clinical, angiographic or ultrasound diagnosis of carotid artery stenosis (e.g. transient ischaemic attack (TIA) or nondisabling stroke not thought to be haemorrhagic), carotid endarterectomy, leg artery stenosis (eg intermittent claudication) or surgery;
3. *Diabetes mellitus* (clinical diagnosis of insulin dependent or maturity onset diabetes).

LDL-C levels were assayed using a direct method and collected without regard for meals (results are about 5% lower than fasting sample). At baseline, 3,421 patients (17%) had LDL-C levels below 2.6 mmol/L; 7,068 patients (34%) had levels greater than 2.6 mmol/mL and less than 3.4 mmol/L; and 10,047 patients (49%) had levels greater than or equal to 3.4 mmol/L. At baseline, 2,030 (19.8%) patients in the simvastatin group and 2,042 (19.9%) in the placebo group had total-C less than 5.0 mmol/L; 3,942 (38.4%) patients in the simvastatin group and 3,941 (38.4%) in the placebo group had levels greater than or equal to 5.0 mmol/L and less than 6.0 mmol/L; and 4,297 (41.8%) patients in the simvastatin group and 4,284 (41.7%) in the placebo group had levels greater than or equal to 6.0 mmol/L.

The major cardiovascular events prevented were non-fatal myocardial infarction, CHD death, stroke and revascularisation procedures. The HPS results showed that simvastatin 40 mg/day significantly reduced: total and CHD mortality (with no evidence of any increase in non-CHD mortality); major coronary events (a composite endpoint comprised of non-fatal MI or CHD deaths); stroke; coronary revascularisation procedures; hospitalisation for angina; and major vascular events, a composite endpoint which was comprised of major coronary events, stroke or revascularisation procedures (see **Table 6**). Risk reductions of approximately one quarter were observed for major vascular events, major coronary events and stroke. These risk reductions are underestimates due to the fact that 33% of the patients in the intention to treat analysis did not comply with the study protocol (i.e. patients allocated placebo took a statin, or patients allocated simvastatin did not take the study drug). Thus, by five years, simvastatin taken consistently would be expected to reduce the risk of these events by about one-third.

Table 6: Summary of risk reductions in HPS

Endpoint	Simvastatin (n=10,269) n (%)	Placebo (n=10,267) n (%)	Absolute risk reduction [1] % (95% CI)	Relative risk reduction % (95% CI)	p-value
Primary					
Mortality	1,328 (12.9%)	1,504 (14.6%)	1.7 (0.8 to 2.7)	12 (6 to 19)	p < 0.001
CHD mortality	571 (5.6%)	689 (6.7%)	1.2 (0.5 to 1.8)	18 (8 to 26)	p < 0.001
Non-CHD mortality	757 (7.4%)	815 (7.9%)	0.6 (-0.2 to 1.3)	8 (-2 to 17)	NS
Secondary					
Major vascular events [2,3]	2,026 (19.7%)	2,575 (25.1%)	5.4 (4.2 to 6.5)	24 (19 to 28)	p < 0.00001
Major coronary events [2,4]	892 (8.7%)	1,205 (11.7%)	3.1 (2.2 to 3.9)	27 (21 to 33)	p < 0.00001
Stroke	448 (4.4%)	588 (5.7%)	1.4 (0.8 to 2.0)	25 (15 to 33)	p < 0.00001
Key tertiary					
Coronary revascularisation	511 (5.0%)	729 (7.1%)	2.1 (1.5 to 2.8)	31 (23 to 38)	p < 0.00001
Hospitalisation for angina	1,036 (10.1%)	1,221 (11.9%)	1.8 (0.9 to 2.7)	17 (9 to 23)	p < 0.0001

[1] *based on difference in crude event rates*

[2] *see **Figure 1** (results by baseline characteristics)*

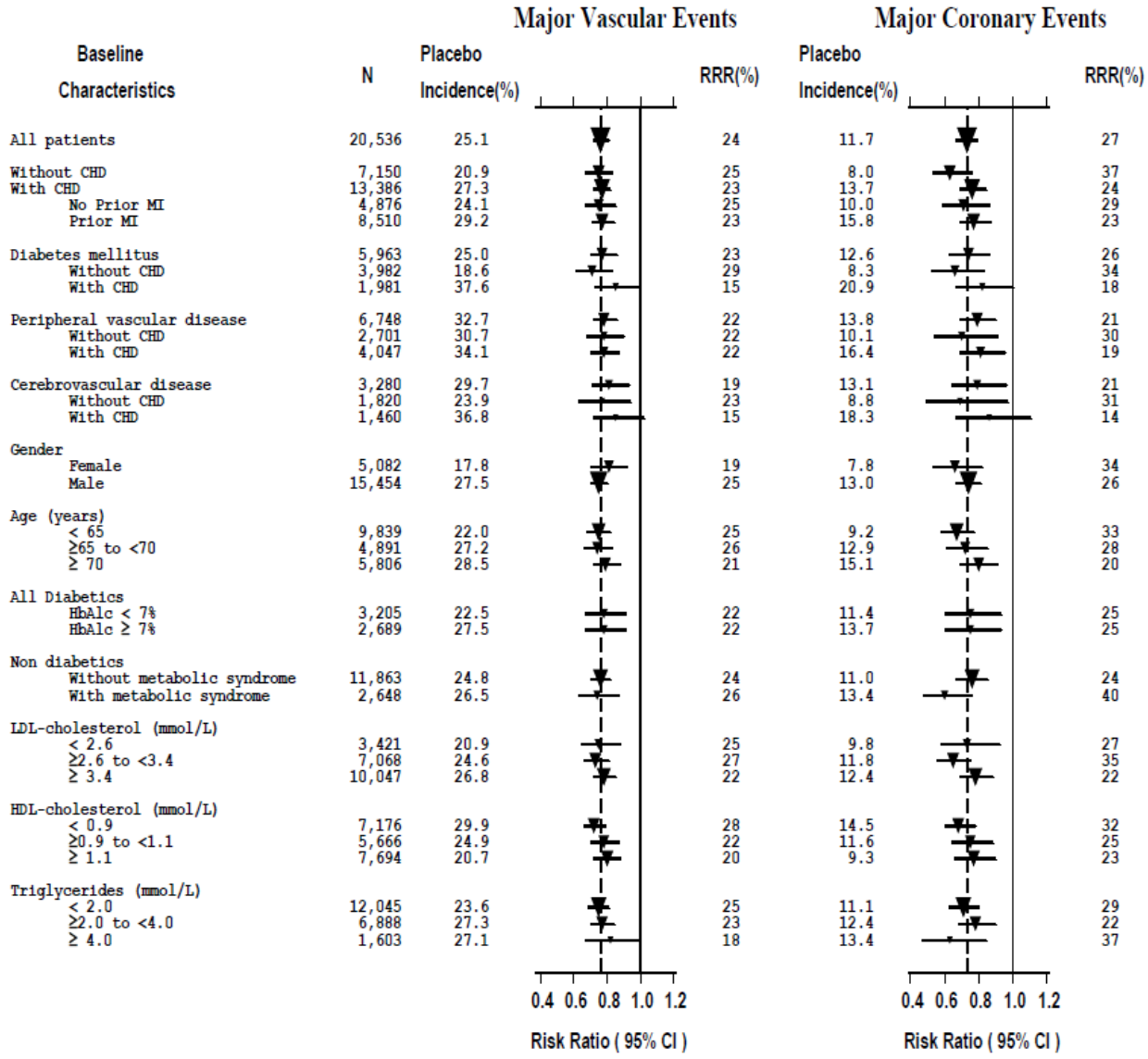
[3] *a composite of non-fatal myocardial infarction, CHD death, stroke, or revascularisation procedures*

[4] *a composite of non-fatal myocardial infarction or CHD deaths*

NS = not statistically significant

The effects of simvastatin on major vascular events and major coronary events were similar in all subgroups of patients (see **Figure 1**).

Figure 1: The beneficial effects of treatment with simvastatin on major vascular events and major coronary events in Heart Protection Study (HPS)



N= number of patients in each subgroup. All subgroups were defined at baseline. In this study, patients were classified with metabolic syndrome if they had abdominal obesity, elevated blood pressure, and low HDL-C; other factors such as fasting TG and insulin resistance were not measured. Placebo incidence is the percentage of patients in the placebo group who had one or more MVE or MCE during the study. The inverted triangles are point estimates of the risk ratio in the simvastatin group, with their 95% confidence intervals represented as a line. If the point estimate fell on the left of the unity line, the observed outcome was better in patients allocated active tablets. Conversely, if it fell on the right, the observed outcome was better in patients allocated placebo. The areas of the triangles are proportional to the number of patients with the relative endpoint. The vertical dashed line represents the point estimate of relative risk in the entire study population.

RRR (%) represents relative risk reduction, i.e., (1−risk ratio) x 100%.

The risk reductions produced by simvastatin in both major coronary events and major vascular events were evident and consistent across all baseline characteristics shown in **Figure 1**. In addition, these risk reductions were evident and consistent regardless of prior treated hypertension, creatinine levels up to the entry limit of 2.3 mg/dL, apolipoprotein A-I and B levels, baseline concomitant cardiovascular medications (i.e. aspirin, beta-blockers, angiotensin converting enzyme (ACE) inhibitors or calcium channel blockers), smoking status, alcohol intake or obesity.

Hypertriglyceridaemia (Fredrickson type IV hyperlipidaemia)

The results of subgroup analyses from a study including a total of 116 patients with hypertriglyceridaemia (Fredrickson type IV hyperlipidaemia) are presented in **Table 7**. This study was a double blind, placebo controlled, parallel study comparing simvastatin 20, 40 and 80 mg/day with placebo. Each treatment group included approximately 30 patients. The respective baseline values for the type IV patients were: total-C = 6.04 mmol/L; LDL-C = 2.59 mmol/L; HDL-C = 0.91 mmol/L; TGs 5.01 mmol/L; VLDL-C = 2.44 mmol/L; non-HDL-C = 5.13 mmol/L. The study demonstrated that simvastatin at doses of 20 to 80 mg/day reduced TGs 21 to 33% (placebo 13%), LDL-C 23 to 35% (placebo +3%), non-HDL-C 26 to 41% (placebo 1%), and raised HDL-C by 9 to 11% (placebo 3%).

Table 7: Six-week, lipid lowering effects of simvastatin in type IV hyperlipidaemia (mean percent change from baseline)**

	Total-C	LDL-C	HDL-C	TG*	VLDL-C*	Non-HDL-C
Placebo	0	3	3	-13	-10	-1
Simvastatin 20 mg/day	-21	-23	9	21	-33	-26
Simvastatin 40 mg/day	-26	-25	9	-21	-35	-32
Simvastatin 80 mg/day	-33	-35	11	-33	-44	-41

* *median percent change*

** *approximately 30 patients in each treatment group*

Dysbetalipoproteinaemia (Fredrickson type III hyperlipidaemia)

Table 8 presents the subgroup analysis results of seven patients with Fredrickson type III hyperlipidaemia (dysbetalipoproteinaemia; apo E2/2 and VLDL-C/TG > 0.25) from a 130 patient, double blind, placebo controlled, three period crossover study. In this study the median baseline values were: total-C = 324 mg/dL (8.39 mmol/L), LDL-C (+ intermediate density lipoproteins (IDL)) = 121 mg/dL (3.13 mmol/L), HDL-C = 31 mg/dL (0.80 mmol/L), TG = 411 mg/dL (4.67 mmol/L), VLDL-C (+ intermediate density lipoproteins (IDL)) = 170 mg/dL (4.40 mmol/L), and non-HDL-C = 291 mg/dL (7.54 mmol/L). At a dosage of 80 mg/day, simvastatin reduced LDL-C including intermediate density lipoproteins (IDL) by 50% (placebo 8%) and VLDL-C + IDL by 59% (placebo 4%).

Table 8: Six-week, lipid lowering effects of simvastatin in type III hyperlipidaemia (mean percent change from baseline)

	Total-C	LDL-C	HDL-C	TG	VLDL-C	Non-HDL-C
Placebo	-8	-8*	-2	+4	-4*	-8
Simvastatin 40 mg/day	-50	-50*	+7	-41	-58*	-57
Simvastatin 80 mg/day	-52	-51*	+7	-38	-60*	-59

* *includes IDL*

5.2 PHARMACOKINETIC PROPERTIES

The inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the beta-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors). Both are measured in plasma following administration of simvastatin.

Absorption and excretion

In a disposition study with ^{14}C-labelled simvastatin, 100mg (20µCi) of drug was administered as capsules (5 x 20mg) and blood, urine and faeces collected. 13% of the radioactivity was recovered in the urine and 60% in faeces. The latter represents absorbed drug equivalents excreted in bile as well as 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 area under the curve (AUC) of total radioactivity, indicating that the majority of chemical species present were inactive or weak inhibitors.

Both simvastatin and beta-hydroxyacid are bound to human plasma proteins (95%). The availability of beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was estimated using an intravenous reference dose of beta-hydroxyacid; the value was found to be less than 5% of the dose.

By analogy to a dog model, simvastatin is well absorbed and undergoes extensive first-pass extraction in the liver, the primary site of action, with subsequent excretion of drug equivalents in the bile. Consequently, availability of active drug to the general circulation is low.

Metabolism

The major metabolites of simvastatin present in human plasma are beta-hydroxyacid and four additional active metabolites. Simvastatin and other HMG-CoA reductase inhibitors are metabolised by CYP3A4 (see **section 4.4 Special warnings and precautions for use: *Myopathy/rhabdomyolysis***). In dose proportionality studies utilising doses of simvastatin 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.

Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4 and/or OATP1B1.

The pharmacokinetic effects of calcium channel blockers on simvastatin and HMG-CoA reductase inhibitors are summarised in **Table 9**. The data show increases in simvastatin acid exposure (AUC) with calcium channel blockers (see **section 4.4 Special warnings and precautions for use: *Myopathy/ rhabdomyolysis***).

Table 9: Effect of co -administered calcium channel blockers on simvastatin systemic exposure and HMG-CoA reductase inhibitory activity

Co-administered drug and dosing regimen	**Dosing of simvastatin**	**Geometric mean ratio** (Ratio* with / without co-administered drug) **No Effect = 1.00**		
			AUC	**C_{max}**
Verapamil SR 240 mg QD on Days 1-7 then 240 mg BID on Days 8-10	80 mg on Day 10	Simvastatin acid †	2.3	2.4
		Simvastatin	2.5	2.1
		Active inhibitors	1.8	1.3
		Total inhibitors	1.8	1.4
Diltiazem 120 mg BID for 10 days	80 mg on Day 10	Simvastatin acid †	2.7	2.7
		Simvastatin	3.1	2.9
		Active inhibitors	2.0	1.6

Co-administered drug and dosing regimen	Dosing of simvastatin	Geometric mean ratio (Ratio* with / without co-administered drug) No Effect = 1.00		
			AUC	C_{max}
		Total inhibitors	1.7	1.5
Amlodipine 10 mg QD for 10 days	80 mg on Day 10	Simvastatin acid †	1.6	1.6
		Simvastatin	1.8	1.5
		Active inhibitors	1.3	0.9
		Total inhibitors	1.3	1.0

* *results based on a chemical assay*

† *simvastatin acid refers to the beta-hydroxyacid of simvastatin*

A single dose of 2 g niacin extended-release co-administered with 20 mg simvastatin increased the AUC and C_{max} of simvastatin acid by approximately 60% and 84%, respectively, compared to administration of 20 mg simvastatin alone. In this study, the effect of simvastatin on niacin pharmacokinetics was not measured.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see **section 4.4 Special warnings and precautions for use: *Myopathy/ rhabdomyolysis*** and **section 4.5 Interactions with other medicines and other forms of interactions**).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genetic toxicology studies of simvastatin showed no evidence of mutagenic activity in bacteria or in mammalian cells *in vitro*, or of clastogenic activity *in vitro* or in mice *in vivo*. *In vitro* and *in vivo* assays showed that simvastatin does not cause DNA damage in rat hepatocytes.

Carcinogenicity

Carcinogenicity studies have been conducted in mice at oral doses ranging from 1 to 400 mg/kg/day and in rats at doses of 1 to 100 mg/kg/day. Hepatocellular adenomas and carcinomas were observed in both sexes of both species at doses greater than 25 mg/kg/day. Plasma drug levels in rats at this no effect dose level, expressed as the area under the curve (AUC) for enzyme inhibitory activity, were three to eleven times greater than in humans at the maximum recommended dose, whereas serum levels at the no effect level in mice were similar to those in humans. Additional findings in mice were increased incidences of pulmonary adenomas at doses greater than 25 mg/kg/day, and of Harderian gland adenomas at 400 mg/kg/day. In rats, the incidence of thyroid follicular adenoma was increased in females at doses greater than 5 mg/kg/day and in males at doses greater than 25 mg/kg/day. These thyroid tumours were associated with focal cystic follicular hyperplasia, and may be a secondary effect reflective of a simvastatin mediated enhancement of thyroid hormone clearance by the liver.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

NOUMED SIMVASTATIN also contain the following inactive ingredients: pregelatinised maize starch, lactose monohydrate, microcrystalline cellulose, butylated hydroxyanisole, ascorbic acid, citric acid monohydrate, magnesium stearate, hypromellose, purified talc, titanium dioxide, iron oxide yellow (5

mg, 10 mg and 20 mg tablets only), red iron oxide (10 mg, 20 mg and 40 mg tablets only), indigo carmine aluminium lake (80 mg tablets only) and quinoline yellow aluminium lake (80 mg tablets only).

6.2 INCOMPATIBILITIES

Refer to **section 4.5 Interactions with other medicines and other forms of interactions**.

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

NOUMED SIMVASTATIN film-coated tablets are packed in PVC/Aluminium blisters in cartons each containing 30 tablets.

Not all strengths may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

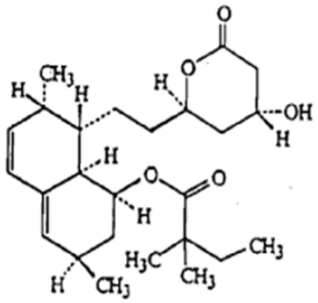
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Simvastatin is a white or almost white, crystalline powder, practically insoluble in water, very soluble in methylene chloride, freely soluble in alcohol.

Chemical Name: (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate

Chemical structure:



Empirical formula: $C_{25}H_{38}O_5$

Molecular Weight: 418.6

CAS Number: 79902-63-9

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Avallon Pharmaceuticals Pty Ltd
Level 5, 7 Eden Park Drive
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Tel: 1800 930 999
www.avallon-pharma.com.au

9. DATE OF FIRST APPROVAL

02 February 2018

10. DATE OF REVISION

15 June 2021

Summary table of changes

Section changed	Summary of new information
2, 6.1	Moved full list of excipients to section 6.1; Added statement on excipient with known effect (lactose monohydrate).
4.4	Updated precaution on myopathy/rhabdomyolysis.
4.8	Added rare and very rare potential adverse effects.
8	Updated sponsor's details.