

SIMVASTATIN VIATRIS

1. Product Name

Simvastatin Viatris 10 mg, 20 mg, 40 mg and 80 mg film coated tablets.

2. Qualitative and Quantitative Composition

Each Simvastatin Viatris tablet contains 10 mg, 20 mg, 40 mg or 80 mg of simvastatin.

Excipient with known effect: lactose.

Allergen declaration: sugars as lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Simvastatin Viatris 10 mg: Pinkish brown coloured, oval, biconvex, film coated tablets with 'BL' debossed on one side and '10' debossed on the other side.

Simvastatin Viatris 20 mg: Peach coloured, oval, biconvex, film coated tablets with 'BL' debossed on one side and '20' debossed on the other side.

Simvastatin Viatris 40 mg: Dull pink coloured, oval, biconvex, film coated tablets with 'BL' debossed on one side and '40' debossed on the other side.

Simvastatin Viatris 80 mg: Pink coloured, capsule shaped, biconvex, film coated tablets with '80' debossed on one side.

4. Clinical Particulars

4.1 *Therapeutic indications*

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

In patients at high risk of CHD (with or without hyperlipidaemia but with a total cholesterol of >3.5 mmol/L), i.e. patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD, simvastatin is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths;
 - Reduce the risk of major vascular events (a composite of non-fatal myocardial infarction, CHD death, stroke, or revascularisation procedures);
 - Reduce the risk of major coronary events (a composite of non-fatal myocardial infarction or CHD deaths);
 - Reduce the risk of stroke;
 - Reduce the need for coronary revascularisation procedures (including coronary artery bypass grafting and percutaneous transluminal coronary angioplasty);
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- Reduce the need for peripheral and other non-coronary revascularisation procedures;
- Reduce the risk of hospitalisation for angina pectoris.

In patients with diabetes, simvastatin reduces the risk of developing peripheral macrovascular complications (a composite of peripheral revascularisation procedures, lower limb amputations, or leg ulcers).

In hypercholesterolaemic patients with coronary heart disease, simvastatin slows the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

Patients with hyperlipidaemia

- Simvastatin is indicated as an adjunct to diet to reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and, apolipoprotein B (apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolaemia including heterozygous familial hypercholesterolaemia (Fredrickson type IIa), or combined (mixed) hyperlipidaemia (Fredrickson type IIb) when response to diet and other non-pharmacological measures is inadequate. Simvastatin therefore lowers the LDL-C/HDL-C and total-C/HDL-C ratios.
- Simvastatin is indicated for the treatment of patients with hypertriglyceridaemia (Fredrickson type IV hyperlipidaemia) with a baseline LDL cholesterol of <3.37 mmol/L and baseline triglyceride of >2.26 mmol/L, despite adequate dietary intervention.
- Simvastatin is indicated for the treatment of patients with primary dysbetalipoproteinaemia (Fredrickson type III hyperlipidaemia) not responding to diet alone with VLDL/TG ratios >0.25, and raised total cholesterol, TG and Apo-E levels.
- Simvastatin is also indicated as an adjunct to diet and other non-dietary measures for the treatment of patients with homozygous familial hypercholesterolaemia to reduce elevated total-C, LDL-C and Apo B.

Paediatric patients with heterozygous familial hypercholesterolaemia

- Simvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, TG, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolaemia (HeFH).

4.2 Dose and method of administration

Dose

The dosage range for simvastatin is 5-80 mg/day, given as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80 mg dose of simvastatin is only recommended 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).

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

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 hyperlipidaemia) i.e., patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD. Medicine therapy can be initiated simultaneously with diet and exercise.

Patients with hyperlipidaemia (who are not in the risk categories above)

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

The usual starting dose is 20 mg/day given as a single dose in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg/day given as a single dose in the evening. Patients who require only a moderate reduction of LDL-C may be started at 10 mg. Adjustments of dosage including starting dose, if required, should be made as specified above.

Patients with homozygous familial hypercholesterolaemia

The recommended dosage for patients with homozygous familial hypercholesterolaemia is simvastatin 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. The 80 mg dose is only recommended when the benefits are expected to outweigh the potential risks (see sections 4.3 and 4.4). 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.

In patients taking lomitapide concomitantly with simvastatin, the dose of simvastatin should not exceed 40 mg/day (see sections 4.4 and 4.5).

Concomitant therapy

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

In patients taking amiodarone, verapamil, diltiazem, amlodipine, ≥ 1 g/day of niacin, or products containing elbasvir or grazoprevir concomitantly with simvastatin, the dose of simvastatin should not exceed 20 mg/day (see sections 4.4 and 4.5).

Special populations

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.

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.

Dosage in paediatric patients (10 to 17 years of age) with heterozygous familial hypercholesterolaemia

The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualised according to the recommended goal of therapy (see section 5.1).

Method of administration

Simvastatin Viatrix tablets may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and breast-feeding (see also section 4.6). Women of child bearing 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 and nefazodone and drugs containing cobicistat (see sections 4.4 and 4.5).
- Concomitant administration of gemfibrozil, ciclosporin, or danazol (see section 4.4).

- Concomitant use with fusidic acid (see section 4.4 and 4.5)

4.4 *Special warnings and precautions for use*

Myopathy/rhabdomyolysis

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 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). Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

In the Scandinavian Simvastatin Survival Study (4S), there was one case of myopathy among 1399 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 6 month controlled clinical studies, there was one case of myopathy among 436 patients taking 40 mg and 5 cases among 669 patients taking 80 mg.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. 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 clinical trial 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 this clinical trial, rhabdomyolysis was defined as a subset of myopathy with CK >40 x ULN plus evidence of end organ damage (e.g. elevated creatinine, dark urine). Approximately half of these 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 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-ezetimibe regimen with less potential for drug-drug interactions should be used (see sections 4.2 and 4.3).

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/or a CK level >10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved (see section 4.8). 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=7367) compared with 0.24% for Chinese patients (n=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.

Interactions with other medicines

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 (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone, or drugs containing cobicistat) is contraindicated. If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment (see sections 4.3, 4.5 and 5.2).

Gemfibrozil, ciclosporine or danazol

Concomitant use of these drugs with simvastatin is contraindicated (see sections 4.3, 4.5 and 5.2).

Fusidic acid

Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy/rhabdomyolysis (see section 4.5). Fusidic acid must not be co-administered with statins (see section 4.3). In patients where the use of systemic fusidic acid is considered essential, simvastatin 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 reintroduced 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 patients receiving concomitant medication with amiodarone (see sections 4.2 and 4.5).

Calcium channel blockers

Verapamil or diltiazem

The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem (see sections 4.2 and 4.5).

Amlodipine

In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amlodipine (see sections 4.2 and 4.5).

Lomitapide

The dose of simvastatin should not exceed 40 mg daily in patients with homozygous familial hypercholesterolaemia (HoFH) receiving concomitant medication with lomitapide (see section 4.5).

Moderate inhibitors of CYP3A4

Patients taking other medicines labelled as having a moderate inhibitor 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 10 mg 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 TG and further increases in 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 resistant 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. Co-administration of elbasvir and grazoprevir with simvastatin has not been studied; however, **the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir** (see section 4.5).

Niacin (≥ 1 g/day)

The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with 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. 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 use 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 non-Chinese patients, co-administration of simvastatin with lipid-modifying doses (≥ 1 g/day) of niacin is not recommended in Asian patients** (see section 4.5).

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).

Prescribing recommendations for interacting agents are summarised in Table 1 (further details are provided in the text (see section 4.5 and 5.1).

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

Interacting agent	Prescribing recommendations
Potent CYP3A4 inhibitors, eg: Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone Cobicistat Gemfibrozil Ciclosporin Danazol Fusidic acid	CONTRAINDICATED with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily
Niacin (≥ 1 g/day)	For Asian patients, not recommended with simvastatin
Amiodarone Verapamil Diltiazem Elbasvir Grazoprevir	Do not exceed 20 mg simvastatin daily
Lomitapide	For patients with HoFH, do not exceed 40 mg simvastatin daily
Niacin (nicotinic acid) ≥ 1 g/day Amlodipine	Do not exceed 20 mg simvastatin daily
Daptomycin	Is not recommended with simvastatin
Grapefruit juice	Avoid grapefruit juice

Myasthenia gravis/ocular myasthenia

In a few cases, statins have been reported to induce new onset or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). Simvastatin should be discontinued in case these conditions occur. There have been reports of recurrences of these conditions when the same or a different statin was (re-) administered.

Hepatic effects

In clinical studies, persistent increases (to more than 3x ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When the medicine was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels. 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 (LFTs) prior to therapy with simvastatin and/or consumed substantial quantities of alcohol.

In 4S, the number of patients with more than one transaminase elevation to >3x ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 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 3x 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 3x ULN 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 1986 simvastatin treated patients in 4S with LFTs at baseline, only 8 (0.4%) developed consecutive LFT elevations to >3x ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. All 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 1105 patients, the 6 month incidence of persistent hepatic transaminase elevations considered medicine-related was 0.7% and 1.8% at the 40 and 80 mg dose respectively.

In the Heart Protection Study, in which 20,536 patients were randomised to receive simvastatin 40 mg/day or placebo, the incidences of elevated transaminases (>3x 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 3 months. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy.

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 thereafter with frequent liver tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3x ULN persist, withdrawal of simvastatin therapy is recommended. Liver biopsy should be considered if elevations persist despite discontinuation of the medicine. Unconfirmed reports of 'drug-induced hepatitis' have been reported with simvastatin.

The medicine should be used with caution in patients who consume substantial quantities of alcohol and/or have a 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 3x ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Immune mediated necrotising 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). 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.

Ophthalmic evaluations

Current long-term data from clinical studies 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 ophthalmic examinations are recommended after five years of treatment, taking into consideration that in the absence of any medicine therapy, an increase in the prevalence of lens opacities with time is expected as a result of aging.

Animal studies

Cataracts have been detected in 2 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 3-11 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 thyroxin 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 thyroxin activity.

In one study involving 183 patients treated with simvastatin, four patients had 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.

New-onset type 2 diabetes mellitus

There is sufficient evidence to support an association between statin use and new-onset type 2 diabetes mellitus; however, the risk appears to be mainly in patients already at increased risk of developing diabetes. Risk factors for the development of diabetes include raised fasting blood glucose, history of hypertension, raised triglycerides and raised body mass. Patients at risk should be monitored both clinically and biochemically according to national guidelines. There is insufficient evidence to confirm or exclude an increased risk for any individual statin or a dose-response relationship. The cardiovascular benefits of statin therapy continue to outweigh the risk of diabetes.

Paediatric use

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least one year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls (see sections 4.2, 4.8 and 5.1). Adolescent females should be counselled on appropriate contraceptive methods while on simvastatin therapy (see sections 4.3 and 4.6). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolaemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

The safety and efficacy of simvastatin in children and adolescents with non-familial hypercholesterolaemia, those aged less than 10 years or pre-menarchal girls have not been studied.

Elderly

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

4.5 Interaction with other medicines and other forms of interaction

Multiple mechanisms may contribute to potential interactions with HMG Co-A 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 medicines 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.

Contraindicated medicines

Concomitant use of the following medicines is contraindicated:

Potent Inhibitors of CYP3A4

Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity; therefore, it is not expected to affect the plasma concentrations of other medicines metabolised by CYP3A4. Potent inhibitors of CYP3A4 (below) 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 sections 4.3, 4.4 and 5.2).

Gemfibrozil, cyclosporine or danazol (see sections 4.3 and 4.4).

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of simvastatin with fusidic acid. Co-administration 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. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins. Where the use of fusidic acid is considered essential, LIPEX should be discontinued throughout the duration of fusidic acid treatment (see section 4.3 and 4.4).

Other medicine interactions

Amiodarone

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with simvastatin (see sections 4.2 and 4.4).

Calcium channel blockers

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil, diltiazem or amlodipine (see sections 4.2 and 4.4).

Lomitapide

The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide (see sections 4.2 and 4.4).

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).

Inhibitors of the transport protein OATP1B1

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

Inhibitors of breast cancer resistant protein (BCRP)

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 sections 4.2 and 4.4).

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).

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 such patients taking this combination is advised.

Daptomycin

The risk of myopathy and/or rhabdomyolysis may be increased by co-administration of HMG-CoA reductase inhibitors and daptomycin (see section 4.4).

Other fibrates

The risk of myopathy is increased by gemfibrozil (see section 4.3) and other fibrates (except fenofibrate); these lipid-lowering medicines 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 and 4.4).

Grapefruit juice

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of medicines 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).

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 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 medicines metabolised by the same isoform.

Digoxin

Concomitant administration of simvastatin and digoxin in normal volunteers resulted in a slight elevation (less than 0.3 ng/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.

Ticagrelor

Co-administration of ticagrelor with simvastatin increased the simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2 to 3-fold. There was no effect of simvastatin on ticagrelor plasma levels. There is the potential for an increase in simvastatin-related adverse reactions such as myopathy and rhabdomyolysis with co-administration; no cases of rhabdomyolysis were reported when ticagrelor was co-administered with simvastatin 40 mg daily or lower. Therefore, concomitant use of ticagrelor with doses of simvastatin greater than 40 mg daily is not recommended.

Other concomitant therapy

In clinical studies, simvastatin was used concomitantly with beta blockers, diuretics and nonsteroidal anti-inflammatory medicines (NSAIDs) without evidence of clinically significant adverse interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

Simvastatin is contraindicated during pregnancy.

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

In two series of 178 and 134 cases where pregnant women took an 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 woman 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 she should be informed of the possibility of foetal injury and discuss the implications with her pregnancy specialist.

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering medicines 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.

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 medicine, 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 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.

Breast-feeding

Animal studies have shown that weight gain during lactation is reduced in 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 medicines are excreted in human milk and because of the potential for serious adverse reactions, women taking simvastatin should not breast feed their infants (see section 4.3).

Fertility

In several studies of over 800 men with hypercholesterolaemia treated with simvastatin 20 mg to 80 mg per day for 12 to 48 weeks, basal testosterone levels were mildly decreased during simvastatin therapy, but there were no consistent changes in LH and FSH. In 86 men treated with simvastatin 20 mg to 80 mg per 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.

4.7 Effects on ability to drive and use machines

Simvastatin has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported rarely in post-marketing experiences.

4.8 Undesirable effects

Simvastatin is generally well-tolerated; for the most part 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 are considered to be definitely, probably or possibly due to simvastatin may be grouped as follows.

Adverse events	Simvastatin (%) (n=2423)	Placebo (%) (n=167)
Body as a whole		
Abdominal pain	2.5	0.6
Asthenia	0.9	0.6
Digestive		
Constipation	2.5	1.2
Flatulence	2.0	0.6
Nausea	1.2	0.6
Acid regurgitation	0.6	0
Diarrhoea	0.8	0
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 the Heart Protection Study involving 20,536 patients treated with 40 mg/day of simvastatin (n=10,269) or placebo (n=10,267), the safety profiles were comparable between patients treated with simvastatin 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 adverse 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). Elevated transaminases (>3x 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, involving 4,444 patients treated with 20-40 mg/day of simvastatin (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 ($\geq 1/10,000$, $<1/1000$) or Very rare ($< 1/10,000$) adverse experiences 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 studies or in marketed use: pruritus, alopecia, dizziness, muscle cramps, myalgia, depression, pancreatitis, paraesthesia, peripheral neuropathy, insomnia, vomiting, anaemia, erectile dysfunction, and interstitial lung disease.

There have been very rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persists despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents (see section 4.4).

Rhabdomyolysis and hepatitis/jaundice occurred rarely and fatal and 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, thrombocytopaenia, eosinophilia, ESR increased, 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 non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Myasthenia gravis or ocular myasthenia associated with statin use has been reported (see section 4.4).

Laboratory test findings

Marked and persistent increases of serum transaminases have been reported infrequently. Elevated alkaline phosphatase and γ -glutamyl transpeptidase have been reported. Liver function test abnormalities have generally been mild and transient. Increases in CK levels, derived from skeletal muscle, have been reported (see section 4.4).

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

Paediatric patients (ages 10-17 years)

In a study involving paediatric patients 10-17 years of age with heterozygous familial hypercholesterolaemia (n=175), the safety and tolerability profile of the group treated with simvastatin was generally similar to that of the group treated with placebo (see sections 4.4 and 5.1).

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 multiform including Stevens-Johnson syndrome, leukopenia, proteinuria, and purpura.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://pophealth.my.site.com/carmreportnz/s/>

4.9 Overdose

A few cases of overdose have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. General measures should be adopted.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitor, ATC code: C10A A01

Mechanism of action

The involvement of low-density lipoprotein-cholesterol (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 high-density lipoprotein-cholesterol (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 β -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 efficacy and safety

In the Scandinavian Simvastatin Survival Study (4S), the effect on total mortality of therapy with simvastatin for a median of 5.4 years was assessed in 4,444 patients with coronary heart disease (CHD) and baseline total-C 212-309 mg/dL (5.5-8.0 mmol/L). In this multicentre, randomised, double-blind, placebo-controlled study, simvastatin reduced the risk of death by 30%, of CHD death by 42%, and of having a hospital-verified nonfatal myocardial infarction by 37%. Simvastatin reduced the risk for undergoing myocardial revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%. In patients with diabetes mellitus the risk of a major coronary event was reduced by 55%. Furthermore, simvastatin significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischaemic attacks) by 28%.

In the Heart Protection Study (HPS), the effects of therapy with simvastatin for a mean duration of 5 years were assessed in 20,536 patients, with or without hyperlipidaemia, who were at high risk of coronary heart disease (CHD) events because of diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or CHD. At baseline, 33% had LDL levels below 116 mg/dL; 25% had levels between 116 mg/dL and 135 mg/dL; and 42% had levels greater than 135 mg/dL.

In this multicentre, randomised, double-blind, placebo-controlled study, simvastatin 40 mg/day compared with placebo reduced the risk of total mortality by 13%, due to a reduction in CHD deaths (18%). Simvastatin also decreased the risk of major coronary events (a composite endpoint comprising non-fatal MI or CHD deaths) by 27%. Simvastatin reduced the need for undergoing coronary revascularisation procedures (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) and peripheral and other non-coronary revascularisation procedures by 30% and 16%, respectively. Simvastatin reduced the risk of stroke by 25%, attributable to a 30% reduction in ischaemic stroke. Furthermore, simvastatin reduced the risk of hospitalisation for angina pectoris by 17%. The risks of major coronary events and major vascular events (a composite endpoint comprising major coronary events, stroke, or revascularisation procedures) were reduced by about 25% in patients with or without CHD, including diabetics and patients with peripheral or cerebrovascular disease. In addition, within the subgroup of patients with diabetes, simvastatin reduced the risk of developing macrovascular complications, including peripheral revascularisation procedures (surgery or angioplasty), lower limb amputations, or leg ulcers by 21%. The risk reductions produced by simvastatin in both major vascular events and major coronary events were evident and consistent regardless of patient age, gender, baseline LDL-C, HDL-C, TG, apolipoprotein A-I, or apolipoprotein B level, presence or absence of hypertension, creatinine levels up to the entry limit of 2.3 mg/dL, presence or absence of baseline cardiovascular medications (i.e., aspirin, beta blockers, angiotensin converting enzyme (ACE) inhibitors, or calcium channel blockers), smoking status, alcohol intake, or obesity. By 5 years, 32% of patients in the placebo group were taking a statin (outside of the study protocol), so that the observed risk reductions underestimate the real effect of simvastatin.

Clinical studies in paediatric patients (10-17 years of age)

In a double-blind, placebo-controlled study, 175 patients (99 adolescent boys and 76 post-menarchal girls) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (HeFH) were randomised to simvastatin or placebo for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

Simvastatin significantly decreased plasma levels of total-C, LDL-C, TG, and Apo B. Results from the extension at 48 weeks were comparable to those observed in the base study.

After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0 - 289.0 mg/dL) in the simvastatin 40 mg group compared to 207.8 mg/dL (range: 128.0 - 334.0 mg/dL) in the placebo group.

Simvastatin decreased the mean baseline total-C by 26.5% (placebo: 1.6% increase from baseline), LDL-C by 36.8% (placebo: 1.1% increase from baseline), median TG by 7.9% (placebo: 3.2%), and mean Apo B levels by 32.4% (placebo: 0.5%), and increased mean HDL-C by 8.3% (placebo: 3.6%).

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolaemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone which is readily hydrolysed *in vivo* to the corresponding β -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 β -hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors). Both are measured in plasma following administration of simvastatin.

In a disposition study with ¹⁴C-labelled simvastatin, 100 mg (20 μ Ci) of medicine was administered as capsules (5 x 20 mg), and blood, urine, and faeces collected. 13% of the radioactivity was recovered in the urine and 60% in faeces. The latter represents absorbed medicine equivalents excreted in bile as well as unabsorbed medicine. 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.

Both simvastatin and L-654,969 are bound to human plasma proteins (95%). The major metabolites of simvastatin present in human plasma are L-654,969 and four additional active metabolites. The availability of L-654,969 to the systemic circulation following an oral dose of simvastatin was estimated using an IV 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 medicine equivalents in the bile. Consequently, availability of active medicine 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 medicine 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.

In a study of patients with severe renal insufficiency (creatinine clearance <30 mL/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately two-fold higher than those in healthy volunteers.

In a study of 12 healthy volunteers, simvastatin at the maximal 80 mg dose had no effect on the metabolism of the probe CYP3A4 substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and therefore, is not expected to affect the plasma levels of other medicines metabolised by CYP3A4.

Although the mechanism is not fully understood, cyclosporine 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 (see section 4.3).

In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4.

In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid.

In a pharmacokinetic study, the co-administration of a single dose of niacin extended-release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin and simvastatin acid and in the C_{max} of simvastatin acid plasma concentrations.

Specific pathways of fusidic acid metabolism in the liver are not known, however, an interaction between fusidic acid and HMG-CoA reductase inhibitors, which are metabolised by CYP-3A4, can be suspected.

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 sections 4.4 and 4.5).

No pharmacokinetic studies have been conducted to date in elderly patients or in patients with renal or hepatic dysfunction.

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 AUC for enzyme inhibitory activity, were 3 to 11 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 dose 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

Simvastatin Viatrix film coated tablet also contains:

- lactose monohydrate
- maize starch
- microcrystalline cellulose
- sodium starch glycolate
- ascorbic acid
- citric acid monohydrate
- pregelatinised maize starch
- colloidal silicon dioxide

- magnesium stearate
- butylated hydroxytoluene
- isopropyl alcohol
- purified water
- hypromellose
- purified talc
- titanium dioxide
- macrogol 400
- red iron oxide
- yellow iron oxide (10 mg and 20 mg tablets only).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Simvastatin Viatris 10 mg, 20 mg, 40 mg and 80 mg film coated tablets are supplied in PVDC/PVC/Aluminium foil blister packs.

Pack sizes of 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 and 500 film coated tablets.

Not all pack sizes or strengths may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Eilerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

13 November 2008

10. Date of Revision of the Text

Summary table of changes

Section	Summary of new information
2	Allergen declaration moved from section 6.1
4.4	Risk of myasthenia gravis and ocular myasthenia with statin use
4.5	Addition of potential drug interaction between ticagrelor and simvastatin
4.8	Myasthenia gravis or ocular myasthenia associated with statin use New website link for reporting adverse reactions
6.1	Moved allergen information to section 2