AUSTRALIAN PRODUCT INFORMATION

ZIMSTAT

Simvastatin tablets

1 NAME OF THE MEDICINE

Simvastatin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Simvastatin is a white crystalline powder, practically insoluble in water and freely soluble in chloroform, methanol and ethanol.

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

Excipients with known effect: Lactose (as monohydrate)

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Zimstat 5 : Dark buff coloured, oval shaped, film-coated tablet, with "G" on one side and "SM" scoreline "5" on the other side.

Zimstat 10 : Dark peach to pink coloured, oval shaped, film-coated tablet with "G" on one side and "SM" scoreline "10" on the other side.

Zimstat 20 : Dark tan coloured, oval shaped film-coated tablet with "G" on one side and "SM" scoreline "20" on the other side.

Zimstat 40 : Pink coloured, oval shaped, film-coated tablet with "G" on one side and "SM40" on the other side.

Zimstat 80 : Pink to brick red coloured capsule shaped, film-coated tablet with "G" on one side and "SM80" on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- ZIMSTAT is indicated as an adjunct to diet for treatment of hypercholesterolaemia.

  Prior to initiating therapy with ZIMSTAT, 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.

- 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

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)

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 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 other than gemfibrozil (see Section 4.3 CONTRAINDICATIONS) or fenofibrate, the dose of simvastatin should not exceed 10 mg/day.

In patients taking amiodarone, verapamil or diltiazem, or products containing elbasvir or grazoprevir 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 (see Section 4.3 CONTRAINDICATIONS, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Myopathy/Rhabdomyolysis and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

In patients taking niacin (nicotinic acid) ≥ 1g/day, the dose of simvastatin should not exceed 40 mg/day (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In patients taking lomitapide concomitantly with simvastatin, the dose of ZIMSTAT 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).

Dosage in Renal Insufficiency

ZIMSTAT 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 < 30mL/min), 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 breastfeeding (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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, 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 and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).
- Concomitant use with fusidic acid hemihydrate (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, 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 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 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 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 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:

<u>Contraindicated Medicines</u>

- **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 and 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 hemihydrate 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 hemihydrate must not be co-administered with statins (see Section 4.3 CONTRAINDICATIONS). In patients where the use of systemic fusidic acid hemihydrate 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. ZIMSTAT therapy may be reintroduced seven days after the last dose of fusidic acid hemihydrate.

<u>Other Medicines</u>

- **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 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).

  - *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 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 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 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 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 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. 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

- **Niacin (≥ 1g/day):** The dose of simvastatin should not exceed 40mg 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 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 coadministered 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 coadministered 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 coadministered 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 ZIMSTAT 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 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL PHARMACOLOGY).

Table 1: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	**Prescribing Recommendations**
Potent CYP3A4 inhibitors, e.g.:	CONTRAINDICATED with simvastatin
Itraconazole	
Ketoconazole	
Posaconazole	
Voriconazole	
Erythromycin	
Clarithromycin	
Telithromycin	
HIV protease inhibitors	
Boceprevir	
Telaprevir	
Nefazodone	
Cobicistat	
Gemfibrozil	
Ciclosporin	
Danazol	

Fusidic acid hemihydrate	
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily
Niacin (≥ 1g/day)	For Asian patients, not recommended with simvastatin
Amiodarone	Do not exceed 20 mg simvastatin daily
Verapamil	
Diltiazem	
Elbasvir	
Grazoprevir	
Lomitapide	For patients with HoFH, do not exceed 40 mg simvastatin daily
Niacin (nicotinic acid) ≥ 1g/day	Do not exceed 40 mg simvastatin daily
Amlodipine	
Daptomycin	Is not recommended with simvastatin
Grapefruit juice	Avoid grapefruit juice

Use in Hepatic Impairment

In clinical studies persistent increases (to more than 3 X 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 concentration. 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 (see Section 5.1 PHARMACODYNAMIC PROPERTIES – CLINICAL TRIALS), the number of patients with more than one ALT elevation to > 3 X 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 > 3 X 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 3 X 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 normal LFTs at baseline, only 8 (0.4%) developed consecutive LFT elevations to >3 X 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 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1105 patients, the 6 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 HPS (see Section 5.1 PHARMACODYNAMIC PROPERTIES – CLINICAL TRIALS), in which 20,536 patients were randomised to receive simvastatin 40 mg/day or placebo, the incidences of elevated transaminases (> 3 X 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 (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 thereafter with frequent liver tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 X 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 (< 3 X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes were not specific to simvastatin and were also observed with comparative lipid-lowering agents. They generally appeared within the first 3 months after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

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.

Ophthalmic Evaluations

Current long-term data from clinical studies, e.g. 4S, do not indicate an adverse effect of simvastatin on 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 drug 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 > 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 to 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 levothyroxine 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 levothyroxine 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.

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-C 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

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial conducted by the innovator company (please consult the Zocor Product Information).

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.

The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

Effects on Laboratory Tests

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 serum CK levels, derived from skeletal muscle, have been reported (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – USE IN HEPATIC IMPAIRMENT).

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 drugs to obtain further information about their potential interactions with simvastatin and/or 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 CYP3A4 Inhibitors

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 Section 4.3 CONTRAINDICATIONS, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS - Myopathy/Rhabdomyolysis and Section 5.2 PHARMACOLOGY – Pharmacokinetics Properties).

Gemfibrozil, cyclosporine or danazol

See Section 4.3 CONTRAINDICATIONS, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS - Myopathy/Rhabdomyolysis.

Fusidic Acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of simvastatin with fusidic acid hemihydrate. 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 hemihydrate and statins. Where the use of fusidic acid is considered essential, ZIMSTAT should be discontinued throughout the duration of fusidic acid hemihydrate treatment (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS - 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 - 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 - 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 - 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 - 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 - 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 coadministering simvastatin with an inhibitor of BCRP, a dose adjustment of simvastatin may be necessary (see SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Myopathy/Rhabdomyolysis).

Niacin (nicotinic acid) (≥ 1g/day)

Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1g/day) of niacin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS - 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 - 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 250mL 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 - 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 (< 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.

Other Concomitant Therapy

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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.

Use in Pregnancy

Pregnancy Category: D

Category D: 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.

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 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 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 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.

Because of the ability of inhibitors of HMG-CoA reductase such as ZIMSTAT to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZIMSTAT is contraindicated during pregnancy. ZIMSTAT 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, ZIMSTAT should be immediately 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 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 ZIMSTAT should not breast feed 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)

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

The clinical adverse events occurring at an incidence of > 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 (HPS) (see Section 5.1 PHARMACODYNAMIC PROPERTIES – CLINICAL TRIALS) involving 20,536 patients treated with simvastatin 40 mg/day of (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 (> 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, (see Section 5.1 PHARMACODYNAMIC PROPERTIES – CLINICAL TRIALS) involving 4444 patients treated with 20 to 40 mg/day of simvastatin (n=2221) or placebo (n=2223), the safety and tolerability profiles were comparable between treatment groups over the median 5.4 years of the study.

The following additional adverse effects were reported either in uncontrolled clinical trials or in marketed use: pruritus, alopecia, dizziness, muscle cramps, myalgia, depression, pancreatitis, paraesthesia, peripheral neuropathy, cognitive impairment, insomnia, vomiting, gynaecomastia, 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 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 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, thrombocytopenia, 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).

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, leucopenia, 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

A few cases of overdosage have been reported. The maximum dose taken was 3.6 g. All patients recovered without sequelae. General measures should be adopted, and liver function should be monitored.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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, ZIMSTAT, 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).

ZIMSTAT 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 ZIMSTAT 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 ZIMSTAT. Since each LDL particle contains one molecule of Apo B, and since little Apo B is found in other lipoproteins, this strongly suggests that

ZIMSTAT 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 ZIMSTAT 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 ZIMSTAT 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 has 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 non-familial forms of hypercholesterolaemia, and in mixed hyperlipidaemia (Fredrickson type IIb) when elevated cholesterol was a cause of concern. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response has been maintained during continuation of therapy. In six controlled clinical studies involving approximately 1700 patients with normal or slightly raised TG (mean 1.9 mmol/L), plasma TG, 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 20 or 40 mg/day for 12 weeks, the following results were observed (see Table 2).

Table 2: Effect of Simvastatin in Patients with Hypercholesterolaemia

	Mean Baseline	Mean Percent Change	
		20 mg once daily (n=166)	**40 mg once daily (n=161)**
Total Cholesterol	8.3 mmol/L	-27: -27	-30: -33
LDL-Cholesterol	6.4 mmol/L	-32: -34	-40: -41
HDL-Cholesterol	1.2 mmol/L	+10: +10	+10: +13
Triglycerides	1.9 mmol/L	-13: -17	-19: -27
VLDL-Cholesterol	0.8 mmol/L	-8(n = 84)*	-28(n = 81)*
Apolipoprotein B	2000 mg/L	-28: -33	-36: -38

* only measured in one study

In a separate study involving 180 patients with combined hyperlipidaemia, simvastatin 10 mg/day for 17 weeks was also shown to be effective in lowering total-C, LDL-C, VLDL-C, TGs and Apo B.

Table 3: Effect of Simvastatin in Patients with Combined Hyperlipidaemia

	Mean Baseline	Mean Percent Change 10 mg once daily (n=56)
Total Cholesterol	7.0 mmol/L	-23
LDL-Cholesterol	4.5 mmol/L	-27
HDL-Cholesterol	1.0 mmol/L	+13
Triglycerides[1]	2.6 mmol/L	-26
VLDL-Cholesterol	1.3 mmol/L	-28
Apolipoprotein B	1710 mg/L	-21

[1] median

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

The results of 4 separate studies depicting the dose response to simvastatin in patients with primary hypercholesterolaemia are presented in Table 4:

Table 4: Dose Response in Patients with Primary Hypercholesterolaemia (Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG*
Lower Dose Comparative Study					
SIMVASTATIN 5 mg**	109	-19	-26	10	-12
SIMVASTATIN 10 mg**	110	-23	-30	12	-15
Scandinavian Simvastatin Survival Study					
Placebo	2223	-1	-1	0	-2
SIMVASTATIN 20 mg**	2221	-28	-38	8	-19
Upper Dose Comparative Study					
SIMVASTATIN 40 mg**	433	-31	-41	9	-18
SIMVASTATIN 80 mg**	664	-36	-47	8	-24
Multicentre Combined Hyperlipidaemia Study					
Placebo	122	1	2	3	-4
	(except LDL-C, N=121)				
SIMVASTATIN 40 mg**	122	-25	-29	13	-28
SIMVASTATIN 80 mg**	123	-31	-36	16	-33
	(except LDL-C, N=121)				

* Median percent change
** In the evening

In the upper dose comparative study, one third of patients obtained a reduction in LDL-C of 53% or more at the 80 mg 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 ≤ 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, 12 patients 15 to 39 years of age with homozygous familial hypercholesterolaemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 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 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 colestyramine decreased the combined incidence of CHD death plus non-fatal myocardial infarction (MI).

In a randomised, double-blind, 3-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 mg, and 80 mg/day for 6 weeks. In a dose-dependent manner simvastatin 40 mg 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, non-fatal 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 4444 patients with CHD and baseline total-C 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=2221) or placebo (n=2223) for a median duration of 5.4 years. Eighty-two percent (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 TG 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 vs 256 deaths in the placebo group). The risk of CHD death was reduced by 42%, 95% CI 27-54%, p=0.00001 (111 vs 189). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent non-fatal MI) by 34%, 95% CI 25-41%, p<0.00001 (431 patients vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. Simvastatin reduced the risk for undergoing myocardial re-vascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%, 95% CI 26-46%, p<0.00001 (252 patients vs 383 patients).

Furthermore, simvastatin significantly reduced the risk of fatal plus non-fatal cerebrovascular events (stroke and transient ischaemic attacks) by 28%, 95% CI 3-46% (p=0.033, 75 patients vs 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 ≥ 60 years of age was decreased by 27% and in patients< 60 years of age by 37%, 95% CI 12-55% (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% CI 9-52% (p=0.012, 60 women vs 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% CI 24-73% (p=0.002, 24 patients vs 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 Multicentre 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/d or placebo. Eighty-nine percent (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 vs 24% placebo, p=0.009) and with new total occlusions (5% vs 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 the Multicentre Anti-Atheroma Study (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, multicentre, 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 angioplasty (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 non-disabling stroke not thought to be haemorrhagic), carotid endarterectomy, leg artery stenosis (e.g. 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 >2.6 mmol/L and < 3.4 mmol/L; and 10,047 patients (49%) had levels ≥ 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 < 5.0 mmol/L; 3,942 (38.4%) patients in the simvastatin group and 3,941 (38.4%) in the placebo group had levels ≥ 5.0 mmol/L and < 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 ≥ 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 5). 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 5: Summary of Risk Reduction in HPS

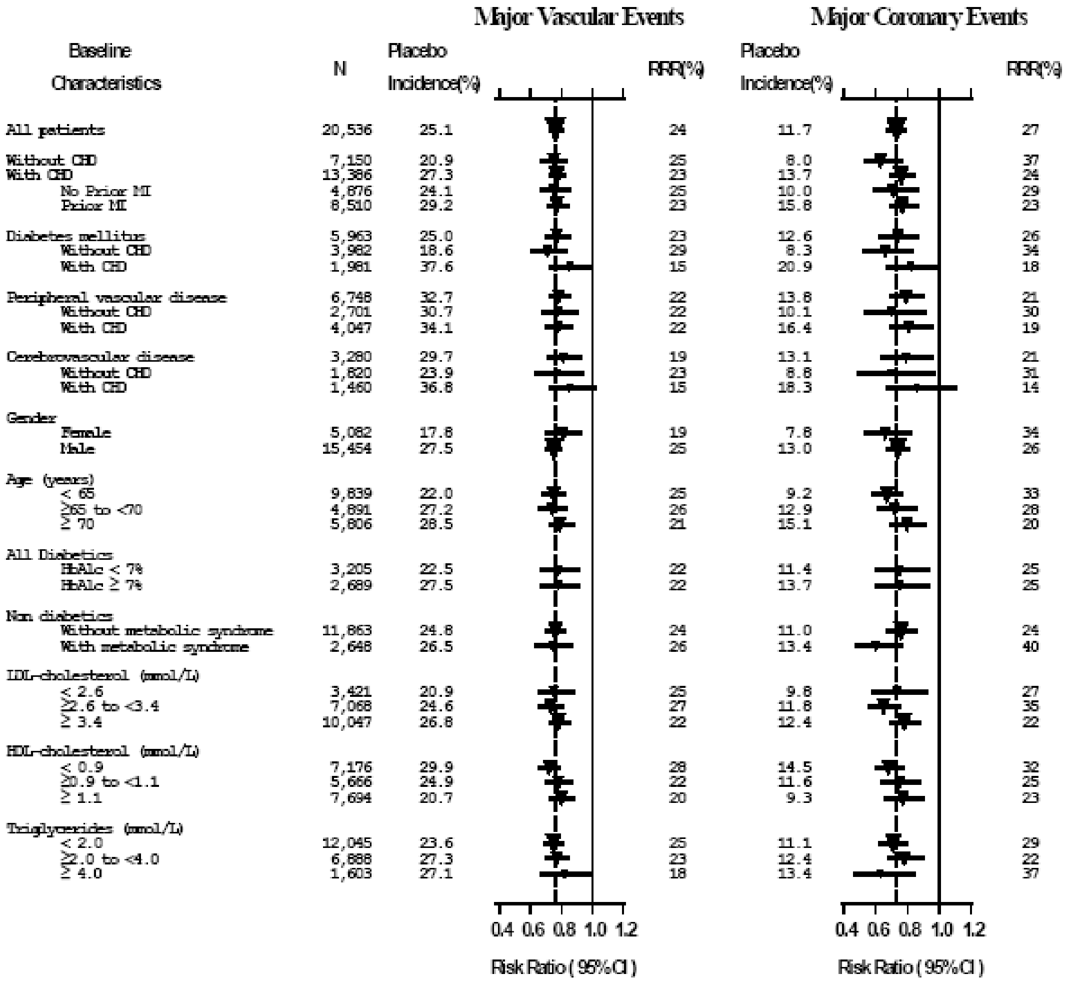
Endpoint	**SIMVASTATIN (N = 10,269) N (%)**	**Placebo (N = 10,267) N (%)**	**Absolute risk reduction [1] % (95% CI)**	**Relative risk reduction % (95% CI)**	**P value**
Primary					
Mortality	1328 (12.9%)	1504 (14.6%)	1.7 (0.8 to 2.7)	12 (6 to 19)	P < 0.001
CHD mortality	571 (5.6%)	689 (6.7%)	1.2 (0.5 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]	2026 (19.7%)	2575 (25.1%)	5.4 (4.2 to 6.5)	24 (19 to 28)	p < 0.00001
Major coronary events [2,4]	892 (8.7%)	1205 (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	1036 (10.1%)	1221 (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 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 simvastatin. 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 6. This study was a double blind, placebo controlled, parallel study, comparing simvastatin 20 mg, 40 mg 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; TG 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 TG 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 6: 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 7 presents the subgroup analysis results of 7 patients with Fredrickson type III hyperlipidaemia (dysbetalipoproteinaemia; apo E2/2 and VLDL-C/TG>0.25) from a 130-patient double-blind, placebo-controlled, 3-period crossover study. In this study the median baseline values were: total-C = 324 mg/dL (8.39 mmol/L), LDL-C (+IDL) = 121 (3.13), HDL-C = 31 (0.80), TG = 411 (4.67), VLDL-C (+IDL) = 170 (4.40), and non-HDL-C = 291 (7.54). 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 7: Six-week, Lipid-lowering Effects of Simvastatin in Type III Hyperlipidaemia
Median 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 β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors). Both are measured in plasma following administration of simvastatin.

Absorption

In a disposition study with ^{14}C-labelled simvastatin, 100 mg (20 microCi) of drug was administered as capsules (5 x 20 mg), and blood, urine, and faeces collected. Thirteen percent of the radioactivity was recovered in the urine and 60 percent in faeces. The latter represents absorbed drug equivalents excreted in bile as well as unabsorbed drug. Less than 0.5 percent of the dose was recovered in urine as HMG-CoA reductase inhibitors. In plasma, the inhibitors account for 14 percent and 28 percent (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 β-hydroxyacid are bound to human plasma proteins (95%). The availability of β-hydroxyacid to the systemic circulation following an oral dose of simvastatin was estimated using an I.V. reference dose of β-hydroxyacid; the value was found to be < 5 percent of the dose.

Metabolism

The major metabolites of simvastatin present in human plasma are β-hydroxyacid and four additional active metabolites. Simvastatin and other HMG-CoA reductase inhibitors are metabolised by CYP 3A4 (see SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Myopathy/Rhabdomyolysis). In dose-proportionality studies utilising doses of simvastatin of 5, 10, 20, 60, 90 and 120 mg there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before a test meal.

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

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

		Geometric mean ratio (Ratio* with/without co-administered drug) No Effect – 1.00		
Co-administered drug and dosing regimen	**Dosing of Simvastatin**		**AUC**	**C_{max}**
Verapamil SR 240 mg QD 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
		Total inhibitors	1.7	1.5
Amlodipine 10 mg QD x 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 chemical assay
† Simvastatin acid refers to the β–hydroxyacid of simvastatin

A single dose of 2 g niacin extended-release co-administered with 20 mg simvastatin increased the AUC and Cmax 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).

Excretion

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.

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 100mg/kg/day. Hepatocellular adenomas and carcinomas were observed in both sexes of both species at doses > 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 > 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 > 5 mg/kg/day and in males at doses > 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

Each tablet for oral administration contains the following non-medicinal ingredients: butylated hydroxyanisole, ascorbic acid, citric acid monohydrate, cellulose - microcrystalline, starch - pregelatinised maize, magnesium stearate, hyprolose, lactose monohydrate, titanium dioxide, triacetin and talc-purified. Iron oxide yellow (CI77492) is a constituent of ZIMSTAT 5 mg, 20 mg and 40 mg tablets and iron oxide red (CI77491) of ZIMSTAT 10 mg, 20 mg, 40 mg and 80 mg tablets. The 40 mg tablet contains polydextrose, macrogol 8000, iron oxide yellow (CI77492) and iron oxide red (CI77491).

6.2 INCOMPATIBILITIES

Not applicable

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.

6.5 NATURE AND CONTENTS OF CONTAINER

Zimstat 5	:	Supplied in PVC/PVDC/Al blister packs of 5, 7, 10, 28, 30, 60, 90 and 100 tablets and HDPE bottles of 10, 28, 30, 60, 90 and 100 tablets.
Zimstat 10	:	Supplied in PVC/PVDC/Al blister packs of 5, 7, 10, 28, 30, 60, 90 and 100 tablets and HDPE bottles of 10, 28, 30, 60, 90 and 100 tablets.
Zimstat 20	:	Supplied in PVC/PVDC/Al blister packs of 5, 7, 10, 28, 30, 60, 90 and 100 tablets and HDPE bottles of 10, 28, 30, 60, 90 and 100 tablets.
Zimstat 40	:	Supplied in PVC/PVDC/Al blister packs of 5, 7, 10, 28, 30, 60, 90 and 100 tablets and HDPE bottles of 10, 28, 30, 60, 90 and 100 tablets.
Zimstat 80	:	Supplied in PVC/PVDC/Al blister packs of 5, 7, 10, 28, 30, 60, 90 and 100 tablets and HDPE bottles of 10, 28, 30, 60, 90 and 100 tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

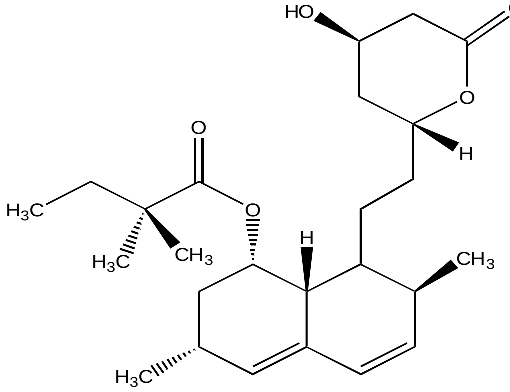
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name : [1S-[1 α, 3 α, 7 β, 8 β (2S*, 4S*),8a β]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl2,2-dimethylbutanoate.

Chemical Structure



Molecular formula : $C_{25}H_{38}O_5$ Molecular weight : 418.57

CAS Number
79902-63-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Millers Point NSW 2000

www.mylan.com.au

9 DATE OF FIRST APPROVAL

18/07/2003

10 DATE OF REVISION

7 February 2020

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.4 Special warnings and precautions for use	Information added regarding simvastatin dose restriction in patients co-administered with elbasvir and grazoprevir.

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