SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Simvastatin Teva 10 mg
Simvastatin Teva 20 mg
Simvastatin Teva 40 mg
Simvastatin Teva 80 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Simvastatin Teva 10 mg:
Each tablet contains 10 mg simvastatin.
Excipients with known effect:
Each tablet contains 70.65 mg lactose monohydrate.

Simvastatin Teva 20 mg:
Each tablet contains 20 mg simvastatin.
Excipients with known effect:
Each tablet contains 141.30 mg lactose monohydrate.

Simvastatin Teva 40 mg:
Each tablet contains 40 mg simvastatin.
Excipients with known effect:
Each tablet contains 282.60 mg lactose monohydrate.

Simvastatin Teva 80 mg:
Each tablet contains 80 mg simvastatin.
Excipients with known effect:
Each tablet contains 565.24 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Simvastatin Teva 10 mg:
Light pink oval-shaped film-coated tablet with a breakline on one side.

Simvastatin Teva 20 mg:
Tan oval-shaped film-coated tablet with a breakline on one side.

Simvastatin Teva 40 mg:
Pink oval-shaped film-coated tablet with a breakline on one side.

Simvastatin Teva 80 mg:

Brick-red oval-shaped film-coated tablet with a breakline on one side.

Tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Coronary Heart Disease:

In patients with coronary heart disease and hypercholesterolemia Simvastatin Teva is indicated to:

- Reduce the risk of total mortality by reducing coronary death;
- Reduce the risk of non-fatal myocardial infarction;
- Reduce the risk for undergoing myocardial revascularization procedures.
- Reduce the risk of stroke and transient ischemic attacks (TIA).

Hyperlipidemia:

Simvastatin Teva is indicated as an adjunct to diet to reduce elevated TOTAL-C LDL-C Apo B and TG and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb). Simvastatin Teva therefore lowers the LDL-C/HDL-C and the total-C/HDL-C ratios.

Homozygous familial hypercholesterolemia:

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

Hypertriglyceridemia (Fredrickson type IV hyperlipidemia):

Simvastatin Teva is indicated for the treatment of patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).

Dysbetalipoproteinemia (Fredrickson type III hyperlipidemia):

Simvastatin Teva is also indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).

4.2 Posology and method of administration

Posology

Recommended Dosing

The usual dosage range is 5 to 40 mg/day. In patients with CHD, Simvastatin Teva can be started simultaneously with diet. The recommended usual starting dose is 10 or 20 mg once a day in the evening. Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter.

Restricted Dosing for 80 mg

Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80-mg dose of Simvastatin Teva should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity [see Special Warnings and Precautions for use (4.4)].

Patients who are currently tolerating the 80-mg dose of Simvastatin Teva who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for the drug-drug interaction.

Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 80-mg dose of Simvastatin Teva, patients unable to achieve their LDL-C goal utilizing the 40-mg dose of Simvastatin Teva should not be titrated to the 80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering.

Co-administration with Other Drugs

Patients taking Verapamil, Diltiazem or Dronedarone
The dose of Simvastatin Teva should not exceed 10 mg/day [see Special Warnings and Precautions for use (4.4), Interaction with other medical products and other forms of interaction (4.5), and Pharmacokinetic properties (5.2)].

Patients taking Amiodarone, Amlodipine or Ranolazine
The dose of Simvastatin Teva should not exceed 20 mg/day [see Special Warnings and Precautions for use (4.5), Interaction with other medical products and other forms of interaction (4.5), and Pharmacokinetic properties (5.2)].

Patients taking Bile Acid Sequestrants
Simvastatin Teva is effective alone or in combination with bile acid sequestrants. Dosing should occur either > 2 hours before or > 4 hours after administration of a bile acid sequestrant.

Patients with Homozygous Familial Hypercholesterolemia
The recommended dosage is 40 mg/day in the evening [see Dosage and Administration, Restricted Dosing for 80 mg (4.2)]. Simvastatin Teva should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Simvastatin exposure is approximately doubled with concomitant use of lomitapide; therefore, the dose of Simvastatin Teva should be reduced by 50% if initiating lomitapide. Simvastatin Teva dosage should not exceed 20 mg/day (or 40 mg/day for patients who have previously taken Simvastatin Teva 80 mg/day chronically, e.g., for 12 months or more, without evidence of muscle toxicity) while taking lomitapide.

Patients with Renal Impairment

Because Simvastatin Teva does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal impairment. However, caution should be exercised when Simvastatin Teva is administered to patients with severe renal impairment; such patients should be started at 5 mg/day and be closely monitored [see Interaction with other medical products and other forms of interaction (4.5) and Pharmacokinetic properties (5.2)].

Chinese Patients Taking Lipid-Modifying Doses (≥1 g/day Niacin) of Niacin-Containing Products

Because of an increased risk for myopathy in Chinese patients taking simvastatin 40 mg co-administered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products, caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day co-administered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg co-administered with lipid-modifying doses of niacin-containing products. The cause of the increased risk of myopathy is not known. It is also unknown if the risk for myopathy with co-administration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients. [Interaction with other medical products and other forms of interaction (4.5).]

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 lactation (see section 4.6).
- Concomitant administration of potent CYP3A4 inhibitors (agents that increase AUC approximately 5 fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and medicinal products containing cobicistat) (see sections 4.4 and 4.5).
- Concomitant administration of gemfibrozil, ciclosporin, or danazol (see sections 4.4 and 4.5).
- In patients with HoFH, concomitant administration of lomitapide with doses > 40 mg simvastatin (see sections 4.2, 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 ten times the upper limit of normal (ULN).

Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma (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).

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. 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% (see sections 4.8 and 5.1).

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C-lowering efficacy. Therefore, the 80-mg dose of simvastatin should only be used in patients with severe hypercholesterolemia and 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 below Measures to reduce the risk of myopathy caused by medicinal product interactions and sections 4.2, 4.3, and 4.5).

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.

Reduced function of transport proteins

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

Patients carrying the SLCO1B1 gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin and increased risk of myopathy. The risk of high dose (80 mg) simvastatin related myopathy is about 1 % in general, without genetic testing. Based on the results of the SEARCH trial, homozygote C allele carriers (also called CC) treated with 80 mg have a 15% risk of myopathy within one year, while the risk in heterozygote C allele carriers (CT) is 1.5%. The corresponding risk is 0.3% in patients having the most common genotype (TT)

(see section 5.2). Where available, genotyping for the presence of the C allele should be considered as part of the benefit-risk assessment prior to prescribing 80 mg simvastatin for individual patients and high doses avoided in those found to carry the CC genotype. However, absence of this gene upon genotyping does not exclude that myopathy can still occur.

Creatine Kinase measurement

Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult.

If CK levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment

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

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

- Elderly (age ≥ 65 years).
- Female gender.
- Renal impairment.
- Uncontrolled hypothyroidism.
- Personal or familial history of hereditary muscular disorders.
- Previous history of muscular toxicity with a statin or fibrate.
- Alcohol abuse.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with a different member of the class should only be initiated with caution. If CK levels are significantly elevated at baseline (> 5 x ULN), treatment should not be started.

Whilst on treatment

If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (>5 x ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are <5 x ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

There have been very 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 creatine kinase, which persist despite discontinuation of statin treatment (see section 4.8).

If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

A higher rate of myopathy has been observed in patients titrated to the 80 mg dose (see section 5.1). Periodic CK measurements are recommended as they may be useful to identify subclinical cases of myopathy. However, there is no assurance that such monitoring will prevent myopathy.
Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)
The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, nefazodone, medicinal products containing cobicistat), as well as gemfibrozil, ciclosporin and danazol. Use of these medicinal products is contraindicated (see section 4.3).

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of amiodarone, amlodipine, verapamil, or diltiazem with certain doses of simvastatin (see sections 4.2 and 4.5). For patients with HoFH, this risk may be increased by concomitant use of lomitapide with simvastatin.

Consequently, regarding CYP3A4 inhibitors, the use of simvastatin concomitantly with itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and medicinal products containing cobicistat is contraindicated (see sections 4.3 and 4.5).

If treatment with potent CYP3A4 inhibitors (agents that increase AUC approximately 5 fold or greater) is unavoidable, therapy with simvastatin must be suspended (and use of an alternative statin considered) during the course of treatment. Moreover, caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, diltiazem (see sections 4.2 and 4.5). Concomitant intake of grapefruit juice and simvastatin should be avoided.

The use of simvastatin with gemfibrozil is contraindicated (see section 4.3). Due to the increased risk of myopathy and rhabdomyolysis, the dose of simvastatin should not exceed 10 mg daily in patients taking simvastatin with other fibrates, except fenofibrate (See sections 4.2 and 4.5.).

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

Simvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Statin therapy may be re-introduced seven days after the last dose of fusidic acid.
In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of simvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

The combined use of simvastatin at doses higher than 20 mg daily with amiodarone, amlodipine, should be avoided. The combined use of simvastatin at doses higher than 10 mg daily with verapamil, or diltiazem should be avoided. In patients with HoFH, the combined use of simvastatin at doses higher than 40 mg daily with lomitapide must be avoided (see sections 4.2, 4.3 and 4.5).

Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy. When co-administering simvastatin with a moderate inhibitor of CYP3A4 (agents that increase AUC approximately 2-5 fold), a dose adjustment of simvastatin may be necessary. For certain moderate CYP3A4 inhibitors e.g. diltiazem, a maximum dose of 20 mg simvastatin is recommended (see section 4.2).

Simvastatin is a substrate of the Breast Cancer Resistant Protein (BCRP) efflux transporter. 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 should be considered depending on the prescribed dose. 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).

Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of HMG-CoA reductase inhibitors and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid), either of which can cause myopathy when given alone.

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 (nicotinic acid). Therefore, physicians contemplating combined therapy with

simvastatin and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid) or products containing niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when the dose of either medicinal product is increased.

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 modified-release nicotinic acid/laropiprant 2000 mg/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 (nicotinic acid) is not recommended in Asian patients.

Acipimox is structurally related to niacin. Although acipimox was not studied, the risk for muscle related toxic effects may be similar to niacin.

Daptomycin

Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. simvastatin) 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 temporarily suspend simvastatin in patients using daptomycin unless the benefits of concomitant administration outweigh the risk.
Consult the prescribing information of daptomycin to obtain further information about this potential interaction with HMG-CoA reductase inhibitors (e.g. simvastatin) and for further guidance related to monitoring. (See section 4.5.).

Hepatic effects

In clinical studies, persistent increases (to > 3 x ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When simvastatin was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels.

It is recommended that liver function tests be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80 mg dose should receive an additional test prior to titration, 3 months after titration to the 80 mg dose, and periodically thereafter (e.g., semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 x ULN and are persistent, simvastatin should be discontinued. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see above 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 etiology is not found, do not restart simvastatin.

The product should be used with caution in patients who consume substantial quantities of alcohol.

As with other lipid-lowering agents, moderate (<3 x ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

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

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, nonproductive 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.

Excipient(s)
Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products 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 drugs to obtain further information about their potential interactions with simvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

Interaction studies have only been performed in adults.

Pharmacodynamic interactions
Interactions with lipid-lowering medicinal products that can cause myopathy when given alone

The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates.

Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see below Pharmacokinetic interactions and sections 4.3 and 4.4). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent.

Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates. Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (see section 4.4).

Pharmacokinetic interactions
Prescribing recommendations for interacting agents are summarized in the table below (further details are provided in the text; see also sections 4.2, 4.3 and 4.4).

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting agents	**Prescribing recommendations**
Potent CYP3A4 inhibitors, e.g., Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g., nelfinavir) Boceprevir Telaprevir Nefazodone Cobicistat Ciclosporin Danazol Gemfibrozil	Contraindicated with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily
Fusidic acid	Is not recommended with simvastatin

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting agents	**Prescribing recommendations**
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with simvastatin
Amiodarone Amlodipine Elbasvir Grazoprevir	Do not exceed 20 mg simvastatin daily
Verapamil Diltiazem	Do not exceed 10 mg simvastatin daily
Lomitapide	For patients with HoFH, do not exceed 40 mg simvastatin daily
Daptomycin	It should be considered to temporarily suspend simvastatin in patients using daptomycin unless the benefits of concomitant administration outweigh the risk (see section 4.4)
Ticagrelor	Doses greater than 40 mg simvastatin daily are not recommended
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Effects of other medicinal products on simvastatin

Interactions involving inhibitors of CYP3A4

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors *(e.g.* nelfinavir), boceprevir, telaprevir, nefazodone and medicinal products containing cobicistat. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11-fold increase in exposure to simvastatin acid.

Combination with itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin , nefazodone and medicinal products containing cobicistat is contraindicated, as well as gemfibrozil, ciclosporin, and danazol (see section 4.3). If treatment with potent CYP3A4 inhibitors (agents that increase AUC approximately 5 fold or greater) is unavoidable, therapy with simvastatin must be suspended (and use of an alternative statin considered) during the course of treatment. Caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil or diltiazem (see sections 4.2 and 4.4).

Fluconazole

Rare cases of rhabdomyolysis associated with concomitant administration of

simvastatin and fluconazole have been reported (see section 4.4).

Ciclosporin
The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin with simvastatin; therefore, use with ciclosporin is contraindicated (see sections 4.3 and 4.4). 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.

Danazol
The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with simvastatin; therefore, use with danazol is contraindicated (see sections 4.3 and 4.4).

Gemfibrozil
Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway and/or OATP1B1 (see sections 4.3 and 4.4). Concomitant administration with gemfibrozil is contraindicated.

Fusidic acid
The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.
If treatment with systemic fusidic acid is necessary, simvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. **Also see section 4.4.**

Amiodarone
The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with simvastatin (see section 4.4). In a clinical trial, myopathy was reported in 6 % of patients receiving simvastatin 80 mg and amiodarone. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone.

Calcium Channel Blockers
- *Verapamil*

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of verapamil with simvastatin 40 mg or 80 mg (see section 4.4). In a pharmacokinetic study, concomitant administration with verapamil resulted in a 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with verapamil.

- *Diltiazem*

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg (see section 4.4). In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with diltiazem.

- *Amlodipine*

Patients on amlodipine treated concomitantly with simvastatin have an increased risk of myopathy. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amlodipine.

- *Lomitapide*

The risk of myopathy and rhabdomyolysis may be increased by concomitant administration of lomitapide with simvastatin (see sections 4.3 and 4.4). Therefore, in patients with HoFH, the dose of simvastatin must not exceed 40 mg daily in patients receiving concomitant medication with lomitapide.

- *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)

Concomitant administration of medicinal products that are inhibitors of BCRP, including products containing elbasvir or grazoprevir, may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy (see section 4.2 and 4.4).

Niacin (nicotinic acid)

Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid). In a pharmacokinetic study, the co-administration of a single dose of nicotinic acid prolonged- release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin and simvastatin acid and in the Cmax of simvastatin acid plasma concentrations.

Ticagrelor

Co-administration of ticagrelor with simvastatin increased 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. Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg daily could cause adverse reactions of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. The concomitant use of ticagrelor with doses of simvastatin greater than 40 mg is not recommended.

Grapefruit juice
Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 liter daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 ml of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

Colchicine
There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal impairment. Close clinical monitoring of such patients taking this combination is advised.

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

Rifampicin
Because rifampicin is a potent CYP3A4 inducer, patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis) may experience loss of efficacy of simvastatin. In a pharmacokinetic study in normal volunteers, the area under the plasma concentration curve (AUC) for simvastatin acid was decreased by 93% with concomitant administration of rifampicin.

Effects of simvastatin on the pharmacokinetics of other medicinal products Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is not expected to affect plasma concentrations of substances metabolised via cytochrome P450 3A4.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Simvastatin is contraindicated during pregnancy (see section 4.3).

Safety in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, simvastatin must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (See sections 4.3 and 5.3).

Breastfeeding

It is not known whether simvastatin or its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions, women taking simvastatin must not breast-feed their infants (see section 4.3).

Fertility

No clinical trial data are available on the effects of simvastatin on human fertility. Simvastatin had no effect on the fertility of male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequencies of the following adverse events, which have been reported during clinical studies and/or post-marketing use, are categorized based on an assessment

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

In HPS (see section 5.1) involving 20,536 patients treated with 40 mg/day of simvastatin (n = 10,269) or placebo (n =10,267), the safety profiles were comparable between patients treated with simvastatin 40 mg and patients treated with placebo over the mean 5 years of the study. Discontinuation rates due to side effects were comparable (4.8% in patients treated with simvastatin 40 mg/day compared with 5.1 % in patients treated with placebo). The incidence of myopathy was < 0.1 % in patients treated with simvastatin 40 mg/day. Elevated transaminases (>3 x ULN confirmed by repeat test) occurred in 0.21 % (n = 21) of patients treated with simvastatin 40 mg/day compared with 0.09 % (n = 9) of patients treated with placebo.

The frequencies of adverse events are ranked according to the following: Very common (> 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1000, < 1/100), Rare (≥ 1/10,000, < 1/1 000), Very Rare (< 1/10,000), Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:
Rare: anaemia

Immune system disorders:
Very rare: anaphylaxis

Psychiatric disorders:
Very rare: insomnia
Not known: depression

Nervous system disorders:
Rare: headache, paraesthesia, dizziness, peripheral neuropathy
Very rare: memory impairment

Eye disorders:
Rare: vision blurred, visual impairment

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

Hepatobiliary disorders:
Rare: hepatitis/jaundice
Very rare: fatal and non-fatal hepatic failure

Skin and subcutaneous tissue disorders:
Rare: rash, pruritus, alopecia
Very rare: lichenoid drug eruptions

Musculoskeletal and connective tissue disorders:
Rare: myopathy* (including myositis), rhabdomyolysis with or without acute renal failure (see section 4.4), myalgia, muscle cramps
* In a clinical trial, myopathy occurred commonly in patients treated with simvastatin 80 mg/day compared to patients treated with 20 mg/day (1.0% vs. 0.02%, respectively) (see sections 4.4 and 4.5).
Very rare: muscle rupture
Not known: tendinopathy, sometimes complicated by rupture, immune-mediated necrotizing myopathy (see section 4.4).

Reproductive system and breast disorders:
Very rare: gynaecomastia
Not known: erectile dysfunction

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

Investigations
Rare: increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase, Y-glutamyl transpeptidase) (see section 4.4 Hepatic effects), elevated alkaline phosphatase; increase in serum CK levels (see section 4.4).
Increases in HbA1c and fasting serum glucose levels have been reported with statins, including simvastatin.

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

The following adverse events have been reported with some statins:

- Sleep disturbances, including nightmares
- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥5.6 mmol/L, BMI > 30 kg/m^2, raised

triglycerides, history of hypertension).

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitor.

ATC Code: C10A A01.

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

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes the ratios of total-to HDL-C and LDL-to HDL-C are reduced.

Clinical efficacy and safety
High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease
In the Heart Protection Study (HPS), the effects of therapy with simvastatin were assessed in 20,536 patients (age 40-80 years), with or without hyperlipidaemia, and with coronary heart disease, other occlusive arterial disease or diabetes mellitus. In this study, 10,269 patients were treated with simvastatin 40 mg/day and 10,267 patients were treated with placebo for a mean duration of 5 years. At baseline, 6,793

patients (33%) had LDL-C levels below 116 mg/dL; 5,063 patients (25%) had levels between 116 mg/dL and 135 mg/dL and 8,680 patients (42%) had levels greater than 135 mg/dL.

Treatment with simvastatin 40 mg/day compared with placebo significantly reduced the risk of all-cause mortality (1328 [12.9%] for simvastatin-treated patients versus 1507 [14.7 %] for patients given placebo; p = 0.0003), due to an 18 % reduction in coronary death rate (587 [5.7 %] versus 707 [6.9 %]; p = 0.0005; absolute risk reduction of 1.2%). The reduction in non- vascular deaths did not reach statistical significance. Simvastatin also decreased the risk of major coronary events (a composite endpoint comprised of non-fatal MI or CHD death) by 27% (p < 0.0001). Simvastatin reduced the need for undergoing coronary revascularization procedures (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) and peripheral and other non-coronary revascularization procedures by 30% (p< 0.0001) and 16% (p = 0.006), respectively. Simvastatin reduced the risk of stroke by 25% (p < 0.0001), attributable to a 30% reduction in ischemic stroke (p < 0.0001). In addition, within the subgroup of patients with diabetes, simvastatin reduced the risk of developing macrovascular complications, including peripheral revascularization procedures (surgery or angioplasty), lower limb amputations or leg ulcers by 21% (p = 0.0293). The proportional reduction in event rate was similar in each subgroup of patients studied, including those without coronary disease but who had cerebrovascular or peripheral artery disease, men and women, those aged either under or over 70 years at entry into the study, presence or absence of hypertension, and notably those with LDL cholesterol below 3.0 mmol/l at inclusion.

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with simvastatin on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5 - 8.0 mmol/L). In this multicenter, randomised, double-blind, placebo- controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet, standard care, and either simvastatin 20-40 mg/day (n = 2,221) or placebo (n = 2,223) for a median duration of 5.4 years. Simvastatin reduced the risk of death by 30% (absolute risk reduction of 3.3%). The risk of CHD death was reduced by 42 % (absolute risk reduction of 3.5 %). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent nonfatal MI) by 34%. Furthermore, simvastatin significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischemic attacks) by 28 %. There was no statistically significant difference between groups in non-cardiovascular mortality.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) evaluated the effect of treatment with simvastatin 80 mg versus 20 mg (median follow-up 6.7 yrs) on major vascular events (MVEs; defined as fatal CHD, non-fatal MI, coronary revascularization procedure, non-fatal or fatal stroke, or peripheral revascularization procedure) in 12,064 patients with a history of myocardial infarction. There was no significant difference in the incidence of MVEs between the 2 groups; simvastatin 20 mg (n = 1553; 25.7%) vs. simvastatin 80 mg (n = 1477; 24.5%); RR 0.94, 95 % CI: 0.88 to 1.01. The absolute difference in LDL-C

between the two groups over the course of the study was 0.35 ± 0.01 mmol/L. The safety profiles were similar between the two treatment groups except that the incidence of myopathy was approximately 1.0 % for patients on simvastatin 80 mg compared with 0.02% for patients on 20 mg. 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%.

Primary Hypercholesterolaemia and Combined Hyperlipidaemia
In studies comparing the efficacy and safety of simvastatin 10, 20, 40 and 80 mg daily in patients with hypercholesterolaemia, the mean reductions of LDL-C were 30, 38, 41 and 47 %, respectively. In studies of patients with combined (mixed) hyperlipidaemia on simvastatin 40 mg and 80 mg, the median reductions in triglycerides were 28 and 33% (placebo: 2%), respectively, and mean increases in HDL-C were 13 and 16 % (placebo: 3 %), respectively.

5.2 Pharmacokinetic properties
Simvastatin is an inactive lactone which is readily hydrolyzed in vivo to the corresponding beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

The pharmacokinetic properties have been evaluated in adults. Pharmacokinetic data in children and adolescents are not available.

Absorption
In man, simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose.

Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicinal product occurred after multiple dosing.

Distribution
The protein binding of simvastatin and its active metabolite is >95%.

Elimination
Simvastatin is a substrate of CYP3A4 (see sections 4.3 and 4.5). The major metabolites of simvastatin present in human plasma are the beta-hydroxyacid and four additional active metabolites. Following an oral dose of radioactive simvastatin to man, 13% of the radioactivity was excreted in the urine and 60% in the faeces within 96 hours. The amount recovered in the faeces represents absorbed medicinal product

equivalents excreted in bile as well as unabsorbed medicinal product. Following an intravenous injection of the betahydroxyacid metabolite, its half-life averaged 1.9 hours. An average of only 0.3% of the IV dose was excreted in urine as inhibitors.

Simvastatin is taken up actively into the hepatocytes by the transporter OATP1B1. Simvastatin is a substrate of the efflux transporter BCRP.

Special Populations
SLCO1B1 polymorphism Carriers of the SLCO1B1 gene c.521T>C allele have lower OATP1B1 activity. The mean exposure (AUC) of the main active metabolite, simvastatin acid is 120% in heterozygote carriers (CT) of the C allele and 221% in homozygote (CC) carriers relative to that of patients who have the most common genotype (TT). The C allele has a frequency of 18% in the European population. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of simvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4).

5.3 Preclinical safety data
Based on conventional animal studies regarding pharmacodynamics, repeated dose toxicity, genotoxicity and carcinogenicity, there are no other risks for the patient than may be expected on account of the pharmacological mechanism. At maximally tolerated doses in both the rat and the rabbit, simvastatin produced no foetal malformations, and had no effects on fertility, reproductive function or neonatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core:
Lactose monohydrate
Pregelatinized starch
Microcrystalline cellulose
Ascorbic acid
Citric acid monohydrate
Magnesium stearate
Butylhydroxyanisole

Coating:
Hypromellose
Lactose monohydrate
Titanium dioxide
Macrogol
Triacetin
Red iron oxide
10mg, 20mg, 80mg: yellow iron oxide
80mg: black iron oxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store in a dry and dark place, below 25°C.

6.5 Nature and contents of container
Simvastatin Teva 10 mg: 30 tablets in PVC/PE/PVDC/Al blisters in a cardboard box.
Simvastatin Teva 20 mg: 30 tablets in PVC/PE/PVDC/Al blisters in a cardboard box.
Simvastatin Teva 40 mg: 10, 30, 60,100 tablets in PVC/PE/PVDC/Al blisters in a cardboard box.
Simvastatin Teva 80 mg: 12, 30 tablets in PVC/PE/PVDC/Al blisters in a cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. LICENCE HOLDER AND MANUFACTURER

Teva Israel Ltd.,
124 Dvora HaNevi'a st., Tel Aviv 6944020.

8. MARKETING AUTHORISATION NUMBER(S)

Simvastatin Teva 10mg: 120.94.30070
Simvastatin Teva 20mg: 120.75.30071
Simvastatin Teva 40mg: 129.18.30737
Simvastatin Teva 80mg: 128.05.30671

The leaflet was revised in December 2021 according to the MOHs guidelines.