SCHEDULING STATUS
S4

1. NAME OF THE MEDICINE
ADCO SIMVASTATIN 10 mg TABLETS
ADCO SIMVASTATIN 20 mg TABLETS
ADCO SIMVASTATIN 40 mg TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ADCO SIMVASTATIN 10 mg tablet contains simvastatin 10 mg and butylhydroxianisole 0,02 % m/m as an antioxidant.
Contains sugar: anhydrous lactose 74,5 mg.

Each ADCO SIMVASTATIN 20 mg tablet contains simvastatin 20 mg and butylhydroxianisole 0,02 % m/m as an antioxidant.
Contains sugar: anhydrous lactose 149 mg.

Each ADCO SIMVASTATIN 40 mg tablet contains simvastatin 40 mg and butylhydroxianisole 0,02 % m/m as an antioxidant.
Contains sugar: anhydrous lactose 298 mg.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablets.

ADCO SIMVASTATIN 10 mg tablets:
White, oblong, biconvex, film-coated tablets, scored on the one side. The tablets are debossed with “SVT” on the unscored side and “10” on the scored side.

ADCO SIMVASTATIN 20 mg tablets:
White, oblong, biconvex, film-coated tablets, scored on the one side. The tablets are debossed with “SVT” on the unscored side and “20” on the scored side.

ADCO SIMVASTATIN 40 mg tablets:
White, oblong, biconvex, film-coated tablets, scored on the one side. The tablets are debossed with “SVT” on the unscored side and “40” on the scored side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypercholesterolaemia
ADCO SIMVASTATIN is indicated, in combination with diet, to decrease elevated serum total cholesterol and LDL-cholesterol in patients with:

- Primary hypercholesterolaemia or
- Heterozygous familial hypercholesterolaemia or
- Combined (mixed) hyperlipidaemia when response to diet or other non-pharmacological measures alone are inadequate.

Coronary heart disease
Patients with established coronary heart disease and hypercholesterolaemia in whom dietary measures have been inadequate or ineffective.
ADCO SIMVASTATIN is indicated to:

- Reduce the risk of total mortality by decreasing coronary death
- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of undergoing myocardial revascularization procedures (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty)
- ADCO SIMVASTATIN is also indicated to slow the progression of coronary atherosclerosis.

4.2 Posology and method of administration
Posology
The patient should be placed on a standard cholesterol-lowering diet before receiving ADCO SIMVASTATIN and should continue on this diet during treatment with ADCO SIMVASTATIN.

Adults
Hypercholesterolaemia
The usual initial dose is 10 mg/day given as a single dose in the evening. The dosage may be adjusted, if needed, but at intervals of not less than 4 weeks. The maximum dosage that may be given is 80 mg daily as a single dose in the evening. If LDL-cholesterol levels fall below 1,94 mmol/l (75 mg/dl) or total plasma cholesterol levels fall below 3,6 mmol/l (140 mg/dl) consideration should be given to a reduction in dose of ADCO SIMVASTATIN.

Coronary heart disease
A starting dose of 20 mg/day may be given as a single dose in the evening.The dosage may be adjusted, if needed, should be made at intervals of not less than 4 weeks, up to a maximum of 80 mg daily as a single dose in the evening.

Dosage in renal insufficiency
Patients with moderate renal insufficiency may not require dosage adjustments due to the fact that ADCO SIMVASTATIN does not undergo significant renal excretion. Implementation of dosages above 10 mg/day require careful consideration and caution in patients with severe renal insufficiency (creatine clearance < 30 ml/min).

Concomitant therapy
Dosing of ADCO SIMVASTATIN should occur either 2 or more hours before or 4 or more hours after administration of a bile acid sequestrant. In patients taking ciclosporin, danazol or greater

than or equal to 1 g/day of niacin concomitantly with ADCO SIMVASTATIN, the dose of ADCO SIMVASTATIN should not exceed 10 mg/day (see sections 4.4 and 4.5).
In patients taking amiodarone, verapamil or diltiazem, or products containing elbasvir or grazoprevir concomitantly with ADCO SIMVASTATIN, the dose of ADCO SIMVASTATIN should not exceed 20 mg/day (see sections 4.4 and 4.5). In patients taking amlodipine concomitantly with ADCO SIMVASTATIN, the dose of ADCO SIMVASTATIN should not exceed 40 mg/day (see sections 4.4 and 4.5).

Special populations
Elderly population:
No dosage adjustment is required for this population.

Paediatric population:
As safety and efficacy have not yet been established, use in paediatric patients is not advised.

Method of administration
For oral use.

4.3. Contraindications
- Hypersensitivity to simvastatin or to any of the excipients listed in section 6.1.
- Simvastatin should not be given to patients with acute liver disease or unexplained persistent raised serum-amino transferase concentrations or those with porphyria.
- Pregnancy and lactation (see section 4.6).
- Concomitant administration of strong CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole; HIV protease inhibitors, such as ritonavir, saquinavir, nelfinavir, boceprevir and telaprevir; erythromycin, clarithromycin, telithromycin; nefazodone and medicines containing cobicistat) (see sections 4.4 and 4.5).
- In patients with homozygous familial hypercholesterolemia (HoFH),
- concomitant administration of lomitapide with doses > 40 mg ADCO SIMVASTATIN (see section 4.2, section 4.4 and section 4.5)
- Concomitant administration of gemfibrozil, ciclosporin or danazol (see sections 4.4 and 4.5).

4.4. Special warnings and precautions for use
Concomitant use of immunosuppressive medicines (especially cyclosporine), fibric acid derivatives and/or niacin with HMG-CoA reductase inhibitors has resulted in rhabdomyolysis, sometimes with acute renal failure.

Agents of the Statin Class FDA Class Warnings for Lipid Lowering
The following effects have been reported with medicines in this class; not all effects listed below have necessarily been associated with ADCO SIMVASTATIN therapy.

Skeletal: myopathy, muscle cramps, rhabdomyolysis, arthralgias, myalgia.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, dizziness, memory loss, vertigo, paraesthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression, psychic disturbances.

Hypersensitivity reactions: an apparent hypersensitivity syndrome has been reported that included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leucopenia, haemolytic anaemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnoea, toxic epidermal necrolysis, erythema multiforme including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, cirrhosis, fulminant hepatic necrosis and hepatoma, anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes, (e.g. nodules, discolouration, dryness of skin/mucous membranes, changes to hair/nails), have been reported.

Reproductive: gynaecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory abnormalities: elevated transaminases, creatine kinase, alkaline phosphatase, gammaglutamyl transpeptidase and bilirubin, thyroid function abnormalities.

Hepatic effects
Marked, persistent elevations in serum transaminases (to more than 3 times the upper limit of normal) have occurred. Upon discontinuation or interruption of simvastatin treatment, the elevated transaminase levels in these patients slowly dropped to pretreatment levels. All patients are advised to undergo liver function tests prior to initiation of therapy, and periodically thereafter, as hepatitis, an indicator of which is an increase in liver enzymes, has also been reported. Caution should be exercised in patients who develop elevated serum transaminase levels. Measurements should be repeated promptly and then performed more frequently in such patients. 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. semiannually) 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 upper limit of normal (ULN) and are persistent, ADCO SIMVASTATIN should be discontinued. Note that ALT may emanate from muscle, therefore ALT rising with creatine kinase (CK) may indicate myopathy (see below Myopathy/Rhabdomyolysis).There have been rare post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including ADCO SIMVASTATIN. If serious liver injury

with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with ADCO SIMVASTATIN, promptly interrupt therapy. If an alternate aetiology is not found, do not restart ADCO SIMVASTATIN. Discontinue treatment with ADCO SIMVASTATIN if the transaminase levels continue to rise, particularly if they rise to three times the upper limit of normal and are persistent. Patients who consume substantial quantities of alcohol and/or have a history of liver disease should use ADCO SIMVASTATIN with caution. The use of simvastatin is contraindicated in patients with active liver diseases or in patients that have unexplained increases in transaminase levels.

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

Chinese patients
Because of an increased risk for myopathy in Chinese patients taking simvastatin 40 mg co-administered with lipid-modifying (greater than or equal to 1 g/day niacin) of niacin-containing products, caution should be used when treating Chinese patients with ADCO SIMVASTATIN doses exceeding 20 mg/day co-administered with lipid-modifying doses of niacin-containing medicines.

Ophthalmic effects
An increase in the prevalence of lens opacities is expected with time as a result of ageing and not necessarily due to the use of simvastatin. No relationship exists between the use of simvastatin and adverse effects on the human lens.

Skeletal muscle effects
Risk of myasthenia gravis and ocular myasthenia. Statins have been reported to either induce new onset, or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8), should these conditions occur, ADCO SIMVASTATIN should be discontinued. There have been reports of recurrences of these conditions when the same or a different statin was (re-) administered.

Myopathy/Rhabdomyolysis

Increased CK levels (from skeletal muscles) have been frequently reported. Marked elevations of CK above ten times the ULN, muscle tenderness and/or diffuse myalgia are symptoms of myopathy. This condition should be considered in any patient presenting with such symptoms. In addition, any unexplained muscle pain, tenderness or weakness should be reported immediately. If there is a potential diagnosis of myopathy, or if there is a significant increase in CK levels, treatment with ADCO SIMVASTATIN should be discontinued immediately.
Concomitant use of ADCO SIMVASTATIN together with immunosuppressive agents including cyclosporine, fibric acid derivatives or lipid lowering doses of niacin (nicotinic acid) could increase the risk of myopathy. The risk / benefit profile of these combinations should therefore be carefully considered.
Patients on HMG-CoA reductase inhibitor therapy have experienced rhabdomyolysis with or without renal impairment 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 ADCO SIMVASTATIN and simvastatin acid plasma levels), which may be due, in part, to interacting medicines that interfere with ADCO SIMVASTATIN metabolism and/or transporter pathways (see section 4.5). A renal transplant patient on cyclosporine and simvastatin experienced muscle fatigue together with a significant increase of CK, after the introduction of therapy with the systemic antifungal agent itraconazole. Cholesterol biosynthesis is inhibited at different stages in the biosynthetic pathway by the HMG-CoA reductase inhibitors and the azole derivative antifungal agents. Simvastatin treatment should therefore be temporarily discontinued in patients receiving cyclosporine and simvastatin, who also require systemic azole derivative antifungal therapy. Patients only receiving simvastatin require careful monitoring if systemic azole derivative antifungal therapy is initiated. 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 ADCO SIMVASTATIN should only be used in patients with severe hypercholesterolaemia 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 medicine is needed, a lower dose of simvastatin or an alternative statin-based regimen with less potential for medicine-medicine interactions should be used (see below Measures to reduce the risk of myopathy caused by medicine interactions and sections 4.2, 4.3, and 4.5).

Reducing the risk of myopathy

Reduced function of transport proteins

Reduced function of hepatic OATP transport proteins can increase the systemic exposure of simvastatin acid 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 acid and increased risk of myopathy. The risk of high dose (80 mg) simvastatin related myopathy is about 1 % in general, without genetic testing.

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
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.

General measures
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 of 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 necrotising myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised 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 ADCO SIMVASTATIN should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes. There have been reports of cognitive impairment (such as memory loss, forgetfulness, amnesia and confusion) associated with statins such as ADCO SIMVASTATIN. These were generally not serious, with variable time-to-symptom onset (between 1 day to years) and symptom resolution (median 3 weeks). Increased glycosylated haemoglobin, fasting serum glucose levels and worsening of glycaemic control have been reported with statins such as ADCO SIMVASTATIN.

Measures to reduce the risk of myopathy caused by medicine interactions (see also section 4.5)

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of ADCO SIMVASTATIN with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole posaconazole, voriconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, such as ritonavir, saquinavir, nelfinavir, boceprevir and telaprevir; the antidepressant nefazodone, or grapefruit juice, medicines containing cobicistat. The combined use of ADCO SIMVASTATIN with gemfibrozil, ciclosporin or danazol is contraindicated (see sections 4.3 and 4.5).

In patients receiving cysclosporin, ADCO SIMVASTATIN should be temporarily discontinued if systemic azole derivatives antifungal therapy is required. The risk of myopathy and rhabdomyolysis is also increased by concomitant use of amiodarone, amlodipine, verapamil, or diltiazem with certain doses of ADCO SIMVASTATIN (see sections 4.2 and 4.5). The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of fusidic acid with statins (see section 4.5). For patients with HoFH, this risk may be increased by concomitant use of lomitapide with ADCO SIMVASTATIN. Consequently, regarding CYP3A4 inhibitors, the use of ADCO SIMVASTATIN concomitantly with itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir, boceprevir, telaprevir), erythromycin, clarithromycin, telithromycin, nefazodone, and medicines containing cobicistat is contraindicated (see sections 4.3 and 4.5). If treatment with potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) is unavoidable, therapy with ADCO SIMVASTATIN must be suspended (and use of an alternative statin considered) during the course of treatment. Moreover, caution should be exercised when combining ADCO 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 ADCO 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 medicine can cause myopathy when given alone. ADCO 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 ADCO SIMVASTATIN and fusidic acid should only be considered on a case by case basis and under close medical supervision. The combined use of ADCO SIMVASTATIN at doses higher than 20 mg daily with amiodarone, amlodipine, verapamil, or diltiazem should be avoided. In patients with HoFH, the combined use of ADCO 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 ADCO SIMVASTATIN, particularly higher ADCO SIMVASTATIN doses, may have an increased risk of myopathy. When co-administering ADCO SIMVASTATIN with a moderate inhibitor of CYP3A4 (medicines that increase AUC approximately 2-5 fold), a dose adjustment of ADCO SIMVASTATIN may be necessary. For certain moderate CYP3A4 inhibitors e.g. diltiazem, a maximum dose of 20 mg ADCO SIMVASTATIN is recommended (see section 4.2).
Simvastatin as in ADCO SIMVASTATIN is a substrate of the Breast Cancer Resistant Protein (BCRP) efflux transporter. Concomitant administration of medicines that are inhibitors of BCRP (e.g. elbasvir and grazoprevir) may lead to increased plasma concentrations of ADCO SIMVASTATIN and an increased risk of myopathy; therefore, a dose adjustment of ADCO SIMVASTATIN should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with ADCO SIMVASTATIN has not been studied; however, the dose of ADCO SIMVASTATIN should not exceed 20 mg daily in patients receiving concomitant treatment with medicines 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.

Daptomycin
Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. simvastatin as in ADCO SIMVASTATIN) co-administered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either medicine can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to temporarily suspend ADCO SIMVASTATIN in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk. Consult the professional information of daptomycin to obtain further information about this potential interaction with HMG-CoA reductase inhibitors (e.g. simvastatin as in ADCO SIMVASTATIN) and for further guidance related to monitoring (see section 4.5).

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

4.5 Interactions with other medicines and other forms of interaction

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

Consult the professional information of all concomitantly used medicines to obtain further information about their potential interactions with ADCO SIMVASTATIN and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

Pharmacodynamic interaction

Interactions with lipid-lowering medicines that can cause myopathy when given alone.

The risk of myopathy and rhabdomyolysis is increased during concomitant administration with fibrates. Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased ADCO SIMVASTATIN plasma levels (see below Pharmacokinetic interactions and sections 4.3 and 4.4). When ADCO SIMVASTATIN and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each medicine. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates. Rare cases of myopathy/rhabdomyolysis have been associated with ADCO SIMVASTATIN co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (see section 4.4).

Pharmacokinetic interactions

Prescribing recommendations for interacting medicines are summarised in the table below (further details are provided in the text; see also section 4.3 and section 4.4).

Medicine Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Medicine Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting medicines	**Prescribing recommendations**
Potent CYP3A4 inhibitors, e.g. Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Boceprevir Telaprevir Nefazodone Cobicistat Cyclosporin Danazol	Contraindicated with ADCO SIMVASTATIN

Gemfibrozil	
Other fibrates (except fenofibrate)	Do not exceed 10 mg ADCO SIMVASTATIN daily
Fusidic acid	Is not recommended with ADCO SIMVASTATIN
Niacin (nicotinic acid) (≥ 1 g/day)	For Chinese patients, not recommended with ADCO SIMVASTATIN
Amiodarone Amlodipine Verapamil Diltiazem Elbasvir Grazoprevir	Do not exceed 20 mg ADCO SIMVASTATIN daily
Lomitapide	For patients with HoFH, do not exceed 40 mg ADCO SIMVASTATIN daily
Daptomycin	It should be considered to temporarily suspend ADCO SIMVASTATIN in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk (see section 4.4)
Ticagrelor	Doses greater than 40 mg ADCO SIMVASTATIN daily are not recommended
Grapefruit juice	Avoid grapefruit juice when taking ADCO SIMVASTATIN

Effects of other medicines on ADCO SIMVASTATIN

Interactions involving inhibitors of CYP3A4

ADCO 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 ADCO SIMVASTATIN therapy. Such inhibitors include itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, nefazodone and medicines containing cobicistat. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxy acid 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 medicines containing cobicistat is contraindicated, as well as gemfibrozil, cyclosporin, and danazol (see section 4.3). If treatment with potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) is unavoidable, therapy with ADCO SIMVASTATIN must be suspended (and use of an alternative statin considered) during the course of treatment. Caution should be exercised when combining ADCO SIMVASTATIN with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, or diltiazem (see section 4.2 and section 4.4).

Fluconazole
Rare cases of rhabdomyolysis associated with concomitant administration of simvastatin (such as ADCO SIMVASTATIN) and fluconazole have been reported (see section 4.4).

Ciclosporin
The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin with ADCO 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 such as ADCO SIMVASTATIN. The increase in AUC for simvastatin such as in ADCO SIMVASTATIN 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 ADCO SIMVASTATIN; therefore, use with danazol is contraindicated (see sections 4.3 and 4.4).

Gemfibrozil
Gemfibrozil increases the AUC of simvastatin by 1,9-fold, possibly due to inhibition of the glucuronidation pathway and/or OATP1B1 (see sections 4.3 and 4.4). Concomitant administration of ADCO SIMVASTATIN with gemfibrozil is contraindicated (see section 4.4). A maximum dose of 10 mg ADCO SIMVASTATIN daily is recommended in patients taking fibrates (other than gemfibrozil) or lipid-lowering doses of niacin (nicotinic acid).

Fusidic acid
The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins (such as ADCO SIMVASTATIN). Co-administration of this combination may cause increased plasma concentrations of both medicines. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, ADCO SIMVASTATIN treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

Amiodarone
The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with ADCO SIMVASTATIN (see section 4.4). The dose of ADCO 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 ADCO 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 ADCO SIMVASTATIN should not exceed 20 mg daily in patients receiving concomitant medication with verapamil.

- Diltiazem

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with ADCO 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 ADCO SIMVASTATIN should not exceed 20 mg daily in patients receiving concomitant medication with diltiazem.

- Amlodipine

Patients on amlodipine treated concomitantly with ADCO 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 ADCO 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 ADCO SIMVASTATIN (see sections 4.3 and 4.4). Therefore, in patients with HoFH, the dose of ADCO SIMVASTATIN must not exceed 40 mg daily in patients receiving concomitant treatment with lomitapide.

Moderate Inhibitors of CYP3A4

Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with ADCO SIMVASTATIN, particularly at higher doses, may have an increased risk of myopathy (see section 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 ADCO SIMVASTATIN 20 mg resulted in a modest increase in the AUC of ADCO SIMVASTATIN and simvastatin acid and in the C_{max} of simvastatin acid plasma concentrations.

Inhibitors of the Transport Protein OATP1B1:

Simvastatin acid is a substrate of the transport protein OATP1B1. Concomitant administration of medicines 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 and section 4.4).

Inhibitors of Breast Cancer Resistant Protein (BCRP):
Concomitant administration of medicines that are inhibitors of BCRP, including products containing elbasvir or grazoprevir, may lead to increased plasma concentrations of ADCO SIMVASTATIN and an increased risk of myopathy (see section 4.4).

Ticagrelor:
Co-administration of ticagrelor with ADCO SIMVASTATIN increased ADCO 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 ADCO 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 ADCO SIMVASTATIN greater than 40 mg is not recommended.

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

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 ADCO 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.

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

Effects of ADCO SIMVASTATIN on the pharmacokinetics of other medicines:
ADCO SIMVASTATIN does not have an inhibitory effect on cytochrome P450 3A4. Therefore, ADCO SIMVASTATIN is not expected to affect plasma concentrations of substances metabolised via cytochrome P450 3A4.
Caution should be exercised in the concomitant use of ADCO SIMVASTATIN with ciclosporine, itraconazole, ketoconazole, fibric acid derivatives, niacin, erythromycin, clarithromycin, HIV protease inhibitors or nefazodone (see 4.4 - Skeletal muscle effects).

Coumarin derivatives
Simvastatin 20 to 40 mg/day slightly enhances the effect of coumarin anticoagulants, as indicated by the prothrombin times [reported as International Normalized Ratio (INR)], which increased from a baseline of 1,7 to 1,8 in normal volunteers and from a baseline of 2,6 to 3,4 in hypercholesterolaemic patients. In order to ensure that no significant changes to prothrombin

times occur in patients taking coumarin anticoagulants, the prothrombin time should be determined prior to starting simvastatin therapy and at frequent intervals during early treatment with simvastatin. Prothrombin times may be monitored at the intervals usually indicated for patients on coumarin anticoagulants, once it has stabilised and been documented. Any dosage alterations to simvastatin should follow the same procedure. Patients taking simvastatin have not experienced bleeding or changes in prothrombin time, in the absence of anticoagulant therapy.

Digoxin
Simvastatin elevates digoxin levels.

Fibric acid derivatives
See section 4.4 – Muscle effects.

Other concomitant therapy
ADCO SIMVASTATIN when used simultaneously with immunosuppressant therapy, itraconazole or niacin, should be monitored cautiously. (See section 4.4– Skeletal muscle effects).

Propranolol
Concomitant administration of a single dose of simvastatin and propranolol in healthy male volunteers, showed a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors. The clinical importance of this finding is unclear. The enantiomers of propranolol remain unchanged in terms of their pharmacokinetic properties.

Mibefradil
Raised concentrations of simvastatin have also occurred in patients given mibefradil.

Laboratory test findings
Liver function test abnormalities have been mild and transient. Significant and persistent increases of serum transaminases, elevated serum CK levels (derived from skeletal muscle), elevated alkaline phophatase and elevated γ-glutamyl transpeptidase have been reported. (see section 4.4).

Bile acid sequestrants
Caution should be exercised in the concomitant use of fibric acid derivatives and niacin. ADCO SIMVASTATIN should be taken 1 hour before or 4 hours after cholestyramine. Concurrent use may decrease the bioavailability of ADCO SIMVASTATIN.

Grapefruit juice
Grapefruit juice inhibits cytochrome P4503A4. Concomitant intake of large quantities (over 1 Litre 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 ADCO SIMVASTATIN should therefore be avoided.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential

Female patients of childbearing potential should not use ADCO SIMVASTATIN, as the active metabolite is fetotoxic and teratogenic in rats.

Pregnancy

ADCO SIMVASTATIN is contraindicated during pregnancy (see section 4.3).
Safety in pregnancy and lactation has not been established. No controlled clinical trials with ADCO SIMVASTATIN have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking ADCO SIMVASTATIN or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with ADCO 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 medicines during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, ADCO SIMVASTATIN must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with ADCO 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 ADCO SIMVASTATIN or its metabolites are excreted in breast milk. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions, women taking ADCO SIMVASTATIN must not breastfeed their babies (see section 4.3).

Fertility

No clinical trial data are available on the effects of ADCO SIMVASTATIN on human fertility. ADCO SIMVASTATIN had no effect on the fertility of male and female rats.

4.7 Effects on ability to drive and use machines

ADCO 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

a) Tabulated summary of adverse reactions

System organ class	**Frequency**	**Side effects**
Blood and the lymphatic system disorders	Less frequent	Anaemia, thrombocytopenia, increased erythrocyte sedimentation rate, eosinophilia
	Frequency unknown	Neutropenia

Immune system disorders	Less frequent	Anaphylaxis, reactions may include lupus-like syndrome, toxic epidermal necrosis, erythema multiforme, including Stevens-Johnson syndrome, fever, malaise, vasculitis, polymyalgia rheumatica, angioedema, eosinophilia, thrombocytopenia, arthritis, urticaria, increased erythrocyte sedimentation rate, arthralgia, photosensitivity, flushing and dyspnoea
Endocrine disorders	Less frequent	Increases in HbA1C and fasting glucose levels, diabetes mellitus
Metabolism and nutrition disorders	Frequency unknown	Mass gain
Psychiatric disorders	Less frequent	Insomnia
	Frequency unknown	Depression, sleep disturbances (including nightmares)
Nervous system disorders	Less frequent	Dizziness, paraesthesia, headache, peripheral neuropathy, cognitive impairment such as memory loss, forgetfulness, amnesia, confusion
	Frequency unknown	Myasthenia gravis
Eye disorders	Less frequent	Blurred vision, photosensitivity, visual impairment
	Frequency unknown	Ocular myasthenia
Cardiac disorders	Less frequent	Atrial fibrillation
Vascular disorders	Less frequent	Vasculitis
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, hypersensitivity pneumonitis
	Frequency unknown	Interstitial lung disease (see section 4.4), respiratory infections, bronchitis, sinusitis
Gastrointestinal disorders	Less frequent	Abdominal pain, cramps, constipation, flatulence, nausea, diarrhoea, dyspepsia, vomiting, dysgeusia and pancreatitis
Hepato-biliary disorders	Less frequent	Hepatitis and jaundice, fatal and non-fatal hepatic failure
Skin and subcutaneous tissue disorders	Less frequent	Skin rashes, pruritus, alopecia, eczema, urticaria, lichenoid medicine eruptions

Musculoskeletal, connective tissue and bone disorders	Less frequent	Muscle cramps, myalgia, (including myositis), arthralgia, rhabdomyolysis (presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure), muscle rupture, polymyalgia, rheumatic,arthritis, arthralgia myopathy
	Frequency unknown	Tendinopathy, sometimes complicated by rupture, immune-mediated necrotising myopathy (IMNM) **
Reproductive system and breast disorders	Less frequent	Gynecomastia
	Frequency unknown	Erectile dysfunction
General disorders and administrative site conditions	Less frequent	Asthenia***, oedema, swelling, fever, flushing, malaise
	Frequency unknown	Fatigue
Investigations	Less frequent	Marked and persistent increases of serum transaminases (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase) (see section 4.4) hepatic effects), and elevated alkaline phosphatase. Liver function test abnormalities. Increases in serum CK levels derived from skeletal muscle (see section 4.4)

b) Description of selected adverse reactions

Laboratory Test Findings

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

The following additional adverse events have been reported with some statins:

- Sleep disturbance
- Sexual dysfunction
- Diabetes mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5,6 mmol/L, BMI > 30kg/m^2, raised triglycerides, history of hypertension).

IMNM** There have been very rare reports of immune-mediated necrotising myopathy (IMNM), an autoimmune myopathy, 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; muscle biopsy showing necrotising myopathy without significant inflammation; improvement with immunosuppressive medicines (see section 4.4).

Asthenia*** An apparent hypersensitivity syndrome, reactions may include angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia,

increased erythrocyte sedimentation rate, eosinophilia, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, malaise, and dyspnoea.

c) Paediatric population
The long-term effects on physical, intellectual, and sexual maturation are unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the ADCO SIMVASTATIN is important. It allows continued monitoring of the benefit/risk balance of the ADCO SIMVASTATIN. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9. Overdose
(See section 4.8 & section 4.4)
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. General measures should be adopted and liver function tests should be performed.
Treatment of overdosage is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Pharmacotherapeutic group: A: 7.5 Serum-cholesterol reducers; HMG-CoA reductase inhibitor
ATC code: C10A A01

Mechanism of action
The cholesterol-lowering agent, simvastatin, is synthetically obtained from lovastatin, which is derived from a fermentation process of *Aspergillus terreus*. The inactive lactone, simvastatin, is hydrolyzed in the liver to beta-hydroxyacid (active form), after oral ingestion. Beta-hydroxyacid is a principal metabolite and inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. This conversion is an early and rate limiting step in the production of cholesterol within the body. The effect of this inhibition, is that simvastatin reduces total plasma cholesterol, by decreasing very low-density lipoprotein (VLDL)- and low-density lipoprotein (LDL)- cholesterol concentrations, as well as apolipoprotein B and plasma triglyceride concentrations. An increase in high-density lipoprotein (HDL)-cholesterol concentrations is also noted.

5.2. Pharmacokinetic properties
Simvastatin is an inactive lactone which is readily hydrolysed *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 medicine occurred after multiple dosing.

Distribution: More than 95 % of simvastatin and its beta-hydroxy metabolite are bound to plasma proteins. Following an oral dose, peak plasma concentrations of simvastatin are seen in 1 to 2 hours.

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 medicine equivalents excreted in bile as well as unabsorbed medicine. 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 acid 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 acid, which may lead to an increased risk of rhabdomyolysis (see section 4.4).

5.3. Preclinical safety data

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core

Lactose anhydrous
Magnesium stearate
Microcrystalline cellulose
Pregelatinised maize starch
Butylhydroxyanisole

Talc

Coating
Hydroxypropylcellulose
Methylhydroxypropyl cellulose
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
24 months.

6.4. Special precautions for storage
Keep well closed. Keep blister in carton until required for use.
Store in a dry place, at or below 25 °C in the original package.

6.5. Nature and contents of container
ADCO SIMVASTATIN 10 mg, 20 mg & 40 mg tablets:
Blister packaging:
The tablets are packed in PVC/PE/PVDC: Al blisters (Primary packaging material). Depending on the pack size one or more blisters are packed into a carton box (*Secondary packaging).*
The white blister packs of PVC/PE/PVDC/Al and the blister packs of PVC/PE/PVDC/Al in Al sachets, are both available as cartons of 10, 20, 30, 50 or 100 tablets, where the tablets are enclosed in blister strips of 10 tablets or 15 tablets each. The white blister packs of PVC/PE/PVDC/Al and the blister packs of PVC/PE/PVDC/Al in Al sachets, are also available as cartons of 14 or 28 tablets, where the tablets are enclosed in blister strips of 14 tablets each.

Container packaging:
A prescribed number of tablets is packed in an HDPE container (Primary packaging material). Each container is sealed with an aluminium seal and closed with a polypropylene closure.
The 300 ml white HDPE tablet containers with child resistant polypropylene closures contain 100 or 300 tablets.

Not all pack sizes will be marketed.

6.6. Special precautions for disposal and other handling
No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:
Adcock Ingram Limited

1 New Road
Erand Gardens,
Midrand 1685.
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S):
ADCO SIMVASTATIN 10 mg: 35/7.5/0277
ADCO SIMVASTATIN 20 mg: 35/7.5/0278
ADCO SIMVASTATIN 40 mg: 35/7.5/0279

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION
20 September 2002

10. DATE OF REVISION OF THE TEXT
26 February 2026

Botswana		
	Product name	**Registration number**
Schedule 2	Adco-Simvastatin 10 mg	BOT1001740A/B/C/D/E/F/G
Schedule 2	Adco-Simvastatin 20 mg	BOT1001741A/B/C/D/E/F/G
Schedule 2	Adco-Simvastatin 40 mg	BOT0801458
Namibia		
NS2	Adco-Simvastatin 10 mg	05/7.5/0130
NS2	Adco-Simvastatin 20 mg	05/7.5/0131
NS2	Adco-Simvastatin 40 mg	05/7.5/0132