SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

ARROW SIMVASTATIN Tablets 10mg (film-coated tablets)
ARROW SIMVASTATIN Tablets 20mg (film-coated tablets)
ARROW SIMVASTATIN Tablets 40mg (film-coated tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

ARROW SIMVASTATIN 10mg Tablet contains 10 mg simvastatin
ARROW SIMVASTATIN 20mg Tablet contains 20 mg simvastatin.
ARROW SIMVASTATIN 40mg Tablet contains 40 mg simvastatin

Contains sugar.

ARROW SIMVASTATIN 10 mg contains 73.43 mg lactose monohydrate
ARROW SIMVASTATIN 20 mg contains 146.86 mg lactose monohydrate
ARROW SIMVASTATIN 40 mg contains 293.72 mg lactose monohydrate

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

ARROW SIMVASTATIN 10: Pink, shield shaped, film-coated tablet with “SV 10” on one side and “Arrow logo” on the other.
ARROW SIMVASTATIN 20: Tan, shield shaped, film-coated tablet with “SV 20” on one side and plain on the other.
ARROW SIMVASTATIN 40: Pink, shield shape, film-coated tablet with “SV 40” on one side and “Arrow logo” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia
ARROW SIMVASTATIN is indicated, in combination with diet, to decrease elevated serum total cholesterol and LDL-cholesterol in patients with

- primary hypercholesterolemia,
- heterozygous familial hypercholesterolemia or
- combined (mixed) hyperlipidemia when response to diet and other nonpharmacological measures is inadequate.

Coronary Heart Disease
ARROW SIMVASTATIN is indicated in patients with coronary heart disease and hypercholesterolemia unresponsive to diet, 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 (coronary artery grafting and percutaneous transluminal coronary angioplasty); and
- Slow the progression of coronary atherosclerosis

Initial/ Date

4.2 Posology and method of administration

Posology

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

Hypercholesterolaemia
The usual starting dose is 10 mg/day given as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg daily given 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) the dose of **ARROW SIMVASTATIN** should be reduced.

Coronary Heart Disease
Patients with coronary heart disease can be treated with a starting dose of 20 mg/day given as a single dose in the evening. Dosing adjustments, if required, should be made at intervals of not less than 4 weeks, up to a maximum of 80mg daily as a single dose in the evening.

Dosage In Renal Insufficiency
ARROW SIMVASTATIN does not undergo significant renal excretion, therefor modification of dosage should not be necessary in patients with mild to moderate renal insufficiency.
In patients with severe renal insufficiency (creatinine clearance less than 30 ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

Concomitant Therapy
ARROW SIMVASTATIN is effective alone or in combination with bile acid sequestrants. When both medicines are prescribed, **ARROW SIMVASTATIN** should be given 1 hour before or 4 hours after cholestyramine administration.
A maximum daily dosage of 10mg **ARROW SIMVASTATIN** is recommended in patients taking ciclosporin, fibrates or niacin concomitantly (See **Special warnings and precautions for use**- Muscle Effects).

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

Paediatric population

Use in paediatric patients is not recommended, as safety and efficacy have not been established.

Method of administration

For oral use.

Initial/ Date

4.3 Contraindications

ARROW SIMVASTIN is contraindicated in patients with:

- Hypersensitivity to SIMVASTATIN, other HMG-CoA reductase inhibitors or to any of the excipients listed in section 6.1.
- Acute or chronic liver diseases
- Unexplained persistent elevations of serum transaminases
- Pregnancy and lactation (See Warnings and Pregnancy and Lactation)
- Concomitant admininistration of potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) (e.g. itraconaxole, ketoconazole, Posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and medicines containing cobicistat) (see section 4.4 and section 4.5)
- In patients with HoFH, concomitant administration of lomitapide with doses > 40 mg ARROW SIMVASTATIN (See section 4.2, section 4.4 and section 4.5)
- Porphyria: safety has not been established
- Concomitant administration of gemfibrozil, cyclosporin, or danazol (see section 4.4 and section 4.5).

4.4 Special Warnings and precautions <u>for use</u>

The active metabolite of **ARROW SIMVASTATIN** is fetotoxic and teratogenic in rats and it should therefor not be used in female patients of childbearing potential.

ARROW SIMVASTATIN is not effective in severe hypertriglyceridemia.

Use in pediatric patients is not recommended, as safety and efficacy have not been established.

Caution should be exercised in the concomitant use of ciclosporin, itraconazole, ketoconazole, fibric acid derivatives, niacin, erythromycin, clarithromycin, HIV protease inhibitors or nefazodone (See Special Precautions, Muscle Effects).

Special Precautions

General:

ARROW SIMVASTATIN should be used with caution in patients who:

- Consume substantial amounts of alcohol and/or who have a history of liver disease
- May be predisposed to developing renal failure secondary to rhabdomyolysis such as in those with severe acute infection, hypotension, severe metabolic, endocrine or electrolyte disorders, uncontrolled seizures, major surgery or trauma. There is increased risk of developing renal failure if rhabdomyolysis occurs.
- Have severe renal impairment.

Hepatic Effects

As hepatitis, evidenced by liver enzyme elevation, has also been reported, it is recommended that liver function tests be performed before treatment begins, and periodically thereafter. Patients titrated to the 80 mg dose should receive an additional test at 3 months. Special attention should be paid to patients who develop elevated serum transaminase levels, and in those patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to three times the upper limit of normal ULN and are persistent, **ARROW SIMVASTATIN** should be discontinued.

ARROW SIMVASTATIN should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contra- indications to the use of **ARROW SIMVASTATIN**.

Muscle Effects

ARROW SIMVASTATIN and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (CK) (more than 10 x the upper limit of normal [ULN]). Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported, 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 ARROW SIMVASTATIN and simvastatin acid plasma levels), which may be due, in part, to

Initial/ Date

interacting medicines that interfere with ARROW SIMVASTATIN metabolism and/or transporter pathways (see section 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. cyclosporin) or in patients who are carriers of the SLCO1B1 c.521T>C genotype.

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.

1. **General measures**

Patients starting therapy with **ARROW SIMVASTATIN** should be advised of the risk of myopathy and should report, promptly, unexplained muscle pain, tenderness or weakness. A creatinine kinase (CK) level above 10 times the Upper Limit of Normal (ULN) in a patient with unexplained symptoms indicates myopathy. ARROW SIMVASTATIN therapy should be discontinued if myopathy is diagnosed or suspected.

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 xULN), 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. INMN is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment (see section 4.8)

Initial/ Date

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 ARROW 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 **ARROW 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 **ARROW SIMVASTATIN**.
ARROW SIMVASTATIN should be used with caution in patients with Type 2 diabetes.

2. Measures to reduce the risk of myopathy caused by drug interactions:

The benefit and risks of using **ARROW SIMVASTATIN** concomitantly with immune-suppressants, fibrates (except fenofibrate) or lipid lowering doses of niacin should be carefully considered, and the dose of **ARROW SIMVASTATIN** should generally not exceed 10 mg/day.
Cautions should be used when prescribing fenofibrate with ARROW SIMVASTATIN, as either medicine can cause myopathy when given alone.
The risk of myopathy and rhabdomyolysis is significantly increased by Concomitant use of ARROW SIMVASTATIN with potent inhibitors of CYP3A4 (such as ciclosporin, itraconazole, ketoconazole, Posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir,~~or~~ nefazodone, medicines containing cobicistat), as well as gemfibrozil, cyclosporin and danazol. Use of these medicines is contraindicated. In patients receiving cysclosporin, **ARROW 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 ARROW SIMVASTATIN (see section 4.2 and section 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 ARROW SIMVASTATIN.

Consequently, regarding CYP3A4 inhibitors, the use of ARROW SIMVASTATIN concomitantly with itraconazole, ketoconazole, posaconasole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and medicines containing cobicistat is contraindicated (see section 4.3 and section 4.5). If treatment with potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) is unavoidable, therapy with ARROW SIMVASTATIN must be suspended (and used of an alternative statin considered) during the course of treatment. Moreover, caution should be exercised when combining ARROW SIMVASTATIN with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, diltiazem (see section 4.2 and section 4.5). Concomitant intake of grapefruit juice and ARROW SIMVASTATIN should be avoided.

The use of ARROW SIMVASTATIN with gemfibrozil is contraindicated (see section 4.3).

ARROW 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 ARROW SIMVASTATIN and fusidic acid should only be considered on a case by case basis and under close medical supervision.

The combined use of ARROW 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 ARROW SIMVASTATIN at doses higher than 40 mg daily with lomitapide must be avoided (see section 4.2, section 4.3 and section 4.5).

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

Simvastatin as in ARROW 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 ARROW SIMVASTATIN and an increased risk of myopathy; therefore, a dose adjustment of ARROW SIMVASTATIN should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with ARROW SIMVASTATIN has not been studied; however, the dose of ARROW 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 ARROW 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 ARROW 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 ARROW SIMVASTATIN) and for further guidance related to monitoring (see section 4.5).

Hepatic effects

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, ARROW SIMVASTATIN should be discontinued. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see above Myopathy/Rhabdomyolysis).

Fatal and non-fatal hepatic failure in patients taking statins, including ARROW SIMVASTATIN may occur. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with ARROW SIMVASTATIN, promptly interrupt therapy. If an alternate aetiology is not found, do not restart ARROW SIMVASTATIN.

ARROW SIMVASTATIN should be used with caution in patients who consume substantial quantities of alcohol.

As with other lipid-lowering medicines, moderate (< 3 x ULN) elevations of serum transaminases have been reported following therapy with simvastatin as in ARROW SIMVASTATIN. These changes appeared soon after initiation of therapy, 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

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.

Lactose warning
ARROW SIMVASTATIN contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. ARROW SIMVASTATIN contains lactose. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp-lactose deficiency, glucose-galactose malabsorption or fructose intolerance should not take **ARROW SIMVASTATIN.**

4.5 Interaction 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 ARROW 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 ARROW 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, including rhabdomyolysis, is increased during concomitant administration with fibrates. Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased

Initial/ Date

ARROW SIMVASTATIN plasma levels (see below Pharmacokinetic interactions and section 4.3 and section 4.4). When ARROW 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 ARROW 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 Gemfibrozil	Contraindicated with ARROW SIMVASTATIN
Other fibrates (except fenofibrate)	Do not exceed 10 mg ARROW SIMVASTATIN daily
Fusidic acid	Is not recommended with ARROW SIMVASTATIN
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with ARROW SIMVASTA
Amiodarone Amlodipine Verapamil Diltiazem Elbasvir	Do not exceed 20 mg ARROW SIMVASTATIN daily
Medicine Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting medicines	Prescribing recommendations
Grazoprevir	
Lomitapide	For patients with HoFH, do not exceed 40 mg ARROW SIMVASTATIN daily
Daptomycin	It should be considered to temporarily suspend ARROW SIMVASTATIN in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk (see section 4.4)

Initial/ Date

Ticagrelor	Doses greater than 40 mg ARROW SIMVASTATIN daily are not recommended
Grapefruit juice	Avoid grapefruit juice when taking ARROW SIMVASTATIN

Effects of other medicines on ARROW SIMVASTATIN

Interactions involving inhibitors of CYP3A4

ARROW 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 ARROW 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 ARROW SIMVASTATIN must be suspended (and use of an alternative statin considered) during the course of treatment. Caution should be exercised when combining ARROW 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 ARROW SIMVASTATIN and fluconazole have been reported (see section 4.4).

Cyclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporin with ARROW SIMVASTATIN; therefore, use with cyclosporin is contraindicated (see section 4.3 and section 4.4). Although the mechanism is not fully understood, cyclosporin 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 ARROW SIMVASTATIN; therefore, use with danazol is contraindicated (see section 4.3 and section 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 section 4.3 and section 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 pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports **of rhabdomyolysis (including**

Initial/ Date

some fatalities) in patients receiving this combination. Co-administration of this combination may cause increased plasma concentrations of both medicines.
If treatment with systemic fusidic acid is necessary, ARROW SIMVASTATIN treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4.

Calcium Channel Blockers

Lomitapide

The risk of myopathy and rhabdomyolysis may be increased by concomitant administration of lomitapide with ARROW SIMVASTATIN (see section 4.3 and section 4.4). Therefore, in patients with HoFH, the dose of ARROW 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 ARROW SIMVASTATIN, particularly higher ARROW 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 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 ARROW SIMVASTATIN and an increased risk of myopathy (see section 4.4).

Ticagrelor:

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

Colchicine:

Myopathy and rhabdomyolysis with the concomitant administration of colchicine and ARROW SIMVASTATIN in patients with renal impairment might occur. 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. ARROW 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 ARROW SIMVASTATIN.

Initial/ Date

Effects of ARROW SIMVASTATIN on the pharmacokinetics of other medicines:

ARROW SIMVASTATIN does not have an inhibitory effect on cytochrome P450 3A4. Therefore, ARROW SIMVASTATIN is not expected to affect plasma concentrations of substances metabolised via cytochrome P450 3A4.

Caution should be exercised in the concomitant use of **ARROW SIMVASTATIN** with ciclosporine, itraconazole, ketoconazole, fibric acid derivatives, niacin, erythromycin, clarithromycin, HIV protease inhibitors or nefazodone (see 4.4 Special warnings and precautions for use - Skeletal Muscle).

Warfarin
Simvastatin has been shown to potentiate the effect of warfarin.
In patients taking Warfarin, prothrombin time should be determined before starting **ARROW 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 Warfarin. If the dose of **ARROW SIMVASTATIN** is changed, 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.

Digoxin
ARROW SIMVASTATIN increases digoxin levels.

Propranolol
The pharmacokinetics of the enantiomers of propranolol was not affected with concomitant administration of single dose simvastatin and propranolol.

Grapefruit juice
Grapefruit juice inhibits cytochrome P4503A4. 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 240ml 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 **ARROW SIMVASTATIN** should therefore be avoided.

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

4.6 Fertility, pregnancy and lactation
The active metabolite of ARROW SIMVASTATIN is fetotoxic and teratogenic in rats and it should therefor not be used in female patients of childbearing potential.

Pregnancy

ARROW SIMVASTATIN is contraindicated during pregnancy (see section 4.3).

Safety in pregnant women has not been established. No controlled clinical trials with ARROW SIMVASTATIN have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received.

Maternal treatment with ARROW 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, ARROW SIMVASTATIN must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant.

Initial/ Date

Treatment with ARROW 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).

Breastfeeding

It is not known whether ARROW SIMVASTATIN or its metabolites are excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions, women taking ARROW SIMVASTATIN must not breastfeed their infants (see section 4.3).

Fertility

No clinical trial data are available on the effects of ARROW SIMVASTATIN on human fertility.

4.7 Effects on ability to drive and use machines

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that **ARROW SIMVASTATIN** therapy does not affect them adversely.

Initial/ Date

4.8 Undesirable effects

Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Frequent	Less frequent	Frequency not known
Gastronintestinal disorders	Pediatric Nausea Vomiting flatulence Dyspepsia Abdominal pain Cramps	Constipation Diarrhoea Pancreatitis	
Blood and the lymphatic system disorders		Anemia Neutropenia Thromboc ytopenia Increased erythrocyte sedimentation rate Eosinophilia	
Vascular disorders		Vasculitis	
Metabolism and nutritional disorders		Increased serum glucose levels Weight gain Pancreatitis	
Endocrine disorders:			
Metabolism and nutrition disorders:			Mass gain has been reported
Nervous system disorders		Headache Dizziness Fatigue Paraesthesia Peripheral neuropathy Cognitive impairment such as memory loss Forgetfulness Amnesia Confusion	
Eye disorder		Photosensitivity Vision blurred Visual impairment	
Respiratory, thoracic and		Dyspnoea,	Interstitial lung disease (see section 4.4)

mediastinal disorders		Hypersensitivity pneumonitis	
Skin and subcutaneous tissue disorders		Skin rash Alopecia Urticaria Pruritis Lichenoid drug eruptions	
Musculoskeletal and connective tissue disorders	Myalgia Muscle cramps	Myopathy Myositis Rhabdomyolysis presenting as muscle pain with elevated creatinine phosphokinase and myoglobinuria leading to renal failure Polymyalgia Rheumatica Arthritis Arthralgia Muscle rupture	Tendinopathy Sometimes complicated by rupture; immune-mediated necrotising myopathy (IMNM)**
General disorders and administrative site conditions		Fever Flushing Malaise Mass gain Asthenia	
Immunse system disorders		Angioedema Lupus-like syndrome Anaphylaxis	
Psychiatric disorders		Insomnia	Depression
Hepato-biliary disorders		Hepatitis/jaundice Fatal and non-fatal hepatic failure	
Reproductive system and breast disorders		Gynecomastia	Erectile dysfunction
General disorders and administration site conditions		Asthenia***	
Investigations		Increase in serum transaminases (alanine aminotransferase, aspartate aminotransferase, y-glutamyl transpeptidase) see section 4.4), elevated alkaline phosphatase; increase in serum	

		CK levels (see section 4.4).	

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 creatine kinase (CK) levels, derived from skeletal muscle, have been reported (see **4.4 Special warnings and precautions for use.**)

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).

Paediatric population

The long-term effects on physical, intellectual, and sexual maturation are unknown.

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).

***Less freguent: 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "Report Drug Reaction Process", found online under SAHPRA's safety publications: https://www.sahpra.org.za/

4.9 Overdose

General measures should be adopted and liver function should be monitored.
Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A7.5 Serum-cholesterol reducers

Simvastatin is a cholesterol-lowering agent derived synthetically from a product of *Aspergillus terreus*. After oral ingestion **ARROW SIMVASTATIN**, which is an inactive lactone, is hydrolyzed to the corresponding beta-hydroxy acid, the active form. This is a principal metabolite and an inhibitor of 3-hydroxy-3- methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the

Initial/ Date

conversion of HMG- CoA to mevalonate, an early and rate limiting step in the biosynthesis of cholesterol. As a result, **ARROW SIMVASTATIN**, reduces total plasma cholesterol, low-density lipoprotein (LDL)- and very low-density lipoprotein (VLDL)- cholesterol concentrations. Apolipoprotein B is also decreased. In addition, **ARROW SIMVASTATIN** moderately increases high-density lipoprotein (HDL)-cholesterol and variably reduces plasma triglycerides.

5.2 Pharmacokinetic properties

Absorption:

There is extensive first-pass extraction by the liver, with oral bioavailability of the active medicine or metabolites being less than 5%.

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:

Simvastin is excreted primarily via the liver, and less than 13% of its metabolites are excreted in the urine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Ascorbic Acid
Butylated Hydroxianisole
Citric Acid Monohydrate
Ethanol Anhydrous
Lactose Monohydrate
Magnesium Stearate
Microcrystalline Cellulose
Pregelatinized Starch
Talc

Tablet coating:
Opadry II Pink

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a dry place at or below 25° C.

Store in the original package/container.

Protect from light.

Initial/ Date

KEEP OUT OF REACH OF CHILDREN.

The blister packs must be kept in the carton until required for use.

6.5 Nature and contents of container

ARROW SIMVASTATIN 10: PVDC coated PVC/PE laminate with hard tempered aluminium foil, blister packs
of 28 or 30 tablets.
ARROW SIMVASTATIN 20: PVDC coated PVC/PE laminate with hard tempered aluminium foil, blister packs
of 28 or 30 tablets.
ARROW SIMVASTATIN 40: PVDC coated PVC/PE laminate with hard tempered aluminium foil, blister packs
of 28 or 30 tablets.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Astral Pharma (Pty) Ltd
125 Meade Street
George
6529
South Africa

8 REGISTRATION NUMBER(S)

ARROW SIMVASTATIN 10: A38/7.5/0707
ARROW SIMVASTATIN 20: A38/7.5/0708
ARROW SIMVASTATIN 40: A38/7.5/0709

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 April 2006

10 DATE OF REVISION OF TEXT

02 September 2022

Initial/ Date