PROFESSIONAL INFORMATION FOR

CIPLA SIMVASTATIN 10 / 20 / 40 / 80 TABLETS

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CIPLA SIMVASTATIN 10, film-coated tablets

CIPLA SIMVASTATIN 20, film-coated tablets

CIPLA SIMVASTATIN 40, film-coated tablets

CIPLA SIMVASTATIN 80, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CIPLA SIMVASTATIN 10: Each film-coated tablet contains 10 mg simvastatin.

CIPLA SIMVASTATIN 20: Each film-coated tablet contains 20 mg simvastatin.

CIPLA SIMVASTATIN 40: Each film-coated tablet contains 40 mg simvastatin.

CIPLA SIMVASTATIN 80: Each film-coated tablet contains 80 mg simvastatin.

Contains sugar:

CIPLA SIMVASTATIN 10: Each film-coated tablet contains 67,70 mg lactose monohydrate.

CIPLA SIMVASTATIN 20: Each film-coated tablet contains 135,40 mg lactose monohydrate.

CIPLA SIMVASTATIN 40: Each film-coated tablet contains 270,80 mg lactose monohydrate.

CIPLA SIMVASTATIN 80: Each film-coated tablet contains 541,60 mg lactose monohydrate.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Film-coated tablets

CIPLA SIMVASTATIN 10: Light pink-coloured, oval, biconvex, intact, film-coated tablets debossed with ‘SVN 10’ on one side and plain on the other side.

CIPLA SIMVASTATIN 20: Tan-coloured, oval, biconvex, intact, film-coated tablets debossed with ‘SVN 20’ on one side and plain on the other side.

CIPLA SIMVASTATIN 40: Pink-coloured, oval, biconvex, intact, film-coated tablets debossed with SVN 40’ on one side and scored on the other side.

CIPLA SIMVASTATIN 80: Pink-coloured, capsule-shaped, biconvex, intact, film-coated tablets debossed with ‘SVN 80’ on one side and break line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

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

- Primary hypercholesterolaemia,
- Heterozygous familial hypercholesterolaemia; or
- Mixed hyperlipidaemia,

when response to diet or other non-pharmacological measures alone is not adequate.

Coronary heart disease

CIPLA SIMVASTATIN is indicated in patients with coronary heart disease and hypercholesterolaemia 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 of undergoing myocardial revascularisation procedures (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty); and
- Slow the progression of coronary atherosclerosis.

4.2 Posology and method of administration

Posology

The patient must follow a cholesterol-lowering diet before initiation of, and while on CIPLA SIMVASTATIN therapy.

Hypercholesterolaemia

Adults

Initial dose: 10 mg daily as a single dose in the evening.

The dose of CIPLA SIMVASTATIN should be reduced if LDL-cholesterol levels fall below 1,94 mmol/L, or total plasma cholesterol levels fall below 3,6 mmol/L.

Coronary heart disease

Adults

Initial dose: 20 mg/day as a single dose in the evening.

Dosage adjustments

If required, the dose should be adjusted at intervals of not less than 4 weeks, up to a maximum of 80 mg daily as a single dose in the evening (see **section 4.4**).

Special populations

Dosage in renal insufficiency

CIPLA SIMVASTATIN does not undergo significant renal excretion; therefore, modification of dose should not be necessary in patients with mild to moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance < 30 mL/min), CIPLA SIMVASTATIN therapy should be closely monitored and doses above 10 mg/day should be implemented with caution.

Concomitant therapy

CIPLA SIMVASTATIN is effective alone or in combination with bile acid sequestrants. When both medicines are prescribed, CIPLA SIMVASTATIN should be given 1 hour before or 4 hours after cholestyramine administration (see **section 4.5**). A maximum daily dose of 10 mg CIPLA SIMVASTATIN is recommended in patients taking ciclosporin, fibrates (other than gemfibrozil) or niacin concomitantly (see **section 4.5**).

The dose should not exceed 20 mg daily in patients receiving concomitant medicines such as amiodarone, verapamil, diltiazem or amlodipine (see **section 4.5**).

Elderly populations

No dosage adjustment is necessary 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.

The tablet should be swallowed whole. CIPLA SIMVASTATIN can be taken with meals or on an empty stomach.

4.3 Contraindications

CIPLA SIMVASTATIN is contraindicated in:

- Patients with known hypersensitivity to simvastatin, other HMG-CoA reductase inhibitors or to any of the excipients in CIPLA SIMVASTATIN (see **section 6.1**).
- Acute or chronic liver disease.
- Unexplained persistent elevations of serum transaminases
- Pregnancy and lactation (see **section 4.4** and **4.6**).
- Porphyria: Safety has not been established.
- Concomitant administration of strong CYP3A4 inhibitors, e.g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, and nefazodone (see **section 4.4** and **4.5**).
- Concomitant administration of gemfibrozil, ciclosporin or danazol (see **section 4.4** and **4.5**).
- In patients with Homozygous Familial Hypercholesterolemia (HoFH), concomitant administration of lomitapide with doses > 40 mg (see **sections 4.4** and **4.5**)

4.4 Special warnings and precautions for use

Muscle effects

Risk of myasthenia gravis and ocular myasthenia.

CIPLA SIMVASTATIN less frequently causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal. Myopathy sometimes takes the form of rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, and fatalities have occurred. The risk of myopathy is increased by high levels of statin activity in plasma. Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

The risk of myopathy

The risk of myopathy, including rhabdomyolysis, is dose related. The risk of myopathy, including rhabdomyolysis, is greater in patients on CIPLA SIMVASTATIN 80, compared with other statin therapies with similar or greater LDL-C lowering efficacy and compared with lower doses of simvastatin. Therefore, the 80 mg dose of CIPLA SIMVASTATIN should be used only in patients who have been taking simvastatin 80 mg chronically (e.g. for 12 months or more) without evidence of muscle toxicity. If, however, a patient who is currently tolerating the 80 mg dose of CIPLA SIMVASTATIN needs to be initiated on an interacting medicine that is contra-indicated (see **section 4.3**) or is associated with a dose cap for simvastatin, that patient should be switched to an alternative statin with less potential for this medicine interaction. Patients should be advised of the increased risk of myopathy, including rhabdomyolysis, and to report promptly any unexplained muscle pain, tenderness or weakness. If symptoms occur, treatment should be discontinued immediately.

All patients starting therapy with CIPLA SIMVASTATIN, or whose dose of CIPLA SIMVASTATIN is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. CIPLA SIMVASTATIN therapy should be discontinued immediately if myopathy is diagnosed or suspected.

In most cases, muscle symptoms and creatine kinase (CK) increases resolved when treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting

therapy with CIPLA SIMVASTATIN or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin, as in CIPLA SIMVASTATIN, have had complicated medical histories, including renal insufficiency usually as a consequence of long standing diabetes mellitus. Such patients merit closer monitoring. CIPLA SIMVASTATIN therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. CIPLA SIMVASTATIN therapy should also be temporarily withheld in any patients experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine, or electrolyte disorders, or uncontrolled epilepsy.

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.

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.

General measures

Patients starting therapy with CIPLA 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. CIPLA SIMVASTATIN 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 x ULN), treatment should not be started.

Whilst on treatment

If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (> 5 x ULN), treatment should be stopped. If muscular

symptoms are severe and cause daily discomfort, even if CK levels are < 5 x ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. 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**)

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.

Surgery

Therapy with CIPLA SIMVASTATIN should be temporarily stopped a few days prior to elective surgery and when any major medical or surgical condition supervenes.

Measures to reduce the risk of myopathy caused by medicine interactions

The benefits and risks of using CIPLA SIMVASTATIN concomitantly with immunosuppressants, fibrates (except fenofibrate) or lipid-lowering doses of niacin should be carefully considered, and the dose of CIPLA SIMVASTATIN should generally not exceed 10 mg/day.

The risk of myopathy and rhabdomyolysis is increased by high levels of CIPLA SIMVASTSTIN activity in plasma. Simvastatin is metabolised by the cytochrome P450 isoform 3A4. Certain medicines which inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy.

Concomitant administration with ciclosporin, itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, HIV-protease inhibitors and nefazodone, is contra-indicated (see **section 4.3** and **4.5**).

Cautions should be used when prescribing fenofibrate with CIPLA SIMVASTATIN, as either medicine can cause myopathy when given alone.

If short-term treatment with potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) is unavoidable, therapy with CIPLA SIMVASTATIN must be suspended (and use of an alternative statin considered) during the course of treatment.

Caution should be exercised when combining CIPLA SIMVASTATIN with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, diltiazem (see **section 4.2** and **section 4.5**).

The combined use of CIPLA SIMVASTATIN with gemfibrozil, ciclosporin or danazol is contraindicated (see **section 4.3** and **section 4.5)**.

Concomitant intake of grapefruit juice and CIPLA SIMVASTATIN should be avoided.

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of amiodarone, amlodipine, verapamil, or diltiazem with certain doses of CIPLA SIMVASTATIN (see **section 4.2** and **section 4.5**).

The combined use of CIPLA 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 CIPLA SIMVASTATIN at doses higher than 40 mg daily with lomitapide must be avoided (see **section 4.3** 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 CIPLA SIMVASTATIN.
CIPLA 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.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin, as in CIPLA SIMVASTATIN, have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. CIPLA SIMVASTATIN therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. CIPLA SIMVASTATIN therapy should also be temporarily withheld in any patients experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine, or electrolyte disorders, or uncontrolled epilepsy.

Persistent increases (to more than 3 x the Upper Limit of Normal – ULN) in serum transaminases have occurred in patients who received simvastatin, as in CIPLA SIMVASTATIN. When treatment was discontinued or interrupted in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.
It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated. There have been post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including CIPLA SIMVASTATIN. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with

CIPLA SIMVASTATIN, promptly interrupt therapy. If an alternate aetiology is not found, do not restart CIPLA SIMVASTATIN. Note that alanine aminotransferase (ALT) may emanate from muscle, therefore ALT rising with CK may indicate myopathy.

Moderate (< 3 x ULN) elevations of serum transaminases have been reported following therapy with CIPLA SIMVASTATIN. These changes appeared soon after initiation of therapy with simvastatin, including CIPLA SIMVASTATIN, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CIPLA SIMVASTATIN.

CIPLA 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 an increased risk of developing renal failure if rhabdomyolysis occurs.
- Have severe renal impairment.

Hepatic effects

Liver function tests, including serum transaminase determinations are recommended prior to initiation of CIPLA SIMVASTATIN therapy and periodically, until one year after the last elevation in dose. CIPLA SIMVASTATIN should be discontinued if the rise in transaminase levels is persistent and/or increases to three times or more the upper limit of normal (ULN).

Chinese patients

Co administration of simvastatin with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) is not recommended in Asian patients, because the incidence of myopathy is higher in Chinese than in non-Chinese patients.

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.

Paediatric population

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

Lactose

CIPLA SIMVASTATIN tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take CIPLA SIMVASTATIN.

4.5 Interaction with other medicines and other forms of interaction

Myopathy caused by medicine interactions

Concomitant administration of medicines that inhibit cytochrome P450 isoenzyme CYP3A4 may result in high plasma levels of CIPLA SIMVASTATIN, thus increasing the risk of myopathy, and is contra-indicated (see **section 43**). Medicines that inhibit cytochrome P450 isoenzyme CYP3A4 include ciclosporin, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors, nefazodone, or large quantities of grapefruit juice (> 1 L daily). If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, or telithromycin is

unavoidable, therapy with CIPLA SIMVASTATIN must be suspended during the course of treatment (see **section 4.4**).

In vitro studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the CIPLA SIMVASTATIN dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with CIPLA SIMVASTATIN.

The combined use of CIPLA SIMVASTATIN with gemfibrozil, ciclosporin, or danazol is contra-indicated (see **section 4.3**).

The risk of myopathy is increased when other medicines that cause myopathy, such as fibrates and niacin, are given with CIPLA SIMVASTATIN. A maximum dose of 10 mg CIPLA SIMVASTATIN daily is recommended in patients taking other fibrates or lipid-lowering doses of niacin (nicotinic acid). The benefits of the combined use of CIPLA SIMVASTATIN with the following medicines should be carefully weighed against the potential risks of combinations: amiodarone, verapamil, diltiazem, or amlodipine (see **Table 1**).

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

Interacting medicines	**Prescribing recommendations**
Strong CYP3A4 inhibitors, e.g.: Itraconazole Ketoconazole Posaconazole	Contra-indicated with CIPLA SIMVASTATIN.

Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g., Nelfinavir) Boceprevir Telaprevir Cobicistat Nefazodone Gemfibrozil Ciclosporin Danazol	
Othe fibrates (except fenofibrate)	Do not exceed 10 mg CIPLA SIMVASTATIN daily.
Fusidic acid	It is not recommended with CIPLA SIMVASTATIN.
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with CIPLA SIMVASTATIN.
Verapamil Diltiazem Amiodarone Amlodipine Elbasvir Grazoprevir	Do not exceed 20 mg CIPLA SIMVASTATIN daily.

Lomitapide	For patients with HoFH, do not exceed 40 mg CIPLA SIMVASTATIN daily
Daptomycin	It should be considered to temporarily suspend CIPLA SIMVASTATIN in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk (see **section 4.4**)
Ticagrelor	Doses greater than 40 mg CIPLA SIMVASTATIN daily are not recommended
Grapefruit juice	Avoid large quantities of grapefruit juice (> 1 L daily).

Effects of other medicines on CIPLA SIMVASTATIN

Interactions involving inhibitors of CYP3A4

CIPLA 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 CIPLA SIMVASTATIN therapy. Such inhibitors include itraconazole, ketoconazole, posaconazole, voriconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors (e.g. ritonavir, saquinavir and nelfinavir), boceprevir, telaprevir, the antidepressant nefazodone, or grapefruit juice and medicines containing cobicistat. Combination of these medicines with CIPLA SIMVASTATIN is contraindicated.

Fluconazole

Cases of rhabdomyolysis associated with concomitant administration of simvastatin (such as CIPLA SIMVASTATIN) and fluconazole have been reported (see **section 4.4**).

Ciclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin with CIPLA SIMVASTATIN; therefore, use with ciclosporin is contraindicated (see **section 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 CIPLA SIMVASTATIN. The increase in AUC for simvastatin acid is likely partly due to inhibition of CYP3A4 and/or OATP1B1.

Danazol

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with CIPLA 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 **sections 4.3** and **4.4**). The co-administration of CIPLA SIMVASTATIN with gemfibrozil is contraindicated (see **section 4.3**). For patients taking fibrates (other than gemfibrozil) or lipid-lowering doses of niacin (nicotinic acid), a maximum daily dose of 10 mg CIPLA SIMVASTATIN is recommended.

Fusidic acid

The risk of myopathy, including rhabdomyolysis, may be higher when systemic Fusidic acid is taken with statins such as CIPLA SIMVASTATIN. Co-administration of these drugs may lead to increased plasma concentrations of both medications. The exact mechanism of this interaction (whether pharmacodynamic, pharmacokinetic, or both) is not fully understood. There have been reports of rhabdomyolysis, including some fatalities, in patients using this combination. If Fusidic

acid treatment is necessary, CIPLA SIMVASTATIN should be discontinued for 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 CIPLA SIMVASTATIN (see **section 4.4**). The dose of CIPLA SIMVASTATIN should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone.

Lomitapide

Lomitapide may increase the risk of myopathy and rhabdomyolysis when taken alongside CIPLA SIMVASTATIN (see **sections 4.3** and **4.4**). Therefore, for patients with HoFH, the dose of CIPLA SIMVASTATIN should not exceed 40 mg daily when used in combination with lomitapide.

Moderate Inhibitors of CYP3A4

Patients using other medicines that moderately inhibit CYP3A4 alongside CIPLA SIMVASTATIN, especially at higher doses, may have an elevated risk of myopathy (see **section 4.4**).

Inhibitors of the Transport Protein OATP1B1

Simvastatin acid is transported by the protein OATP1B1. Taking medicines that inhibit OATP1B1 alongside simvastatin may result in higher plasma concentrations of simvastatin acid, increasing the risk of myopathy (see **sections 4.3** and **4.4**).

Calcium Channel Blockers

The risk of myopathy and rhabdomyolysis is higher when CIPLA SIMVASTATIN is taken with calcium channel blockers such as verapamil, diltiazem, and amlodipine (see **section 4.4**). Co-administration with these calcium channel blockers increases exposure to simvastatin acid

(diltiazem 2,7-fold, amlodipine 1,6-fold, verapamil 2,3-fold), likely due to inhibition of CYP3A4. As a result, the dose of CIPLA SIMVASTATIN should not exceed 20 mg daily in patients using calcium channel blockers concurrently.

Inhibitors of Breast Cancer Resistant Protein (BCRP)

Taking medicines that inhibit BCRP, including those containing elbasvir or grazoprevir, alongside CIPLA SIMVASTATIN may result in higher plasma concentrations of CIPLA SIMVASTATIN and an increased risk of myopathy (see **section 4.4**).

Niacin (nicotinic acid)

Myopathy and rhabdomyolysis have been linked to the co-administration of simvastatin with high doses of niacin (nicotinic acid) (≥ 1 g/day).

Ticagrelor

The co-administration of ticagrelor with CIPLA SIMVASTATIN doses exceeding 40 mg daily may lead to adverse reactions related to CIPLA SIMVASTATIN, and the potential benefits should be carefully considered. CIPLA SIMVASTATIN does not affect ticagrelor plasma levels. Therefore, using ticagrelor with CIPLA SIMVASTATIN doses greater than 40 mg is not recommended.

Grapefruit juice

Grapefruit juice inhibits cytochrome P450 3A4, and consuming large amounts (more than 1 liter daily) alongside simvastatin leads to a seven-fold increase in exposure to simvastatin acid. Even consuming 240 mL of grapefruit juice in the morning with simvastatin in the evening causes a 1,9-fold increase. Therefore, grapefruit juice should be avoided during treatment with CIPLA SIMVASTATIN.

Colchicine

Cases of myopathy, including rhabdomyolysis have been reported with simvastatin, as in CIPLA SIMVASTATIN, co-administered with colchicine, and caution should be exercised when prescribing CIPLA SIMVASTATIN with colchicine.

Daptomycin

The concurrent use of HMG-CoA reductase inhibitors (such as CIPLA SIMVASTATIN) and daptomycin may increase the risk of myopathy and/or rhabdomyolysis (see **section 4.4**).

Rifampicin

Due to rifampicin being a strong inducer of CYP3A4, patients undergoing long-term rifampicin treatment (such as for tuberculosis) may experience a reduced effectiveness of CIPLA SIMVASTATIN. A pharmacokinetic study in healthy volunteers showed that the area under the plasma concentration curve (AUC) for simvastatin acid was reduced by 93 % when rifampicin was administered concurrently.

Digoxin

CIPLA SIMVASTATIN may cause increases in digoxin levels.

Warfarin

A possible increase in the anticoagulant effect of the coumarin anticoagulants may occur. Patients taking a coumarin anticoagulant should have their INR determined before starting CIPLA SIMVASTATIN therapy. The INR should be monitored frequently enough in the early stages of therapy until stabilised. Once a stable INR has been documented, INR can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. When there is a dose adjustment of CIPLA SIMVASTATIN, this procedure should be repeated.

Bile acid sequestrant

CIPLA SIMVASTATIN should be taken 1 hour before or 4 hours after cholestyramine. Concurrent use may decrease the bioavailability of CIPLA SIMVASTATIN.

Propranolol

The pharmacokinetics of the enantiomers of propranolol were unaffected when simvastatin and propranolol were administered together in a single dose.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

The active metabolite of CIPLA SIMVASTATIN is fetotoxic and teratogenic in rats, and it should therefore not be used in female patients of child-bearing potential.

Pregnancy

Safety in pregnancy has not been established.

Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received.

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

Safety in breastfeeding has not been established.

It is not known whether CIPLA 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 CIPLA SIMVASTATIN must not breastfeed their babies (see **section 4.3**).

Fertility

No data is available on the effects of CIPLA SIMVASTATIN on human fertility.

4.7 Effects on ~~the~~ ability to drive and use machines

CIPLA SIMVASTATIN may cause dizziness or vertigo. Therefore, patients should be advised not to drive or operate machinery until individual susceptibility is known.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infection and infestations	*Frequent*	Upper respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders	*Less frequent*	Anaemia, neutropenia.
Immune system disorders	*Less frequent*	An apparent hypersensitivity syndrome has been reported. Reactions may include angioedema, lupus-like syndrome, polymyalgia rheumatica,

MedDRA system organ class	Frequency	Adverse reactions
		dermatomyositis, vasculitis, thrombocytopenia, increased erythrocyte sedimentation rate (ESR), eosinophilia, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, malaise, dyspnoea, toxic epidermal necrosis (TEN), erythema multiforme, including Stevens-Johnson syndrome, anaphylaxis.
	Frequency unknown	Purpura, leukopenia, haemolytic anaemia, positive ANA, asthenia, chills.
Endocrine disorders	*Less frequent*	Increases in HbA1C and fasting glucose levels, diabetes mellitus
Metabolism and nutrition disorders	*Frequency unknown*	Weight gain
Psychiatric disorders	*Less frequent*	Insomnia.
	Frequency unknown	Depression, sleep disturbances (including nightmares).
Nervous system disorders	*Less frequent*	Dizziness, headache, fatigue, asthenia, paraesthesia, peripheral neuropathy, cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion).
	Frequency unknown	Myasthenia gravis.
Eye disorders	*Less frequent*	Photosensitivity, vision blurred, visual impairment.

MedDRA system organ class	Frequency	Adverse reactions
	Frequency unknown	Ocular myasthenia.
Ear and labyrinth disorders	*Frequent*	Vertigo.
Cardiac disorders	*Frequent*	Atrial fibrillation.
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea, hypersensitivity pneumonitis.
	Frequency unknown	Interstitial lung disease, bronchitis, sinusitis.
Gastrointestinal disorders	*Frequent*	Nausea, vomiting, flatulence, dyspepsia, abdominal pain, cramps.
	Less frequent	Constipation, diarrhoea, pancreatitis, gastritis.
Hepato-biliary disorders	*Less frequent*	Hepatitis/ jaundice, fatal and non-fatal hepatic failure.
Skin and subcutaneous tissue disorders	*Less frequent*	Skin rash, alopecia, eczema, pruritus, Lichenoid drug eruptions.
	Frequency unknown	Skin changes (nodules, discolouration, dryness of skin/mucous membranes, changes to hair or nails).
Musculoskeletal and connective tissue disorders	*Frequent*	Myalgia, muscle cramps
	Less Frequent	Myopathy, myositis, arthralgia, rhabdomyolysis (presenting as muscle pain with elevated creatine

MedDRA system organ class	Frequency	Adverse reactions
		phosphokinase and myoglobinuria leading to renal failure), muscle rupture.
	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 administration site conditions	*Less Frequent*	Asthenia, oedema, swelling.
Investigations	*Less frequent* *Frequent*	Marked and persistent increases of serum transaminases and elevated alkaline phosphatase and gamma-glutamyl transpeptidase, liver function test abnormalities. Increases in serum creatine kinase (CK) levels derived from skeletal muscle (see **section 4.4**)

Description of selected adverse reactions

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

- Sleep disturbances, including nightmares.
- 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**).

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. 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 the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

(See **section 4.4** and **4.8**) General measures should be adopted, and liver function should be monitored. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: A 7.5 Serum-cholesterol reducers.

ATC code: C10A A01

Mechanism of action

Simvastatin is a cholesterol-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion simvastatin, an inactive lactone, is hydrolysed 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 catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol. As a result, simvastatin, reduces total plasma cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol concentrations. Apolipoprotein B is also decreased. In addition, 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

Simvastatin 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 hydroxyanisole

Citric acid monohydrate

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Pregelatinized starch

Coating (Opadry)

Hydroxypropyl cellulose

Hypromellose

Iron oxide black (E172)

Iron oxide red (E172)

Iron oxide yellow (E172)

Talc

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place at or below 25 ºC. Protect from light.

Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

CIPLA SIMVASTATIN is packed in white, opaque PVC/PVDC and aluminium foil blister strips of 10 tablets, packed in 30's.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9 Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

CIPLA SIMVASTATIN 10: A40/7.5/0397

Namibia: NS2 10/7.5/0195

CIPLA SIMVASTATIN 20: A40/7.5/0398

Namibia: NS2 10/7.5/0194

CIPLA SIMVASTATIN 40: A38/7.5/0370

Namibia: NS2 06/7.5/0295

CIPLA SIMVASTATIN 80: A38/7.5/0371.

Namibia: NS2 06/7.5/0296

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 11 February 2005

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

10 July 2026