# PROFESSIONAL INFORMATION

## SCHEDULING STATUS

S4

## 1. NAME OF THE MEDICINE

SIMITRI 145 mg/20 mg and 145 mg/40 mg, film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SIMITRI 145/20: Each film-coated tablet contains 145 mg fenofibrate and 20 mg simvastatin.

SIMITRI 145/40: Each film-coated tablet contains 145 mg fenofibrate and 40 mg simvastatin.

Excipients with known effect:

Contains sugar.

SIMITRI 145/20 contains 160,1 mg lactose (as monohydrate) and 145 mg of sucrose per film-coated tablet.

SIMITRI 145/40 contains 194,7 mg lactose (as monohydrate) and 145 mg of sucrose per film-coated tablet.

SIMITRI 145/20 contains 0,7 mg of lecithin (derived from soybean (E322)) and 0,17 mg of Sunset Yellow (E110).

SIMITRI 145/40 contains 0,8 mg of lecithin (derived from soybean (E322)).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets.

SIMITRI 145/20: Tan, oval, film-coated tablet, with 145/20 on one side. The tablet dimensions are approximately 19.3 x 9.3 mm.

SIMITRI 145/40: Brick-red, oval, film-coated tablet, with 145/40 on one side. The tablet dimensions are approximately 19.3 x 9.3 mm.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

SIMITRI is indicated as adjunctive therapy to diet and exercise in high cardiovascular risk adult patients with mixed dyslipidaemia to reduce triglycerides and increase high-density lipoprotein (HDL) cholesterol levels when low-density lipoprotein (LDL) cholesterol levels are adequately controlled with the corresponding dose of simvastatin monotherapy.

### 4.2 Posology and method of administration

Secondary causes of hyperlipidaemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemia, obstructive liver disease, pharmacological treatment (like oral oestrogens), alcoholism should be adequately treated, before SIMITRI therapy is considered, and patients should be placed on a standard cholesterol and triglycerides-lowering diet which should be continued during treatment.

**Posology**

The recommended dose is one tablet per day.

Grapefruit juice should be avoided (see section 4.5).

Response to treatment should be monitored by determination of serum lipid values (total cholesterol (TC), LDL-C, triglycerides (TG)).

***Elderly patients (≥ 65 years old)***

No dose adjustment is necessary.

The usual dose is recommended, except for decreased renal function with estimated glomerular filtration rate < 60 mL/min/1,73 $m^2$ where SIMITRI is contraindicated (see section 4.3).

***Patients with renal impairment***

SIMITRI is contraindicated in patients with moderate to severe renal insufficiency whose estimated glomerular filtration rate is < 60 mL/min/1,73 $m^2$ (see section 4.3).

SIMITRI should be used with caution in patients with mild renal insufficiency whose estimated glomerular filtration rate is 60 to 89 mL/min/1,73 $m^2$ (see section 4.4).

***Patients with hepatic impairment***

SIMITRI has not been studied in patients with hepatic impairment and is therefore contraindicated in this population (see section 4.3).

***Paediatric population***

SIMITRI is contraindicated in children and adolescents up to 18 years old (see section 4.3).

**Concomitant therapy**

In patients taking products containing elbasvir or grazoprevir concomitantly with SIMITRI the dose of simvastatin should not exceed 20 mg/day (see sections 4.4 and 4.5).

**Method of administration**

Oral administration.

The tablet should be swallowed whole with a glass of water.

The tablets should not be crushed or chewed.

The tablet can be taken with or without food (see section 5.2).

## 4.3 Contraindications

- Hypersensitivity to fenofibrate and simvastatin, peanut, soy or to any of the excipients listed in section 6.1 (also see section 4.4).
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Known gallbladder disease.

- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia.
- Moderate to severe renal insufficiency (estimated glomerular filtration rate < 60 mL/min/1,73 $m^2$).
- Concomitant administration of potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and medicines containing cobicistat) (see sections 4.4 and 4.5).
- Concomitant administration of gemfibrozil, ciclosporin, or danazol (see sections 4.4 and 4.5).
- Concomitant administration of glecaprevir, pibrentasvir, elbasvir or grazoprevir (see section 4.5).
- Paediatric population (age below 18 years).
- Pregnancy and breastfeeding (see section 4.6).
- Personal history of myopathy and/or rhabdomyolysis with statins and/or fibrates or confirmed creatine phosphokinase elevation above 5 times the upper limit of normal (ULN) under previous statin treatment (see section 4.4).
- Concomitant administration of amiodarone, verapamil, amlodipine or diltiazem (see section 4.5).

## 4.4 Special warnings and precautions for use

**Muscle**

Skeletal muscle toxicity, including cases of rhabdomyolysis with or without renal failure, has been reported with administration of lipid-lowering substances like fibrates and statins. The risk of myopathy with statins and fibrates is known to be related to the dose of each component and to the nature of the fibrate.

n few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). SIMITRI should be discontinued in case of

aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

***Reduced function of transport proteins***

Reduced function of hepatic organic anion transporting polypeptides (OATP) transport proteins can increase the systemic exposure of simvastatin and increase the risk of myopathy and rhabdomyolysis. Reduced function can occur as the result of inhibition by interacting medicines (e.g. ciclosporin) or in patients who are carriers of the SLCO1B1 c.521T>C genotype.
Patients carrying the SLCO1B1 gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin and increased risk of myopathy. The risk of high dose (80 mg) simvastatin related myopathy is about 1 % in general, without genetic testing. Based on the results of the SEARCH trial, homozygote C allele carriers (also called CC) treated with 80 mg have a 15 % risk of myopathy within one year, while the risk in heterozygote C allele carriers (CT) is 1,5 %. The corresponding risk is 0,3 % in patients having the most common genotype (TT) (see section 5.2).

***Immune-mediated necrotising myopathy (IMNM)***

There have been rare reports of immune-mediated necrotising myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterised by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive antiHMG-CoA reductase antibody; muscle biopsy showing necrotising myopathy; and improvement with immunosuppressive medicines. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressives may be required. Consider risk of IMNM carefully prior to initiation of another statin. If therapy is initiated with another statin, monitor for signs and symptoms of IMNM.

***Measures to reduce the risk of myopathy caused by medicine interactions***

The risk of muscle toxicity may be increased if SIMITRI is administered with another fibrate, statin, niacin, fusidic acid or other specific concomitant substances (for specific interactions see section

4.5). Medical practitioners contemplating combined therapy with SIMITRI and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid) or medicines containing niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness or weakness, particularly during the initial months of therapy and when the dose of either medicine is increased.

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (see sections 4.3 and 4.5).

Simvastatin is a substrate of the breast cancer resistant protein (BCRP) efflux transporter. Concomitant administration of products that are inhibitors of BCRP (e.g. elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of simvastatin should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with simvastatin has not been studied; however, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medicine with products containing elbasvir or grazoprevir (see section 4.5).

The risk of myopathy is increased by high levels of hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitory activity in plasma (i.e. elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting medicines that interfere with simvastatin metabolism and/or transporter pathways (see section 4.5).

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

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

*Creatine kinase measurement*

Creatine kinase should not be measured following strenuous exercise or in the presence of any plausible alternative cause of creatine kinase increase as this makes value interpretation difficult. If creatine kinase levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

*Before the treatment*

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

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

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

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.

To establish a reference baseline value, creatine phosphokinase levels should be measured, 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 creatine kinase levels are significantly elevated at baseline (> 5 x ULN), treatment should not be started.

If myopathy is suspected for any other reason, treatment should be discontinued.

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

**Hepatic disorders**

Increases in transaminase levels have been reported in some patients treated with simvastatin or fenofibrate. In the majority of cases these elevations were transient, minor and asymptomatic without the need for treatment discontinuation.

Transaminase levels must be monitored before treatment begins, every 3 months during the first 12 months of treatment and thereafter periodically. Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if aspartate aminotransferase (AST) or also known as serum glutamic oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT) or also known as serum glutamic pyruvic transaminase (SGPT) levels increase to more than 3 times the upper limit of the normal range.

When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus) and diagnosis is confirmed by laboratory testing, SIMITRI therapy should be discontinued.

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

**Pancreatitis**

Pancreatitis has been reported in patients taking fenofibrate (see sections 4.3 and 4.8). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridaemia, induced pancreatic enzymes increase or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

**Renal function**

SIMITRI is contraindicated in moderate to severe renal impairment (see section 4.3).

SIMITRI should be used with caution in patients with mild renal insufficiency whose estimated glomerular filtration rate is 60 to 89 mL/min/1,73 $m^2$ (see section 4.2).

Reversible elevations in serum creatinine have been reported in patients receiving fenofibrate monotherapy or co-administered with statins. Elevations in serum creatinine were generally stable

over time with no evidence for continued increases in serum creatinine with long term therapy and tended to return to baseline following discontinuation of treatment.

During clinical trials, 10 % of patients had a creatinine increase from baseline greater than 30 µmol/L with co-administered fenofibrate and simvastatin versus 4,4 % with statin monotherapy. 0,3 % of patients receiving co-administration had clinically relevant increases in creatinine to values > 200 µmol/L.

Treatment should be interrupted when creatinine level is 50 % above the upper limit of normal. It is recommended that creatinine is measured during the first 3 months after initiation of treatment and periodically thereafter.

**Interstitial lung disease**

Cases of interstitial lung disease have been reported with some statins and with fenofibrate, 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, SIMITRI therapy should be discontinued.

**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, body mass index (BMI) > 30 kg/$m^2$, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

**Veno-thromboembolic events**

In the FIELD study, a statistically significant increase was reported in the incidence of pulmonary embolism (0,7 % in the placebo group versus 1,1 % in the fenofibrate group; p = 0,022) and a statistically non-significant increase in deep vein thrombosis (placebo 1,0 % 48/4900 patients)

versus fenofibrate 1,4 % (67/4895); p = 0,074. The increased risk of venous thrombotic events may be related to the increased homocysteine level, a risk factor for thrombosis and other unidentified factors. The clinical significance of this is not clear. Therefore, caution should be exercised in patients with history of pulmonary embolism.

**Excipients**

SIMITRI contains lactose (as monohydrate). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take SIMITRI.

SIMITRI contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take SIMITRI.

SIMITRI contains less than 1 mmol sodium (23 mg) per one tablet, that is to say essentially sodium-free.

SIMITRI 145/20 contains Sunset Yellow (E110) that may cause allergic reactions.

## 4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed with SIMITRI.

**Interactions relevant to monotherapies**

***Inhibitors of CYP3A4***

Simvastatin is a substrate of cytochrome P450 3A4.

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

Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin

therapy. Such inhibitors include itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), cobicistat and nefazodone. Combination with itraconazole, ketoconazole, posaconazole, HIV protease inhibitors (e.g. nelfinavir), cobicistat, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated (see section 4.3). If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with SIMITRI must be suspended during treatment. Caution should be exercised when combining SIMITRI with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, or diltiazem (see sections 4.3 and 4.4).
Consult the prescribing information of all concomitantly used medicines to obtain further information about their potential interactions with simvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

***Danazol***

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with simvastatin. The dose of simvastatin should not exceed 10 mg daily in patients taking danazol. Therefore, the co-administration of SIMITRI with danazol is contraindicated (see section 4.3).

***Ciclosporin***

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin with simvastatin. Although the mechanism is not fully understood, ciclosporin has been shown to increase the plasma exposure (AUC) to simvastatin acid, presumably due in part to inhibition of CYP3A4 and OATP-1B1 transporter. Because the dose of simvastatin should not exceed 10 mg daily in patients taking ciclosporin, the co-administration of SIMITRI with ciclosporin is contraindicated (see section 4.3).

***Amiodarone, amlodipine, diltiazem and verapamil***

The risk of myopathy and rhabdomyolysis is increased by concomitant use of amiodarone, amlodipine, diltiazem or verapamil with simvastatin 40 mg per day.

In a clinical trial, myopathy was reported in 6 % of patients receiving simvastatin 80 mg and amiodarone, versus 0,4 % in patients on simvastatin 80 mg only.
Concomitant administration of amlodipine and simvastatin caused a 1,6-fold increase in exposure of simvastatin acid.
Concomitant administration of diltiazem and simvastatin caused a 2,7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4.
Concomitant administration of verapamil and simvastatin resulted in a 2,3-fold increase in plasma exposure to simvastatin acid, presumably due, in part, to inhibition of CYP3A4.
Therefore, the dose of SIMITRI should not exceed 145 mg/20 mg daily in patients taking amiodarone, amlodipine, diltiazem or verapamil.

***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 simvastatin and an increased risk of myopathy (see sections 4.2 and 4.4).

***Other statins and fibrates***

Gemfibrozil increases the AUC of simvastatin acid by 1,9-fold, possibly due to inhibition of the glucuronidation pathway. The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of gemfibrozil with simvastatin. The risk of rhabdomyolysis is also increased in patients concomitantly receiving other fibrates or statins. Therefore, the co-administration of SIMITRI with gemfibrozil, other fibrates or statins is contraindicated (see section 4.3).

***Niacin (nicotinic acid)***

Cases of myopathy/rhabdomyolysis have been associated with concomitant administration of statins and niacin (nicotinic acid) at lipid-modifying doses (≥ 1 g/day), knowing that niacin and statins can cause myopathy when given alone.
Medical practitioners contemplating combined therapy with SIMITRI and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid) or medicines containing niacin should carefully weigh the potential

benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness or weakness, particularly during the initial months of therapy and when the dose of either medicine is increased.

***Fusidic acid***

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

***Grapefruit juice***

Grapefruit juice inhibits CYP3A4. Concomitant intake of large quantities (over 1 litre (L) daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in plasma 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 in plasma exposure to simvastatin acid. Intake of grapefruit juice during treatment with SIMITRI should therefore be avoided.

***Colchicine***

There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal insufficiency. Therefore, close clinical monitoring of such patients taking colchicine and SIMITRI is advised.

***Vitamin K antagonists***

Fenofibrate and simvastatin enhance effects of vitamin K antagonists and may increase the risk of bleeding. It is recommended that the dose of those oral anticoagulants is reduced by about one third at the start of treatment and then gradually adjusted if necessary, according to INR

(international normalised ratio) monitoring. INR should be determined before starting SIMITRI and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR has been documented, it can be monitored at the intervals usually recommended for patients on those oral anticoagulants. If the dose of SIMITRI is changed or discontinued, the same procedure should be repeated. SIMITRI therapy has not been associated with bleeding in patients not taking anticoagulants.

***Glitazones***

Some cases of reversible paradoxical reduction of high-density lipoprotein- cholesterol (HDL-C) have been reported during concomitant administration of fenofibrate and glitazones. Therefore, it is recommended to monitor HDL-C if SIMITRI is
co-administered with a glitazone and stopping either therapy if HDL-C is too low.

***Rifampicin***

Because rifampicin is a potent CYP3A4 inducer that interferes with simvastatin metabolism, patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis) may experience loss of efficacy of simvastatin. In normal volunteers, the plasma exposure to simvastatin acid was decreased by 93 % with concomitant administration of rifampicin.

**Effects on the pharmacokinetics of other medicines**

Fenofibrate and simvastatin are not CYP3A4 inhibitors or inducers. Therefore, SIMITRI is not expected to affect plasma concentrations of substances metabolised via CYP3A4.
Fenofibrate and simvastatin are not inhibitors of CYP2D6, CYP2E1 or
CYP1A2. Fenofibrate is a mild to moderate inhibitor of CYP2C9 and a weak inhibitor of CYP2C19 and CYP2A6.
Patients receiving co-administration of SIMITRI and medicines metabolised by CYP2C19, CYP2A6 or especially CYP2C9 with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these medicines is recommended.

**Interaction between simvastatin and fenofibrate**

Effects of repeated administration of fenofibrate on the pharmacokinetics of single or multiple doses of simvastatin have been investigated in two small studies (n = 12) followed by a larger one (n = 85) in healthy subjects.

In one study the AUC of the simvastatin acid (SVA), a major active metabolite of simvastatin, was reduced by 42 % (90 % CI 24 % - 56 %) when a single dose of 40 mg simvastatin was combined with repeated administration of 160 mg fenofibrate. In the other study repeated co-administration of both 80 mg simvastatin and 160 mg fenofibrate led to a reduction in the AUC of the SVA of 36 % (90 % CI 30 % - 42 %). In the larger study a reduction of 21 % (90 % CI 14 % - 27 %) in AUC of SVA was observed after repeated co-administration of 40 mg simvastatin and 145 mg fenofibrate in the evening. This was not significantly different from the 29 % (90 % CI 22 % - 35 %) reduction in AUC of SVA observed when co-administration was 12 hours apart: 40 mg simvastatin in the evening and 145 mg fenofibrate in the morning.

Whether fenofibrate had an effect on other active metabolites of simvastatin was not investigated. The exact mechanism of interaction is not known. In the available clinical data, the effect on LDL-C reduction was not considered to be significantly different to simvastatin monotherapy when LDL-C is controlled at the time of initiating treatment.

The repeated administration of 40 or 80 mg simvastatin, the highest dose registered, did not affect the plasma levels of fenofibric acid at steady state.

Prescribing recommendations for interacting substances are summarised in the table below (see sections 4.2 and 4.3).

| **Interacting substances** | **Prescribing recommendations** |
|---|---|
| Potent CYP3A4 inhibitors:<br>Itraconazole<br>Ketoconazole<br>Fluconazole<br>Posaconazole<br>Erythromycin | Contraindicated with SIMITRI. |

| Interacting substances | Prescribing recommendations |
|---|---|
| Clarithromycin<br>Telithromycin<br>HIV protease inhibitors (e.g. nelfinavir)<br>Nefazodone<br>Cobicistat | |
| Danazol<br>Ciclosporin | Contraindicated with SIMITRI. |
| Gemfibrozil<br>Other statins and fibrates | Contraindicated with SIMITRI. |
| Amiodarone<br>Verapamil<br>Diltiazem<br>Amlodipine | Contraindicated with SIMITRI 145/40. |
| Elbasvir<br>Grazoprevir | Contraindicated with SIMITRI 145/40. |
| Glecaprevir<br>Pibrentasvir | Contraindicated with SIMITRI. |
| Niacin (nicotinic acid) ≥ 1 g/day | Avoid with SIMITRI unless clinical benefit outweighs the risk. Monitor patients for any signs and symptoms of muscle pain, tenderness or weakness. |
| Fusidic acid | Patients should be closely monitored. Temporary suspension of SIMITRI treatment may be considered. |
| Grapefruit juice | Avoid when taking SIMITRI. |
| Vitamin K antagonists | Adjust the dose of these oral anticoagulants according to INR monitoring. |
| Glitazones | Monitor HDL-C and stop either therapy (glitazone or SIMITRI) if HDL-C is too low. |

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

***SIMITRI***

As simvastatin is contraindicated during pregnancy (see hereafter), SIMITRI is contraindicated during pregnancy (see section 4.3).

***Fenofibrate***

There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have shown embryo-toxic effects at doses in the range of maternal toxicity (see section 5.3). The potential risk for humans is unknown. Therefore, fenofibrate should not be administered to women who are pregnant.

***Simvastatin***

Simvastatin is contraindicated during pregnancy. Safety in pregnant women has not been established. Maternal treatment with simvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. For these reasons, simvastatin must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

**Breastfeeding**

It is unknown whether fenofibrate, simvastatin and/or their metabolites are excreted in human milk. Therefore, SIMITRI is contraindicated during breastfeeding (see section 4.3).

**Fertility**

Reversible effects on fertility have been observed in animals (see section 5.3).

There are no clinical data on fertility from the use of SIMITRI.

## 4.7 Effects on ability to drive and use machines

Fenofibrate has no or negligible influence on the ability to drive a vehicle and use machines. Dizziness has been reported in post-marketing experience with simvastatin. This adverse reaction should be considered when driving a vehicle or using machines while taking SIMITRI.

## 4.8 Undesirable effects

**Summary of the safety profile**

The most commonly reported adverse drug reactions (ADRs) during SIMITRI therapy are increased blood creatinine, upper respiratory tract infection, increased platelet count, gastroenteritis and increased alanine aminotransferase.

**Tabulated list of adverse reactions**

During four double blind clinical trials of 24-week duration 1 237 patients have received treatment with co-administered fenofibrate and simvastatin. In a pooled analysis of these four trials, the rate of discontinuation due to treatment emergent adverse reactions was 5,0 % (51 subjects on 1 012) after 12 weeks of treatment with 145 mg/20 mg fenofibrate and simvastatin per day and 1,8 % (4 subjects on 225) after 12 weeks of treatment with 145 mg/40 mg fenofibrate and simvastatin per day.

Treatment emergent adverse reactions reported in patients receiving co-administration of fenofibrate and simvastatin occurring are listed below by system organ class and frequency.

The adverse reactions of SIMITRI are in line with what is known from its two active substances: fenofibrate and simvastatin.

The frequencies of adverse reactions are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data).

***Adverse reactions observed with the co-administration of fenofibrate and simvastatin (SIMITRI)***

| System organ class | Adverse reactions | Frequency |
|---|---|---|
| Infections and infestations | Upper respiratory tract infection, gastroenteritis | Common |
| Blood and lymphatic system disorders | Increased platelet count | Common |
| Hepato-biliary disorders | Increased alanine aminotransferase | Common |
| Skin and subcutaneous tissue disorders | Dermatitis and eczema | Uncommon |
| Investigations | Increased blood creatinine (see sections 4.3 and 4.4) | Very common |

a

b

c

**Description of selected adverse reactions**

Blood creatinine increased: 10 % of patient had a creatinine increase from baseline greater than 30 pmol/L with co-administered fenofibrate and simvastatin versus 4,4 % with statin monotherapy. 0,3 % of patients receiving co-administration had clinically relevant increases in creatinine to values > 200 pmol/L.

***Additional information on the individual active substances of the fixed dose combination***

Additional adverse reactions associated with the use of medicines containing simvastatin or fenofibrate observed in clinical trials and post-marketing experience that may potentially occur with SIMITRI are listed below. Frequency categories are based on information available from simvastatin and fenofibrate.

| System organ class | Adverse reactions (fenofibrate) | Adverse reactions (simvastatin) | Frequency |
|---|---|---|---|
| Blood and lymphatic system disorders | Decreased haemoglobin, | Anaemia | Rare |

d

| System organ class | Adverse reactions (fenofibrate) | Adverse reactions (simvastatin) | Frequency |
|---|---|---|---|
| | decreased white blood cell count | | |
| Immune system disorders | Hypersensitivity | | Rare |
| | | Anaphylaxis | Very rare |
| Metabolism and nutrition disorders | | Diabetes mellitus**** | Not known |
| Psychiatric disorders | | Insomnia | Very rare |
| | | Sleep disorder, including nightmares, depression | Not known |
| Nervous system disorders | Headache | | Uncommon |
| | | Paraesthesia, dizziness, peripheral neuropathy, memory impairment/memory loss | Rare |
| | Myasthenia gravis | Myasthenia gravis | Not known |
| Eye disorders | | Blurred vision, visual impairment | Rare |
| | Ocular myasthenia | Ocular myasthenia | Not known |

| System organ class | Adverse reactions (fenofibrate) | Adverse reactions (simvastatin) | Frequency |
|---|---|---|---|
| Vascular disorders | Thromboembolism (pulmonary embolism, deep vein thrombosis)* | | Uncommon |
| Respiratory, thoracic and mediastinal disorders | | Interstitial lung disease | Not known |
| Gastrointestinal disorders | Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, flatulence) | | Common |
| | Pancreatitis* | | Uncommon |
| | | Constipation, dyspepsia | Rare |
| Hepato-biliary disorders | Increased transaminases | | Common |
| | Cholelithiasis | | Uncommon |
| | Complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic) | | Not known |
| | | Increased gamma-glutamyl transferase | Rare |
| | | Hepatitis/jaundice, | Very rare |

| System organ class | Adverse reactions (fenofibrate) | Adverse reactions (simvastatin) | Frequency |
|---|---|---|---|
| | | hepatic failure | |
| Skin and subcutaneous tissue disorders [a] | Severe cutaneous reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) | | Not known |
| | Cutaneous hypersensitivity (e.g. rash, pruritus, urticaria) | | Uncommon |
| | Alopecia, photosensitivity reactions | | Rare |
| | | Hypersensitivity syndrome*** | Rare |
| | | Lichenoid drug eruptions | Very rare |
| Musculoskeletal and connective tissue disorders [b] | Muscle disorders (e.g. myalgia, myositis, muscular spasms and weakness) | | Uncommon |
| | Rhabdomyolysis with or without renal failure (see section 4.4) | | Rare |

| System organ class | Adverse reactions (fenofibrate) | Adverse reactions (simvastatin) | Frequency |
|---|---|---|---|
| | | Myopathy**, Immune-mediated necrotising myopathy (see section 4.4), | Rare |
| | | Tendinopathy | Not known |
| | | Muscle rupture | Very rare |
| Reproductive system and breast disorders | Sexual dysfunction | | Uncommon |
| | | Erectile dysfunction | Not known |
| | | Gynecomastia | Very rare |
| General disorders and administration site conditions | | Asthenia | Rare |
| Investigations | Increased blood homocysteine level (see section 4.4)***** | | Very common |
| | Increased blood urea | | Rare |
| | | Increased blood alkaline phosphatase, increased blood creatine phosphokinase level | Rare |
| | | Increased glycosylated haemoglobin, increased blood glucose | Not known |

**Description of selected adverse reactions**

***Pancreatitis***

* In the FIELD study, a randomised placebo-controlled trial performed in 9 795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0,8 % versus 0,5 %; p = 0,031).

***Thromboembolism***

* In the FIELD study, a statistically significant increase was reported in the incidence of pulmonary embolism (0,7 % (32/4 900 patients) in the placebo group versus 1,1 % (53/4 895 patients) in the fenofibrate group; p = 0,022) and a statistically non-significant increase in deep vein thromboses (placebo: 1,0 % (48/4 900 patients) versus fenofibrate 1,4 % (67/4 895 patients); p = 0,074).

***Myopathy***

** In a clinical trial, myopathy occurred commonly in patients treated with 80 mg simvastatin per day compared to patients treated with 20 mg per day (1,0 % vs 0,02 %, respectively).

***Hypersensitivity syndrome***

*** An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, erythrocyte sedimentation rate (ESR) increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

***Diabetes mellitus***

**** 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.

***Increased blood homocysteine level***

***** In the FIELD study the average increase in blood homocysteine level in patients treated with fenofibrate was 6,5 µmol/L and was reversible on discontinuation of fenofibrate treatment.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of SIMITRI is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Abbott Laboratories South Africa Pharmacovigilance: pv.southafrica@abbott.com.

## 4.9 Overdose

**SIMITRI**

No specific antidote is known. If an overdose is suspected, symptomatic treatment and appropriate supportive measures should be provided as required.

***Fenofibrate***

Only anecdotal cases of fenofibrate overdose have been received. In the majority of cases no overdose symptoms were reported. Fenofibrate cannot be eliminated by haemodialysis.

***Simvastatin***

A few cases of simvastatin overdose have been reported. The maximum dose taken was 3,6 g. All patients recovered without sequelae. There is no specific treatment in the event of overdose. In this case, symptomatic and supportive measures should be adopted.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and class: A 7.5 Serum-cholesterol reducers

Pharmacotherapeutic group: Lipid modifying substances, HMG-CoA reductase inhibitors in combination with other lipid modifying substances

ATC code: C10BA04

**Mechanism of action**

***Fenofibrate***

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of peroxisome proliferator-activated receptor (PPARa). Through activation of PPARa, fenofibrate activates lipoprotein lipase production and reduces production of apoprotein CIII. Activation of PPARa also induces an increase in the synthesis of apoproteins AI and AII.

***Simvastatin***

Simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active beta hydroxy acid form which has a potent activity in inhibiting HMG-CoA reductase (3-hydroxy-3 methylglutaryl-CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

***SIMITRI***

SIMITRI contains fenofibrate and simvastatin, which have different modes of action as described above.

**Pharmacodynamic effects**

***Fenofibrate***

Studies with fenofibrate on lipoprotein fractions show decreases in levels of low-density lipoprotein (LDL) and very-low-density lipoprotein cholesterol (VLDL-C).

High-density lipoprotein (HDL) cholesterol levels are frequently increased. LDL and VLDL triglycerides are reduced. The overall effect is a decrease in the ratio of low- and very-low-density lipoproteins to high-density lipoproteins. Fenofibrate also has a uricosuric effect leading to reduction in uric acid levels of approximately 25 %.

***Simvastatin***

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

***SIMITRI***

The respective effects of simvastatin and fenofibrate are complementary.

## 5.2 Pharmacokinetic properties

The geometric mean ratios and 90 % CIs for the comparison of AUC, $AUC_{(0-t)}$ and $C_{max}$ of the active metabolites, fenofibric acid and simvastatin acid, of the fixed dose combination SIMITRI 145/40 and the co-administration of the separate 145 mg fenofibrate and 40 mg simvastatin tablets as used in the clinical program, were all within the 80 – 125 % bioequivalence interval.

**Absorption**

Maximum plasma concentrations ($C_{max}$) of fenofibrate occur within 2 to 4 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual. Fenofibrate is water-insoluble and must be taken with food to facilitate absorption. The

use of micronised fenofibrate and NanoCrystal® technology for the formulation of the fenofibrate 145 mg tablet enhances its absorption.

Contrary to previous fenofibrate formulations, the maximum plasma concentration and overall exposure of this formulation is independent from food intake. A food-effect study involving administration of this formulation of fenofibrate 145 mg tablets to healthy male and female subjects under fasting conditions and with a high fat meal indicated that exposure (AUC and $C_{max}$) to fenofibric acid is not affected by food. Therefore, fenofibrate in SIMITRI may be taken without regard to meals.

Kinetic studies following the administration of a single dose and continuous treatment have demonstrated that the medicine does not accumulate. Simvastatin is an inactive lactone which is readily hydrolyzed *in vivo* to the corresponding

beta hydroxy acid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver. The rate of hydrolysis in human plasma is very slow.

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 hydroxy acid 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 the medicine occurred after multiple dosing.

**Distribution**

Fenofibric acid is strongly bound to plasma albumin (more than 99 %).

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

**Biotransformation and elimination**

After oral administration, fenofibrate is rapidly hydrolysed by esterases to the active metabolite fenofibric acid. No unchanged fenofibrate can be detected in the plasma. Fenofibrate is not a substrate for CYP3A4. No hepatic microsomal metabolism is involved.
The medicine is excreted mainly in the urine. Practically all the medicine is eliminated within 6 days. Fenofibrate is mainly excreted in the form of fenofibric acid and its glucuronide conjugate. In elderly patients, the fenofibric acid apparent total plasma clearance is not modified.
Kinetic studies following the administration of a single dose and continuous treatment have demonstrated that the medicine does not accumulate. Fenofibric acid is not eliminated by haemodialysis.
Mean plasma half-life: the plasma elimination half-life of fenofibric acid is approximately 20 hours.
Simvastatin is a substrate of CYP3A4 and of the efflux transporter BCRP. Simvastatin is taken up actively into the hepatocytes by the transporter OATP1B1. The major metabolites of simvastatin present in human plasma are the beta hydroxy acid 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 beta hydroxy acid metabolite, its half-life averaged 1,9 hours. An average of only 0,3 % of the intravenous dose was excreted in urine as inhibitors.
Effects of repeated administration of fenofibrate on the pharmacokinetics of single or multiple doses of simvastatin have been investigated in two small studies (n = 12) followed by a larger one (n = 85) in healthy subjects.
In one study the AUC of the simvastatin acid (SVA), a major active metabolite of simvastatin, was reduced by 42 % (90 % CI 24 % – 56 %) when a single dose of 40 mg simvastatin was combined with repeated administration of fenofibrate 160 mg. In the other study [Bergman *et al*, 2004] repeated co-administration of both simvastatin 80 mg and fenofibrate 160 mg led to a reduction in the AUC of the SVA of 36 % (90 % CI 30 % – 42 %). In the larger study a reduction of 21 % (90 % CI 14 % – 27 %) in AUC of SVA was observed after repeated co-administration of simvastatin 40 mg and fenofibrate 145 mg in the evening. This was not significantly different from the 29 % (90 %

CI 22 % – 35 %) reduction in AUC of SVA observed when co-administration was 12 hours apart: simvastatin 40 mg in the evening and fenofibrate 145 mg in the morning.

Whether fenofibrate had an effect on other active metabolites of simvastatin was not investigated.

The exact mechanism of interaction is not known. In the available clinical data, the effect on LDL-C reduction was not considered to be significantly different to simvastatin monotherapy when LDL-C is controlled at the time of initiating treatment.

The repeated administration of simvastatin 40 mg or 80 mg, the highest dose registered, did not affect the plasma levels of fenofibric acid at steady state.

**Special populations**

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

## 5.3 Preclinical safety data

No preclinical studies have been performed with the fixed dose combination SIMITRI.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

**Tablet core**

Ascorbic acid (E300)

Butylhydroxyanisole (E320)

Citric acid monohydrate (E330)

Crospovidone (E1202)

Docusate sodium

Hypromellose (E464)

Lactose monohydrate

Magnesium stearate (E572)

Silicified microcrystalline cellulose (consists of cellulose, microcrystalline and silica, colloidal anhydrous)

Sodium laurilsulfate

Starch, pregelatinised (maize)

Sucrose.

**Film-coating**

**Composition of Opadry**

Iron oxide red (E172)

Iron oxide yellow (E172) (only in SIMITRI 145/20)

Lecithin (derived from soy bean (E322))

Poly (vinyl alcohol), partially hydrolysed (E1203)

Sunset Yellow (E110) (only in SIMITRI 145/20)

Talc (E553b)

Titanium dioxide (E171)

Xanthan gum (E415).

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

2 years.

Store at or below 30 °C.

## 6.4 Special precautions for storage

KEEP OUT OF REACH AND SIGHT OF CHILDREN.

SIMITRI does not require any special storage conditions.

### 6.5 Nature and contents of container

Alu/Alu blister strip containing 10 tablets. One (1) , Three (3), six (6) or nine (9) blister strips are packed in an outer cardboard carton.

Pack sizes: 10, 30,60 and 90.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place

219 Golf Club Terrace

Constantia Kloof

1709

South Africa

## 8. REGISTRATION NUMBERS

SIMITRI 145/20: 57/7.5/0594.592

SIMITRI 145/40: 57/7.5/0595.593

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 March 2026

## 10. DATE OF REVISION OF THE TEXT

N/A

## NAME AND ADDRESS OF MANUFACTURER

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