PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

EZESIM 10/10 tablets

EZESIM 10/20 tablets

EZESIM 10/40 tablets

EZESIM 10/80 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITON

EZESIM 10/10: Each tablet contains 10 mg ezetimibe and 10 mg simvastatin.

EZESIM 10/20: Each tablet contains 10 mg ezetimibe and 20 mg simvastatin.

EZESIM 10/40: Each tablet contains 10 mg ezetimibe and 40 mg simvastatin.

EZESIM 10/80: Each tablet contains 10 mg ezetimibe and 80 mg simvastatin.

EZESIM 10/10 contains sugar (lactose monohydrate, 51,48 mg)

EZESIM 10/20 contains sugar (lactose monohydrate, 112,95 mg)

EZESIM 10/40 contains sugar (lactose monohydrate, 235,90 mg)

EZESIM 10/80 contains sugar (lactose monohydrate, 481,80 mg)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

EZESIM 10/10: White to off-white capsule shaped uncoated tablets debossed with "G" on one side and "321, on other side.

EZESIM 10/20: White to off-white capsule shaped uncoated tablets debossed with "G" on one side and "322" on other side.

EZESIM 10/40: White to off-white capsule shaped uncoated tablets debossed

with "G" on one side and "323" on other side.

EZESIM 10/80: White to off-white capsule shaped uncoated tablets de bossed with "G" on one side and "324" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia

EZESIM is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG) and non-high-density lipoprotein cholesterol (non-HDL-C) and to moderately increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

EZESIM is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH.

4.2 Posology and method of administration

Posology:

The patient should be placed on a standard cholesterol-lowering diet before receiving **EZESIM** and should continue on this diet during treatment with **EZESIM**. The dosage should be individualised according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response.

Hypercholesterolaemia:

The dosage range is 10/10 mg/day up to 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reductions.

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Patients who require a larger reduction in LDL-C (greater than 55 %) may be started at 10/40 mg/day.

After initiation or titration of **EZESIM**, lipid levels may be analysed after 2 weeks and the dosage adjusted, if needed.

Dosage in patients with Homozygous Familial Hypercholesterolaemia:

The recommended dosage for patients with Homozygous Familial Hypercholesterolaemia is **EZESIM** 10/40 mg/day or 10/80 mg/day in the evening. **EZESIM** should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Special populations

Use in the elderly:

No dosage adjustment is required for elderly patients.

Use in hepatic impairment:

No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6). Treatment with **EZESIM** is contraindicated in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score greater than 9) liver dysfunction as safety and efficacy have not been demonstrated (see section 4.3 and 4.4).

Use in renal impairment:

No dosage adjustment is required for patients with moderate renal insufficiency. If treatment in patients with severe renal insufficiency (creatinine clearance less than or equal to 30 mL/min) is deemed necessary, dosages above 10/10 mg/day should be implemented cautiously (see section 5.2).

Paediatric population

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Treatment with **EZESIM** is contraindicated as safety and efficacy have not been demonstrated (see section 4.3).

Co-administration with other medicines:

Dosing of **EZESIM** should occur either 2 or more hours before or 4 or more hours after administration of a bile acid sequestrant.

In patients taking ciclosporin, danazol or greater than or equal to 1 g/day of niacin concomitantly with **EZESIM**, the dose of **EZESIM** should not exceed 10/10 mg/day (see sections 4.4 and 4.5).

In patients taking amiodarone or verapamil concomitantly with **EZESIM**, the dose of **EZESIM** should not exceed 10/20 mg/day (see sections 4.4 and 4.5).

Method of administration:

EZESIM is for oral use and should be taken as a single daily dose in the evening, with or without food.

4.3 Contraindications

- Hypersensitivity to ezetimibe, simvastatin or to any of the ingredients of **EZESIM**.
- Active liver disease or unexplained persistent elevations of serum transaminases; moderate to severe hepatic impairment.
- Pregnancy and lactation (see section 4.6).
- Children, as safety and efficacy have not been demonstrated.
- Concomitant administration of potent CYP3A4 inhibitors (medicines that increase AUC approximately 5-fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir,

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).
- In patients with HoFH, concomitant administration of lomitapide with doses > 10/40 mg **EZESIM** (see sections 4.2, 4.4 and 4.5).

4.4 Special warnings and precautions for use

The dose of **EZESIM** should not exceed 10/10 mg daily in patients receiving concomitant medicine with ciclosporin, danazol or ≥ 1 g/day of niacin. The combined use of **EZESIM** with these medicines should be avoided (see section 4.5).

Ciclosporin concentrations should be monitored in patients receiving **EZESIM** and ciclosporin (see section 4.5).

Hepatic impairment:

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, **EZESIM** is contraindicated in these patients (see section 4.3).

Potent CYP3A4 inhibitors

Use of **EZESIM** concomitantly with potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors or nefazodone) should be avoided.

If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with **EZESIM** should be suspended during the course of treatment. Concomitant use with other medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided.

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Fibrates (especially gemfibrozil):

There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates, especially gemfibrozil. The safety and effectiveness of ezetimibe administered with fibrates have not been formally studied. Therefore, the concomitant use of **EZESIM** and fibrates should be avoided (see sections 4.3 and 4.5).

Amiodarone, verapamil

The dose of **EZESIM** should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of **EZESIM** at doses higher than 10/20 mg daily with amiodarone or verapamil should be avoided.

Myopathy/rhabdomyolysis:

All patients starting therapy with **EZESIM**, or whose dose of **EZESIM** is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. **EZESIM** should be discontinued immediately 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 treatment in the following situations:

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

- Alcohol abuse.

If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with any statin-containing medicine (such as **EZESIM**) should only be initiated with caution. If CK levels are significantly elevated at baseline (> 5 X ULN), treatment should not be started.

Simvastatin may cause myopathy manifested as muscle pain, tenderness or weakness with CK above 10 times the ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

The presence of symptoms, and/or a CK level-greater than 10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from simvastatin treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting **EZESIM** treatment or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

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.

Cases of myopathy and rhabdomyolysis have been reported in ezetimibe treatment. Most patients who developed rhabdomyolysis were taking a statin

concomitantly with ezetimibe. However, rhabdomyolysis has been reported with ezetimibe monotherapy and with the addition of ezetimibe to other medicines known to be associated with increased risk of rhabdomyolysis.

The risk of myopathy/rhabdomyolysis is increased by use of EZESIM with the following:

Potent inhibitors of CYP3A4:

Itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone, particularly with higher doses of **EZESIM** (see section 4.5).

Other medicines:

Fibrates, or greater than or equal to 1 g/day of niacin, particularly with higher doses of **EZESIM** (see section 4.5).

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

Ciclosporin or danazol particularly with higher doses of **EZESIM** (see section 4.5).

Amiodarone or verapamil with higher doses of **EZESIM** (see section 4.5). In an ongoing clinical trial, myopathy has been reported in 6 % of patients receiving simvastatin 80 mg and amiodarone.

Diltiazem:

Patients on diltiazem treated concomitantly with **EZESIM** 10/80 mg have a slightly increased risk of myopathy. The risk of myopathy in patients taking simvastatin 40 mg with diltiazem is similar to that in patients taking simvastatin 40 mg without diltiazem (see section 4.5).

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Fusidic acid:

Patients on fusidic acid treated concomitantly with **EZESIM** may have an increased risk of myopathy and rhabdomyolysis (see section 4.5). Patients should be closely monitored; temporary suspension of **EZESIM** treatment may be considered.

For patients with HoFH, this risk may be increased by concomitant use of lomitapide with **EZESIM** (see section 4.5). Patients should be closely monitored; temporary suspension of **EZESIM** treatment may be considered

Many patients who developed rhabdomyolysis on therapy with simvastatin had complicated medical histories, including renal insufficiency, usually as a consequence of long-standing diabetes mellitus. Such patients taking **EZESIM** need closer monitoring. Therapy with **EZESIM** should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Daptomycin:

Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. simvastatin and ezetimibe/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 **EZESIM** in patients taking daptomycin. Consult the prescribing

information of daptomycin to obtain further information about this potential interaction with HMG-CoA reductase inhibitors (e.g. simvastatin and ezetimibe/simvastatin) and for further guidance related to monitoring. (see section 4.5).

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Reduced function of transport proteins

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

Patients carrying the SLCO1B1 gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin acid and increased risk of myopathy. The risk of high dose (80 mg) simvastatin (as contained in **EZESIM**) related myopathy is about 1 % in general, without genetic testing. 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). Where available, genotyping for the presence of the C allele should be considered prior to prescribing 10/80 mg **EZESIM** for individual patients and high doses avoided in those found to carry the CC genotype. However, absence of this gene upon genotyping does not exclude that myopathy can still occur.

Simvastatin (as contained in **EZESIM**) 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 simvastatin and an increased risk of Myopathy, therefore, a dose adjustment of **EZESIM** should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with simvastatin has not been studied, however, the dose of **EZESIM** should not exceed 10/20 mg daily in patients receiving **EZESIM** concomitantly with medicines containing elbasvir or grazoprevir (see section 4.5).

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Anticoagulants:

If **EZESIM** is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored (see section 4.5).

Liver enzymes:

In controlled co-administration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (≥ 3 times the ULN) have been observed (see section 4.8).

It is recommended that liver function tests be performed before treatment with **EZESIM** begins and thereafter when clinically indicated. Patients titrated to the 10/80 mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80 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 times the ULN and are persistent, **EZESIM** should be discontinued.
Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy.

There have been reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with **EZESIM**, promptly interrupt therapy. If an alternate aetiology is not found, do not restart **EZESIM**.

EZESIM 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 persistent transaminase elevations are contraindications

to the use of **EZESIM** (see section 4.3).

Hepatic impairment:

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, **EZESIM** is contraindicated (see section 4.3).

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 **EZESIM** 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.

Interstitial lung disease:

Cases of interstitial lung disease have been reported with some statins, including simvastatin (as contained in **EZESIM**), 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, **EZESIM** therapy should be discontinued.

Porphyria:

Simvastatin has been classified as probably porphyrinogenic and should therefore only be prescribed for compelling reasons and precautions should be considered in all patients.

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Myasthenia gravis and ocular myasthenia:

There is a risk of myasthenia gravis and ocular myasthenia with the use of statin containing medicines, such as **EZESIM**.

Paediatric population:

The safety and efficacy of ezetimibe co-administered with doses of simvastatin above 40 mg daily have not been studied in paediatric patients aged 10 to 17 years. Ezetimibe has not been studied in patients younger than 10 years of age or in pre-menarche girls (see sections 4.2 and 4.8). The long-term efficacy of therapy with ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Excipient warnings:

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

4.5 Interaction with other medicines and other forms of interaction

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with simvastatin.

EZESIM is bioequivalent to co-administered ezetimibe and simvastatin.

CYP3A4 Interactions

No clinically significant pharmacokinetic interactions have been observed between ezetimibe and medicines known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9 and 3A4, or N-acetyltransferase.

Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity, therefore, it is not expected to affect the plasma concentrations of other medicines metabolised by CYP3A4.

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Pharmacodynamic Interactions

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

The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration of simvastatin with fibrates. Additionally, there is a pharmacokinetic interaction of simvastatin with gemfibrozil resulting in increased simvastatin plasma levels (see below Pharmacokinetic interactions and sections 4.3 and 4.4). Cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (see section 4.4).

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of **EZESIM** with fibrates is not recommended (see section 4.4).

Pharmacokinetic Interactions

Prescribing recommendations for interacting medicines are summarised in the table below:

Medicine Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting medicines	**Prescribing recommendations**
Potent CYP3A4 inhibitors, e.g. Itraconazole* Ketoconazole* Posaconazole Voriconazole	*If treatment is unavoidable, then **EZESIM** should be discontinued. All other potent CYP3A4 Inhibitors should be avoided.

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Erythromycin* Clarithromycin* Telithromycin* HIV protease inhibitors (e.g. nelfinavir) Boceprevir Telaprevir Nefazodone Cobicistat Ciclosporin Danazol Gemfibrozil	
Other Fibrates Fusidic acid	Not recommended with **EZESIM**
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with **EZESIM**
Amiodarone Amlodipine Verapamil Diltiazem Niacin (≥1 g/day) Elbasvir Grazoprevir	Do not exceed 10/20 mg **EZESIM** daily
Lomitapide Daptomycin	For patients with HoFH, do not exceed 10/40 mg **EZESIM** daily
Grapefruit juice	Avoid grapefruit juice when taking **EZESIM**

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Ezetimibe

Antacids

Concomitant antacid administration with **EZESIM** decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

Cholestyramine:

Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) by approximately 55 %.
The incremental LDL-C reduction due to adding **EZESIM** to cholestyramine may be lessened by this interaction.

Fibrates:

Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1,5 and 1,7-fold respectively, however these increases are not considered clinically significant. The safety and effectiveness of **EZESIM** administered with fibrates have not been established. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of **EZESIM** with fibrates is not recommended until use in patients is studied.

Simvastatin:

CYP3A4 interactions:

Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity, therefore it is not expected to affect the plasma concentrations of other medicines metabolised by CYP3A4. The following potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of the simvastatin component of

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

EZESIM (see sections 4.3 and 4.4): itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors and nefazodone.

Fluconazole:

Cases of rhabdomyolysis associated with concomitant administration of simvastatin and fluconazole have been reported (see section 4.4).

Ciclosporin or danazol:

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin or danazol, particularly with higher doses of **EZESIM** (see sections 4.3 and 4.4).

In a study of 8 post-renal transplant patients with creatinine clearance of greater than 50 mL/min on a stable dose of ciclosporin, a single 10 mg dose of ezetimibe resulted in a 3,4-fold (range 2,3 to 7,9-fold) increase in the mean AUC for total ezetimibe compared to healthy patients. In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13,2 mL/min/1,73 m^2) receiving multiple medicines, including ciclosporin, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects. In a two-period crossover study in 12 healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of ciclosporin on day 7 resulted in a mean 15 % increase in ciclosporin, AUC (range 10 % decrease to 51 % increase) compared to a single 100 mg dose of ciclosporin alone (see section 4.4).

Fusidic acid:

Patients on fusidic acid treated concomitantly with **EZESIM**, may have an increased risk of myopathy and rhabdomyolysis (see section 4.4).

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.

Co-administration of fusidic acid and **EZESIM** may cause increased plasma concentrations of both medicines.

If treatment with systemic fusidic acid is necessary, **EZESIM** treatment should be discontinued throughout the duration of the fusidic acid treatment.

Amiodarone or verapamil:

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of **EZESIM** therefore, the dose of **EZESIM** should not exceed 10/20 mg daily in patients receiving concomitant medicine with amiodarone (see section 4.4).

Diltiazem:

Patients on diltiazem treated concomitantly with **EZESIM** 10/80 mg have a slightly increased risk of myopathy, therefore, the dose of **EZESIM** should not exceed 10/20 mg daily in patients receiving concomitant medicine with diltiazem (see section 4.4).

Amlodipine:

Patients on amlodipine treated concomitantly with simvastatin (as contained in **EZESIM**) have an increased risk of myopathy. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1,6-fold increase in exposure of simvastatin acid. Therefore, the dose of **EZESIM** should not exceed 10/20 mg daily in patients receiving concomitant medicine with amlodipine.

Lomitapide:

The risk of myopathy and rhabdomyolysis may be increased by concomitant administration of lomitapide with simvastatin (see sections 4.3 and 4.4). Therefore, in patients with HoFH, the dose of **EZESIM** must not exceed 10/40 mg daily in

patients receiving concomitant medication with lomitapide.

Moderate Inhibitors of CYP3A4:

Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with **EZESIM**, particularly higher **EZESIM** 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 sections 4.3 and 4.4).

Inhibitors of Breast Cancer Resistant Protein (BCRP):

Concomitant administration of medicines that are inhibitors of BCRP, including medicines 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).

Grapefruit juice:

Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 litre daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 mL of grapefruit juice in the morning and administration of simvastatin in the evening also resulted in a 1,9-fold increase. Intake of grapefruit juice during treatment with **EZESIM** should therefore be avoided.

Colchicine:

There have been reports of myopathy and rhabdomyolysis with the concomitant

administration of colchicine and simvastatin, in patients with renal impairment. Close clinical monitoring of such patients taking this combination is advised.

Rifampicin:

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

Niacin:

Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (see section 4.4).

Daptomycin:

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

Effect of EZESIM on the pharmacokinetics of other products

Anticoagulants:

Ezetimibe:

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of healthy adult males. However, there have been post-marketing reports of increased International Normalized Ratio in patients who had ezetimibe added to warfarin or fluindione (see section 4.4). The effect of **EZESIM** on prothrombin time has not been studied.

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Simvastatin:

In two clinical studies, one in healthy subjects and the other in hypercholesterolaemic patients, simvastatin 20 to 40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalised Ratio (INR), increased from a baseline of 1,7 to 1,8 and from 2,6 to 3,4 in the volunteer and patient studies, respectively. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting **EZESIM** and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of **EZESIM** is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy:

EZESIM is contraindicated during pregnancy (see section 4.3).

No controlled clinical trials with simvastatin have been conducted in pregnant women. Reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. The safety of **EZESIM** in pregnant women has not been established.

Maternal treatment with **EZESIM** may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. For this reason, **EZESIM** should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with **EZESIM** should be suspended for the duration

of pregnancy or until it has been determined that the woman is not pregnant.

No clinical data on exposed pregnancies are available for ezetimibe.

Breastfeeding:

EZESIM is contraindicated during lactation (see section 4.3.).

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether the active ingredients of **EZESIM** are excreted into human breast milk; therefore, women who are nursing should not take **EZESIM**.

Fertility:

No clinical trial data are available on the effects of ezetimibe or simvastatin on human fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported when taking **EZESIM**.

4.8 Undesirable effects

a. Summary of the safety profile

The most common adverse effects include headache, abdominal pain and diarrhoea. The commonest adverse effect with simvastatin is gastrointestinal disturbances.

b. Tabulated summary of adverse reactions

Adverse effects with EZESIM:

System Organ Class	**Frequency**	**Side effects**

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Blood and lymphatic system disorders	Frequency unknown	Thrombocytopenia, anaemia
Immune system disorders	Frequency unknown	Hypersensitivity, anaphylaxis, hypersensitivity syndrome
Metabolism and nutrition disorders	Less frequent Frequency unknown	Decreased weight Decreased appetite
Psychiatric disorders	Less frequent Frequency unknown	Sleep disorder, insomnia Depression, memory loss, forgetfulness, amnesia, memory impairment, confusion, sleep disturbances, nightmares
Nervous system disorders	Frequent Less frequent Frequency unknown	Headache Dizziness, paraesthesia Peripheral neuropathy, memory impairment, myasthenia gravis
Eye disorders	Frequency unknown	Ocular myasthenia
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Cough, dyspnoea, interstitial lung disease
Vascular disorders	Frequency unknown	Hot flush, hypertension
Gastrointestinal disorders	Frequent Less frequent	Flatulence Abdominal pain, abdominal discomfort, upper abdominal pain, dyspepsia, nausea,

		vomiting, abdominal distension, diarrhoea, dry mouth, gastroesophageal reflux disease
	Frequency unknown	Constipation, pancreatitis, gastritis
Hepato-biliary disorders	Frequency unknown	Hepatitis, jaundice, fatal and non-fatal hepatic failure, cholelithiasis, cholecystitis
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Pruritus, rash, urticaria Alopecia, erythema multiforme, angioedema
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent Frequency unknown	Myalgia, pain in limb Arthralgia, muscle spasms, muscular weakness, musculoskeletal pain and discomfort, neck pain, pain in extremity, back pain Muscle cramps, myopathy, myositis, rhabdomyolysis (with or without renal failure), tendinopathy, tendon rupture, immune-mediated necrotising myopathy
Reproductive system and breast disorders	Frequency unknown	Erectile dysfunction, sexual dysfunction
General disorders	Less frequent	Asthenia, fatigue, malaise,

and administrative site conditions	Frequency unknown	peripheral oedema, chest pain Pain
Investigations	Frequent Less frequent Frequency unknown	Increased ALT and/or AST, increased blood creatinine kinase (CK) Increased blood bilirubin blood uric acid, gamma-glutamyl transferase and international normalised ratio, protein present in the urine Elevated alkaline phosphatase, abnormal liver function test results, increases in HbA1c and fasting serum glucose levels, diabetes mellitus

Adverse effects with Ezetimibe:

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Frequent	Viral infection, pharyngitis, sinusitis, upper respiratory tract infection
Immune system disorders	Less frequent	Hypersensitivity reactions, anaphylaxis and angioedema
Blood and lymphatic system	Less frequent	Thrombocytopenia

disorders		
Psychiatric disorders	Less frequent	Depression
Nervous system disorders	Frequent Less frequent	Headache Dizziness, paraesthesia
Respiratory, thoracic and mediastinal disorders	Frequent	Coughing
Gastrointestinal disorders	Frequent Less frequent	Abdominal pain, diarrhoea Nausea, pancreatitis
Hepato-biliary disorders	Less frequent Frequency unknown	Hepatitis, cholelithiasis, cholecystitis Raised liver enzymes
Skin and subcutaneous tissue disorders	Less frequent	Rash and urticaria, erythema mulitforme
Musculoskeletal, and connective tissue disorders	Frequent Less frequent	Back pain, myalgia Arthralgia, myopathy/rhabdomyolysis (see section 4.4)
General disorders and administration site conditions	Frequent	Fatigue, chest pain
Investigations	Less frequent	Increased CPK, elevations of liver transaminases

Adverse effects with Simvastatin:

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Anaemia, thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity syndrome (including angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, increased erythrocyte sedimentation rate, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea, malaise)
Psychiatric disorders	Less frequent Frequency unknown	Insomnia Reversible cognitive impairment, depression
Nervous system disorders	Less frequent Frequency unknown	Dizziness, paraesthesia, peripheral neuropathy, memory impairment, headache Myasthenia gravis
Eye disorders	Frequency unknown	Ocular myasthenia
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Dyspnoea, interstitial lung disease

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Gastrointestinal disorders	Frequent Less frequent	Gastrointestinal disturbances Constipation, abdominal pain, dyspepsia, diarrhoea, nausea, vomiting and pancreatitis
Hepato-biliary disorders	Less frequent	Hepatitis/jaundice, hepatic failure
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Alopecia, pruritus and rash Amyopathic dermatomyositis, vesiculobullous eruptions
Musculoskeletal, and connective tissue disorders	Less frequent	Muscle cramps, myopathy, rhabdomyolysis, dermatomyositis, polymyositis
Renal and urinary disorders	Frequency unknown	Proteinuria, renal failure
Reproductive system and breast disorders	Frequency unknown	Sexual dysfunction, erectile dysfunction, impotence, decreased libido, testicular pain
General disorders and administration site conditions	Frequency unknown	Asthenia
Investigations	Frequency unknown	Hyperglycaemia, diabetes mellitus

Reporting of suspected adverse reactions:

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Reporting of 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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Signs and symptoms:

Ezetimibe*:*

In clinical studies, administration of ezetimibe, 50 mg/day to healthy subjects for up to 14 days, or 40 mg/day to patients with primary hypercholesterolaemia for up to 56 days, was generally well-tolerated.

A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Simvastatin*:*

A few cases of overdosage have been reported; the maximum dose taken was 3,6 g. All patients recovered without sequelae.

Management of overdose:

No specific treatment of overdosage with **EZESIM** can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed. Co-administration of ezetimibe (1 000 mg/kg) and simvastatin (1 000 mg/kg) was well-tolerated in acute, oral toxicity studies in mice and rats. No clinical signs of toxicity were observed in these animals. The estimated oral LD_{50} for both species was ezetimibe greater than or equal to 1 000 mg/kg and simvastatin greater than or equal to 1 000 mg/kg.

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors in combination with other lipid modifying agents

ATC code: C10BA02

Pharmacological classification: A 7.5 Serum-cholesterol reducers

Mechanism of action

Ezetimibe*:*

Ezetimibe inhibits the intestinal absorption of cholesterol and related plant sterols. Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver.

Ezetimibe in animals inhibited the absorption of (^{14}C)-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinylestradiol, or the fat-soluble vitamins A and D.

Simvastatin*:*

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active beta-hydroxy acid form which inhibits HMG-CoA reductase (3 hydroxy-3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low -density 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-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also decreases

during treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes, the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

5.2 Pharmacokinetic Properties

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with simvastatin.

Absorption:

EZESIM:

EZESIM is bioequivalent to co-administered ezetimibe and simvastatin.

Ezetimibe:

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10 mg tablets.

Simvastatin:

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, consistent with extensive hepatic first-pass extraction. The major metabolites of simvastatin present in human plasma are the beta-hydroxy acid and four additional active metabolites.

Relative to the fasting state, the plasma profiles of both active and total inhibitors

are not affected when simvastatin was administered immediately before a test meal.

Distribution:

Ezetimibe:

Ezetimibe and ezetimibe-glucuronide are bound 99,7 % and 88 to 92 % to human plasma proteins, respectively.

Simvastatin:

Both simvastatin and the beta-hydroxy acid are bound to human plasma proteins (95 %).

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicine occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1,3 to 2,4 hours post-dose.

Biotransformation:

Ezetimibe:

Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all animal species evaluated. Ezetimibe and ezetimibe -glucuronide are the major medicine-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total medicine in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Simvastatin:

PROPOSED PROFESSIONAL INFORMATION FOR EZESIM

Simvastatin is an inactive lactone which is readily hydrolysed *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 its primary site of action, with subsequent excretion of medicine equivalents in the bile. Consequently, availability of active medicine to the systemic circulation is low.

Elimination:

Ezetimibe:

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93 % of the total radioactivity in plasma. Approximately 78 % and 11 % of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Simvastatin:

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, an average of only 0,3 % of the IV dose was excreted in urine as inhibitors.

Pharmacokinetics in special patient groups:

Elderly Patients:

Ezetimibe:

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (65 years or older) than in the young (18 to 45 years).

Simvastatin:

In a study including 16 elderly patients between 70 and 78 years of age who received simvastatin 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45 % compared with 18 patients between 18 to 30 years of age.

Renal Insufficiency:

Ezetimibe:

After a single 10 mg dose of ezetimibe as monotherapy in patients with severe renal disease [mean creatinine clearance (CrCl) ≤ 30 mL/min], the mean AUC for total ezetimibe was increased approximately 1,5-fold, compared to healthy subjects.

One patient (post-renal transplant and receiving multiple medicines, including ciclosporin) showed a 12-fold greater exposure to total ezetimibe.

Simvastatin:

In a study of patients with severe renal insufficiency (creatinine clearance < 30 mL/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately 2- fold higher than those in healthy patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated hydroxy anisole

Citric acid monohydrate

Croscarmellose sodium

Hypromellose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Propyl gallate

Sodium lauryl sulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep container tightly closed.

Store in the original packaging.

6.5 Nature and contents of container

Bottles: White high-density polyethylene (HDPE) containers containing 30 tablets.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Forrester Pharma (Pty) Ltd

2 Waterford Mews

Waterford Place

Century City

7441

Cape Town

South Africa

8. REGISTRATION NUMBERS

EZESIM 10/10: 51/7.5/0949

EZESIM 10/20: 51/7.5/0950

EZESIM 10/40: 51/7.5/0951

EZESIM 10/80: 51/7.5/0952

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 26 January 2021

10. DATE OF REVISION OF THE TEXT

07 June 2023