PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MEZIBE PLUS 10/10 Tablets

MEZIBE PLUS 10/20 Tablets

MEZIBE PLUS 10/40 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **MEZIBE PLUS 10/10** tablet contains 10 mg ezetimibe and 10 mg simvastatin.

Contains sugar: lactose monohydrate 57,23 mg per tablet

Each **MEZIBE PLUS 10/20** tablet contains 10 mg ezetimibe and 20 mg simvastatin.

Contains sugar: lactose monohydrate 124,45 mg per tablet

Each **MEZIBE PLUS 10/40** tablet contains 10 mg ezetimibe and 20 mg simvastatin.

Contains sugar: lactose monohydrate 258,90 mg per tablet

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

MEZIBE PLUS 10/10

White to off-white, capsule shaped uncoated tablets, debossed with **'L'** on one side and plain on other side.

MEZIBE PLUS 10/20

White to off-white, capsule shaped uncoated tablets, debossed with **'I'** on one side and plain on other side.

MEZIBE PLUS 10/40

White to off-white, capsule shaped uncoated tablets, debossed with **'F'** on one side and plain on other side.

CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia

MEZIBE PLUS is indicated as an 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 Hypercholesterolemia (HoFH)

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

4.2 Posology and method of administration

The patient should be placed on a standard cholesterol-lowering diet before receiving **MEZIBE PLUS** and should continue on this diet during treatment with **MEZIBE PLUS**. The dosage should be individualized 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. Patients who require a larger reduction in LDL-C (> 55%) may be started at 10/40 mg/day. After initiation or titration of

MEZIBE PLUS, lipid level may be analysed after 2 weeks and dosages adjusted, if needed.

Dosage in patients with Homozygous Familial Hypercholesterolaemia

The recommended dosage for patients with homozygous familial hypercholesterolaemia is **MEZIBE PLUS** 10/40 mg/day or 10/80 mg/day in the evening. **MEZIBE PLUS** 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 to 6). Treatment with **MEZIBE PLUS** 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 has not been demonstarated(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

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

Co-administration with Other Medicines

Dosing of **MEZIBE PLUS** 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 **MEZIBE PLUS**, the dose of **MEZIBE PLUS** should not exceed 10/10 mg/day (see sections 4.4and 4.5).

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

Method of administration

MEZIBE PLUS is for oral administration and should be taken as a single dose in the evening, with or without food

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients of **Mezibe Plus**
- 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 (agents 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 simvastatin/ezetimibe (see sections 4.2,4.4 and 4.5)

4.4. Special warnings and precautions for use

The dose of **MEZIBE PLUS** 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 **MEZIBE PLUS** with these medicines should be avoided (See Section 4.5). Ciclosporin concentrations should be monitored in patients receiving **MEZIBE PLUS** and ciclosporin (see section 4.5).

Hepatic insufficiency

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

Potent CYP3A4 inhibitors

Use of **MEZIBE PLUS** 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 **MEZIBE PLUS** 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.

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 **MEZIBE PLUS** and fibrates should be avoided (see sections 4.3 and 4.5)

Amiodarone, verapamil:

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

Myopathy/rhabdomyolysis:

All patients starting therapy with MEZIBE PLUS, or whose dose of MEZIBE PLUS is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. MEZIBE PLUS 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 **MEZIBE PLUS**) 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 **MEZIBE PLUS** 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 MEZIBE PLUS with the following:

Potent inhibitors of CYP3A4:

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

Other medicines*:*

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

Amiodarone or verapamil with higher doses of **MEZIBE PLUS** (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 MEZIBE PLUS 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).

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

For patients with HoFH, this risk may be increased by concomitant use of lomitapide with **MEZIBE PLUS** (see section 4.5). Patients should be closely monitored; temporary suspension of **MEZIBE PLUS** 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 MEZIBE PLUS need closer monitoring. Therapy with MEZIBE PLUS 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 **MEZIBE PLUS** 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).

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 SLCO1B1c.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 **MEZIBE PLUS**)

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 80 mg **MEZIBE PLUS** 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 **MEZIBE PLUS**) 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 **MEZIBE PLUS** should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with simvastatin has not been studied; however, **the dose of MEZIBE PLUS should not exceed 10/20 mg daily in patients receiving MEZIBE PLUS concomitantly with medicines containing elbasvir or grazoprevir** (see section 4.5).

Anticoagulants:

If **MEZIBE PLUS** 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 (greater than or equal to 3 times the ULN) have been observed (see section 4.8)

It is recommended that liver function tests be performed before treatment with **MEZIBE PLUS** begins and thereafter when clinically indicated. Patients titrated to the 10/80 mg dose should receive anadditional 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, MEZIBE PLUS 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 **MEZIBE PLUS** promptly interrupt therapy. If an alternate aetiology is not found, do not restart **MEZIBE PLUS**.
MEZIBE PLUS 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 **MEZIBE PLUS** (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, **MEZIBE PLUS** 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 **MEZIBE PLUS** 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 **MEZIBE PLUS**), 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, **MEZIBE PLUS** 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

Paediatric population

The safety and efficacy of ezetimibe co-administered with doses simvastatin above 40mg 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.

Risk of myasthenia gravis and ocular myasthenia with statin use

Lactose:

MEZIBE PLUS contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp total lactase deficiency or glucose-galactose malabsorption should not take **MEZIBE PLUS**.

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.

MEZIBE PLUS 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.

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 coadministered 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 (see section 5.3). Although the relevanceof this preclinical finding to humans is unknown, co-administration of **MEZIBE PLUS** 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 Erythromycin* Clarithromycin* Telithromycin* HIV protease inhibitors (e.g. nelfinavir) Boceprevir Telaprevir Nefazodone Cobicistat Ciclosporin	*If treatment is unavoidable, then MEZIBE PLUS should be discontinued. All other potent CYP3A4 Inhibitors should be avoided.

Danazol Gemfibrozil	
Other Fibrates Fusidic acid	Not recommended with **MEZIBE PLUS**
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with **MEZIBE PLUS**
Amiodarone Amlodipine Verapamil Diltiazem Niacin (≥1 g/day) Elbasvir Grazoprevir	Do not exceed 10/20 mg **MEZIBE PLUS** daily
Lomitapide Daptomycin	For patients with HoFH, do not exceed 10/40 mg **MEZIBE PLUS** daily
Grapefruit juice	Avoid grapefruit juice when taking **MEZIBE PLUS**

EZETIMIBE:

Antacids:

Concomitant antacid administration with MEZIBE PLUS 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

MEZIBE PLUS 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 **MEZIBE PLUS** 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 **MEZIBE PLUS** with fibrates is not recommended until use in patients is studied.

SIMVASTATIN:

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 **MEZIBE PLUS** (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 **MEZIBE PLUS** (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 **MEZIBE PLUS** 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 **MEZIBE PLUS** may cause increased plasma concentrations of both medicines.

If treatment with systemic fusidic acid is necessary, **MEZIBE PLUS** 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 **MEZIBE PLUS**, therefore, the dose of **MEZIBE PLUS** 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 **MEZIBE PLUS** 10/80 mg have a slightly increased risk of myopathy, therefore, the dose of **MEZIBE PLUS** 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 **MEZIBE PLUS**) 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 **MEZIBE PLUS** 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 **MEZIBE PLUS** 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 **MEZIBE PLUS**, particularly higher **MEZIBE PLUS** 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 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).

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 **MEZIBE PLUS** 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 lipidmodifying 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 HMGCoA reductase inhibitors (e.g. simvastatin and ezetimibe/simvastatin) and daptomycin (see section 4.4).

Effect of MEZIBE PLUS 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 postmarketing reports of increased International Normalized Ratio in patients who had ezetimibe added to warfarin or fluindione (see section 4.4). The effect of **MEZIBE PLUS** on prothrombin time has not been studied.

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 **MEZIBE PLUS** 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 **MEZIBE PLUS** 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

MEZIBE PLUS is contraindicated during pregnancy.

No controlled clinical studies with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. The safety of **MEZIBE PLUS** in pregnant women has not been established.

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

Breastfeeding

MEZIBE PLUS 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 components of **MEZIBE PLUS** are excreted in human breast milk; therefore women who are nursing should not take **MEZIBE PLUS**

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 reported. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported.when taking **MEZIBE PLUS**

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 MEZIBE PLUS

MEZIBE PLUS		
System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Frequency unknown	Anaemia, thrombocytopaenia
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	Insomnia, sleep disorder Depression, memory loss, forgetfulness, amnesia, memory impairment, confusion, sleep disturbances, nightmares
Nervous system disorders	Frequent Less frequent	Headache, dizziness, paraesthesia
	Frequency unknown	Memory impairment, peripheral neuropathy,
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Cough, dyspnoe, interstitial lung disease
Vascular disorders	Frequency unknown	Hot flush, hypertension

Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Flatulence, Abdominal pain, abdominal discomfort abdominal distension, upper abdominal pain, diarrhoea, dry mouth, dyspepsia, gastrooesophageal reflux disease, nausea, vomiting Constipation, gastritis, pancreatitis
Hepato-biliary disorders	Frequency unknown	Cholecystitis, cholelithiasis, fatal and non-fatal hepatic failure, hepatitis/jaundice
Skin and Subcutaneous tissue disorders	Less frequent Frequency Unknown	Pruritus, rash, urticarial Alopecia, erythema multiforme, angioedema

Musculoskeletal and connective tissue disorders	Frequent Less frequent Frequency Unknown	Myalgia,pain in limb Arthralgia; back pain; muscle spasms; muscular weakness; musculoskeletal pain/discomfort, neck pain, pain in extremity Muscle cramps, myopathy, myositis, immune-mediated necrotizing myopathy,tendinopathy, tendon rupture rhabdomyolysis (with or without acute renal failure)
Reproductive system and breast disorders	Frequency unknown	Erectile Dysfunction, sexual dysfunction
General disorders and administration site conditions	Less frequent Frequency unknown	Asthenia, fatigue, malaise, oedema peripheral, 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:

Ezetimibe		
System Organ Class	**Frequency**	**Side Effect**
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 disorders	Less frequent	Thrombocytopenia
Psychiatric disorders	Less frequent	Depression
Nervous system disorders	Frequent Less frequent	Headache, Dizziness, paraesthesia
Respiratory, thoracic and mediastinal disorders	Frequent	Coughing
Gastro-intestinal disorders	Frequent Less frequent	Abdominal pain and diarrhoea Nausea, pancreatitis

Hepatobiliary 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		
System Organ Class	**Incidence**	**Adverse Reaction**
Blood and lymphatic system disorders	Less frequent	Anaemia, thrombocytopenia
Immune System disorders	Less frequent	Hypersensitivity syndrome
Psychiatric disorders	Less frequent Frequency unknown	Insomnia Reversible cognitive impairment, depression
Nervous system disorders	Less frequent Frequency Unknown	Dizziness, paresthesia, peripheral neuropathy, memory impairment,headache Myasthenia Gravis
Eye Disorders	Frequency unknown	Ocular myasthenia
Respiratory,	Frequency unknown	Dyspnoea, interstitial lung disease

thoracic and mediastinal disorders		
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 and rhabdomyolysis dermatomyositis, polymyositis, myasthenia gravis
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:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care

providers are asked to report any suspected adverse reactions to SAHPRA via the '**6.04 Adverse Drug Reaction 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 **MEZIBE PLUS** can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed. Co-administration of ezetimibe (1000 mg/kg) and simvastatin (1000 mg/kg) was reported to be well-tolerated in acute, oral toxicity studies in mice and rats. No clinical signs of toxicity were reported in these animals. The estimated oral LD_{50} for both species was ezetimibe greater than or equal to 1 000 mg/kg simvastatin greater than or equal to 1 000 mg/kg.

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 localizes 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 inhibits 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 protein (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 is seen when ezetimibe is co-administered with simvastatin.

Absorption:

MEZIBE PLUS:

MEZIBE PLUS 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 (Cmax) 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) has 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 is 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 is 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 show that no accumulation of simvastatin occurs after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurs 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) is observed in all animal species evaluated.

Ezetimibe and ezetimibe-glucuronide are the major active ingredient-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total active ingredient 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:

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 simvastatin equivalents in the bile. Consequently, availability of active simvastatin to the systematic circulation is low.

Elimination:

Ezetimibe:

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

Simvastatin:

Following an oral dose of radioactive simvastatin, 13 % of the radioactivity is excreted in the urine and 60 % in the faeces within 96 hours. The amount recovered in the faeces represents absorbed simvastatin equivalents excreted in bile as well as unabsorbed simvastatin. Following an intravenous injection of the beta-hydroxy acid metabolite an average of only 0,3 % of the IV dose is 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 receive simvastatin 40 mg/day, exhibit an increase in mean plasma levels of HMG-CoA reductase inhibitory activity of approximately 45 % compared with 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) less than or equal to 30 ml/min), the mean AUC for total ezetimibe is 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 less than 30 ml/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor are approximately 2-fold higher than those in healthy patients.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Antioxidants: Butylatedhydroxyanisole 0,02 % and propyl gallate 0,005 %.

Excipients: Butylated hydroxyl anisole, citric acid monohydrate, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and propyl gallate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ºC. Do not remove the blisters from the carton until required for use. Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Cartons containing 3 strips of 10 tablets packed in Cold form blister laminate packs composed of oriented polyamide, aluminium foil and PVC with backing of aluminium foil coated with heat seal lacquer on the inner side

6.6 Special precautions for disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd.

14 Lautre Road

Stormill, Ext.1, Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER

MEZIBE PLUS 10/10 mg: 50/7.5/0640

MEZIBE PLUS 10/20 mg: 50/7.5/0641

MEZIBE PLUS 10/40 mg: 50/7.5/0642

9. DATE OF FIRST AUTHORISATION

13 April 2021

10. DATE OF REVISION OF THE TEXT

29 August 2023