Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MEZIBE 10 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg ezetimibe.

Contains Sugar: Lactose monohydrate 63 mg/ tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to off white capsule shaped uncoated tablet with 'E 10' debossed on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypercholesterolaemia

MEZIBE 10, administered with an HMG-CoA reductase inhibitor (statin) or alone, is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C) and low-density lipoprotein cholesterol (LDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous familial hypercholesterolaemia (HoFH)

MEZIBE 10, administered with a statin, 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 on an appropriate lipid-lowering diet and weight loss program where indicated and should continue on this diet during treatment with **MEZIBE 10**.

The recommended dose of **MEZIBE 10** is 10 mg once daily, used alone, with a statin or with fenofibrate.

MEZIBE 10 can be administered at any time of the day, with or without food.

Use in the elderly

No dosage adjustment is required for elderly patients (see section 5.2).

Use in paediatric patients

Children ≥ 10 years: No dosage adjustment is required (see section 5.2).

Children < 10 years: No clinical data on safety and efficacy are available; therefore, treatment with **MEZIBE 10** is contraindicated.

Use in hepatic impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with **MEZIBE 10** is contraindicated in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) hepatic impairment due to unknown effects. (See section 4.3).

Concomitant use with bile acid sequestrants

Dosing of **MEZIBE 10** should occur at least 2 hours before or 4 hours after administration of a bile acid sequestrant.

Method of administration

For oral use

4.3 Contraindications

- Hypersensitivity to ezetimibe or to any of the excipients of **MEZIBE 10** (see section 6.1).

- Pregnancy and lactation (see section 4.6).
- Moderate to severe hepatic impairment (Child Pugh score ≥ 7).
- Children under the age of 10 years.
- **MEZIBE 10** co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

4.4 Special warnings and precautions for use

When **MEZIBE 10** is to be administered with a statin, please refer to the professional information for that particular medicine.

Liver enzymes

In controlled co-administration trials in patients receiving **MEZIBE 10** with a statin, consecutive transaminase elevations (≥ 3 times the upper limit of normal (ULN)) have been observed. When **MEZIBE 10** is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin (see section 4.8.).

Skeletal muscle

In post-marketing experience with **MEZIBE 10**, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with **MEZIBE 10**. However, rhabdomyolysis has been reported with **MEZIBE 10** monotherapy and with the addition of **MEZIBE 10** to other medicines known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a creatine phosphokinase (CPK) level >10 times the ULN, **MEZIBE 10**, any statin, and any of these other medicines that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with **MEZIBE 10** should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness (see section 4.8)

Hepatic impairment

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, **MEZIBE 10** is contraindicated (see section 4.3 and 5.2).

Paediatric population

The safety and efficacy of **MEZIBE 10** co-administered with doses of simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age.

The safety and efficacy of **MEZIBE 10** co-administered with simvastatin have not been studied in paediatric patients < 10 years of age (see sections 4.2).

The long-term efficacy of therapy with **MEZIBE 10** in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Fibrates

The safety and efficacy of **MEZIBE 10** administered with fibrates have not been established. The co-administration of **MEZIBE 10** with fibrates other than fenofibrate has not been studied.

Fenofibrate

If cholelithiasis is suspected in a patient receiving **MEZIBE 10** and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see sections 4.5 and 4.8). Alternative lipid-lowering therapy should be considered.

Ciclosporin

Caution should be exercised when initiating **MEZIBE 10** in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving **MEZIBE 10** and ciclosporin (see section 4.5).

Anticoagulants

If **MEZIBE 10** is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Lactose monohydrate

MEZIBE 10 contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take **MEZIBE 10.**

4.5 Interaction with other medicines and other forms of interaction

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 medicine metabolising enzymes. 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.

In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Antacids

Concomitant antacid administration 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 area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) by approximately 55 %. The incremental low-

density lipoprotein cholesterol (LDL-C) reduction due to adding **MEZIBE 10** to cholestyramine may be lessened by this interaction (see section 4.2).

Fibrates

In patients receiving fenofibrate and **MEZIBE 10**, medical practitioner should be aware of the possible risk of cholelithiasis and gallbladder disease (see sections 4.4 and 4.8).

If cholelithiasis is suspected in a patient receiving **MEZIBE 10** and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see section 4.8).
Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations (approximately 1,5- and 1,7- fold respectively).
Co-administration of **MEZIBE 10** with other fibrates has not been studied.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe increased cholesterol in the gallbladder bile but not in all species (see section 5.3). A lithogenic risk associated with the therapeutic use of **MEZIBE 10** cannot be ruled out.

Statins

No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

Ciclosporin

In a study of eight post-renal transplant patients with creatinine clearance of > 50 mL/min on a stable dose of ciclosporin, a single 10-mg dose of **MEZIBE 10** resulted in a 3,4-fold (range 2,3- to 7,9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study. In a different study, a renal transplant patient with severe renal impairment (creatinine clearance of 13,2 mL/min/1,73 m^2) who was receiving

ciclosporin and multiple other medicines demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in twelve 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. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating **MEZIBE 10** in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving **MEZIBE 10** and ciclosporin (see section 4.4).

Anticoagulants

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased INR in patients who had **MEZIBE 10** added to warfarin or fluindione. If **MEZIBE 10** is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

MEZIBE 10 is contraindicated during pregnancy and lactation (see section 4.3).

Pregnancy

No clinical data are available on the use of **MEZIBE 10** during pregnancy.

Lactation

MEZIBE 10 should not be used during lactation. Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.

Fertility

No clinical trial data are available on the effects of ezetimibe on human fertility. Ezetimibe had no effect on the fertility of male or female.

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.

4.8 Undesirable effects

MEZIBE 10 when administered alone		
System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Frequent	viral infections, pharyngitis, sinusitis
Metabolism and nutrition disorders	Less frequent	decreased appetite
Vascular disorders	Less frequent	hot flush, hypertension
Respiratory, thoracic and mediastinal disorders	Frequent	cough
Gastrointestinal disorders	Frequent	abdominal pain, diarrhoea, flatulence
	Less frequent	dyspepsia, gastroesophageal reflux disease, nausea

Musculoskeletal, connective tissue and bone disorders	Frequent	arthralgia, back pain
	Less frequent	muscle spasms, neck pain
General disorders and administration site conditions	Frequent	headache, fatigue
	Less frequent	chest pain, pain
Investigations	Less frequent	Increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), increased blood creatine phosphokinase, increased gamma-glutamyl transferase, abnormal liver function test

MEZIBE 10 when administered with a statin		
System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Frequent	pharyngitis, sinusitis, upper respiratory tract infection
Nervous system disorders	Frequent	headache, dizziness
	Less frequent	paraesthesia
Gastrointestinal disorders	Frequent	abdominal pain, constipation, diarrhoea, flatulence, nausea
	Less frequent	dry mouth, gastritis
Skin and subcutaneous tissue disorders	Less frequent	pruritus, rash, urticaria

Musculoskeletal, connective tissue and bone disorders	Frequent	myalgia, arthralgia, back pain
	Less frequent	muscular weakness, pain in extremity
General disorders and administration site conditions	Frequent	chest pain, fatigue
	Less frequent	asthenia, peripheral oedema
Investigations	Frequent	increased ALT and/or AST

MEZIBE 10 when administered with fenofibrate		
System organ class	**Frequency**	**Adverse reaction**
Gastrointestinal disorders	Frequent	abdominal pain

Post-marketing data		
System organ class	**Frequency**	**Adverse reaction**
Blood and the lymphatic system disorders	Frequency unknown	thrombocytopenia
Immune system disorders	Frequency unknown	hypersensitivity reactions (anaphylaxis, rash, urticaria, angioedema)
Psychiatric disorders	Frequency unknown	depression
Respiratory, thoracic and mediastinal disorders	Frequency unknown	dyspnoea
Gastrointestinal disorders	Frequency unknown	pancreatitis

Hepatobiliary disorders	Frequency unknown	hepatitis, cholelithiasis, cholecystitis
Skin and subcutaneous tissue disorders	Frequency unknown	erythema multiforme
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	myopathy/ rhabdomyolysis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **MEZIBE 10** is important. It allows continued monitoring of the benefit/risk balance of **MEZIBE 10**. 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/

4.9 Overdose

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated.

In the event of an overdose, symptomatic and supportive measures should be employed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.5 Serum-cholesterol reducers. Pharmacotherapeutic group: Other lipid modifying agents.

ATC code: C10A X09.

Mechanism of action

Ezetimibe inhibit the intestinal absorption of cholesterol and related plant sterols.

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [^{14}C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat-soluble vitamins A and D.

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 10 to 17 years of age. The safety and efficacy of ezetimibe co-administered with simvastatin have not been studied in paediatric patients < 10 years of age.

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.

5.2 Pharmacokinetic properties

Absorption

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. Ezetimibe can be administered with or without food.

Distribution

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

Biotransformation

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 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.

Elimination

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.

Special populations

Paediatric population

The absorption and metabolism of ezetimibe are similar between children 10 years of age or older and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population less than 10 years of age are not available.

Elderly

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

LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic impairment

After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1, 7-fold in patients with mild hepatic impairment (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score > 9) hepatic impairment, **MEZIBE 10** is contraindicated in these patients (see section 4.4).

Renal impairment

After a single 10-mg dose of ezetimibe in patients with severe renal disease (mean CrCl ≤ 30 mL/min/1, 73 m^2), the mean AUC for total ezetimibe was increased approximately 1, 5-fold, compared to healthy subjects. This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

An additional patient in this study (post-renal transplant and receiving multiple medicines, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Gender

Plasma concentrations for total ezetimibe are slightly higher (approximately 20 %) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with **MEZIBE 10**. Therefore, no dosage adjustment is necessary on the basis of gender.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, lactose monohydrate, magnesium stearate, povidone, pregelatinised starch, sodium lauryl sulphate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at or below 25 °C in the original pack.

Do not remove the blisters from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Each carton contains 28 or 30 tablets packed in cold form blister or aclar blister packs.

The aclar blister pack comprises of clear transparent PVC film laminated with aclar on the inner side. A lidding laminate comprising of hard tempered, aluminum foil coated with heat seal lacquer on inner side. Each blister strip contains 10 or 14 tablets.

The cold form blister pack comprises of oriented polyamide, aluminium foil and PVC film coating with backing of hard tempered aluminium foil coated with heat seal lacquer. Each blister strip contains 10 or 14 tablets.

6.6 Special precautions for disposal

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage 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(S)

48/7.5/0637

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

February 2021

10. DATE OF REVISION OF THE TEXT

February 2021