Approved Professional Information for Medicines for Human Use:

MIBEZIT

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MIBEZIT 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MIBEZIT 10 mg tablet contains 10 mg ezetimibe.

Contains sugar.

Each 10 mg tablet contains lactose monohydrate 83 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

MIBEZIT 10 mg are white to off white, capsule shaped, flat faced with beveled edge, uncoated tablets, debossed with “10” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypercholesterolaemia

MIBEZIT, 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)

MIBEZIT 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

Posology

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 MIBEZIT.

The recommended dose is 10 mg once daily, used alone, with a statin, or with fenofibrate. MIBEZIT can be administered at any time of the day, with or without food.

Special populations

Elderly population

No dosage adjustment is required for elderly patients (see section 5.1)

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with ezetimibe is contra-indicated in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score greater than 9) liver dysfunction due to unknown effects (See section 4.3).

Co-administration with bile acid sequestrants

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

Paediatric population

Children 10 years of age or older: No dosage adjustment is required (see section 5.1)

Children under 10 years of age: No clinical data on safety and efficacy are available, therefore treatment is contra-indicated.

Method of administration

MIBEZIT is for oral use and can be administered at any time of the day, with or without food.

4.3 Contraindications

- Hypersensitivity to any ezetimibe or component of MIBEZIT.
- Pregnancy, as no clinical data on exposed pregnancies is available. Lactation, as it is not known whether ezetimibe is excreted into human breast milk.
- Children below the age of 10 years.
- Moderate to severe hepatic impairment (Child Pugh score 7 or more).

(When MIBEZIT is to be administered with a statin, please refer to the Professional Information for that particular medication.)

4.4 Special warnings and precautions for use

Liver enzymes

In controlled co-administration trials in patients receiving 10 mg tablet with a statin, consecutive transaminase elevations (≥ 3 X the upper limit of normal [ULN]) have been observed. When MIBEZIT 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 MIBEZIT cases of myopathy and rhabdomyolysis have been reported. If myopathy is suspected based on muscle symptoms or is confirmed by a creatine phosphokinase (CPK) level > 10 times the ULN, MIBEZIT, any statin, and any of these other medicines that the patient is taking concomitantly should be immediately discontinued. All patients

starting therapy with MIBEZIT 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, MIBEZIT is not recommended (see section 5.2).

Paediatric population

Efficacy and safety of MIBEZIT co-administered with simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys (Tanner Stage II or above) and in girls who were at least one year post-menarche. In this limited controlled study, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of ezetimibe for a treatment period > 33 weeks on growth and sexual maturation have not been studied (see sections 4.2 and 4.8).

The safety and efficacy of MIBEZIT 10 mg 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 MIBEZIT co-administered with simvastatin have not been studied in paediatric patients < 10 years of age (see sections 4.2 and 4.8).

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

Fibrates

The safety and efficacy of MIBEZIT administered with fibrates have not been established.

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

Anticoagulants

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

Excipients: lactose intolerance

This medicine contains lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take MIBEZIT.

4.5 Interaction with other medicines and other forms of interaction

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) approximately 55 %. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding MIBEZIT to cholestyramine may be lessened by this interaction (see section 4.2).

Fibrates

In patients receiving fenofibrate and MIBEZIT, medical practitioners 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 MIBEZIT and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see section 4.8).

Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1,5- and 1,7-fold respectively). Co-administration of MIBEZIT with other

fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. A lithogenic risk associated with the therapeutic use of this medicine cannot be ruled out.

Statins

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

Ciclosporin

In a study of post-renal transplant patients with creatinine clearance of > 50 mL/min on a stable dose of ciclosporin, a single 10 mg dose of MIBEZIT 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 who was receiving ciclosporin and multiple other medications demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in 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 MIBEZIT in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving MIBEZIT 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 healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had MIBEZIT

added to warfarin or fluindione. If MIBEZIT 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

MIBEZIT co-administered with a statin is contraindicated during pregnancy and lactation (see section 4.3), please refer to the Professional Information for that particular statin.

Pregnancy

MIBEZIT is contraindicated in pregnancy (see section 4.3). No clinical data are available on the use of MIBEZIT during pregnancy.

Lactation

MIBEZIT 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 rats.

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

The most frequently observed adverse reactions are headache, abdominal pain, diarrhoea, flatulence, myalgia, fatigue and increased liver enzymes (ALT and/or AST).

In post-marketing experience with MIBEZIT cases of myopathy and rhabdomyolysis have been reported (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies of MIBEZIT (as a monotherapy or co-administered with a statin) or MIBEZIT reported from post-marketing use either administered alone or with a statin are listed in the table below. These reactions are presented by system organ class and by frequency.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Blood and lymphatic system disorders			Thrombocytopaenia
Immune system disorders			Hypersensitivity; including rash; Urticaria; Anaphylaxis and

			Angio-oedema
Metabolism and nutrition disorders		Decreased appetite	
Psychiatric disorders			Depression
Nervous system disorders	Headache	Paraesthesia	Dizziness
Vascular disorders		Hot flush; Hypertension	
Respiratory, thoracic and mediastinal disorders		Cough	Dyspnoea
Gastrointestinal disorders	Abdominal pain; Diarrhoea; Flatulence	Dyspepsia; Gastro oesophageal reflux disease; Nausea; Dry mouth; Gastritis	Pancreatitis; Constipation
Hepatobiliary disorders			Hepatitis; Cholelithiasis; Cholecystitis

Skin and subcutaneous tissue disorders		Pruritus; Rash; Urticaria	Erythema multiforme
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia; Muscle Spasms; Neck pain; Back pain; Muscular weakness; Pain in extremity.	Myopathy/Rhabdomyolysis (see section 4.4)
General disorders and administration site conditions	Fatigue	Chest pain; Pain; Asthenia; Increased oedema peripheral	
Investigations	Increased ALT and/or AST	Blood CPK; increased Gamma-Glutamyl transferase; Abnormal liver function test	

MIBEZIT **co-administered with fenofibrate**

Gastrointestinal disorders: abdominal pain (common)

Clinically important elevations (> 3 X ULN, consecutive) in serum transaminases have been observed when MIBEZIT was co-administered with fenofibrate (4,5 %) compared with fenofibrate monotherapy (2,7 %). Corresponding incidence rates for cholecystectomy were also higher MIBEZIT was co-administered with fenofibrate (1,7 %) compared with fenofibrate monotherapy (0,6 %).

Paediatric (6 to 17 years of age) patients

In the paediatric patient group (6 - 10 years old), higher elevations of ALT and/or AST (≥ 3 X ULN, consecutive) were observed in ezetimibe administered patients (1,1 %) compared to the placebo group (0 %). There were no elevations of CPK (≥ 10 X ULN). No cases of myopathy were reported.

When ezetimibe was administered with simvastatin in paediatric patients (10 - 17 years old), higher elevations of ALT and/or AST (≥ 3 X ULN, consecutive) were observed in ezetimibe/simvastatin patients (3 %) compared to the simvastatin monotherapy group (2 %); these figures were respectively 2 % and 0 % for elevation of CPK (≥ 10 X ULN). No cases of myopathy were reported.

Patients with coronary heart disease and acute coronary syndrome (ACS) event history

In patients treated with either ezetimibe/simvastatin 10/40 mg (some titrated up to ezetimibe/simvastatin 10/80 mg) or simvastatin 40 mg (some titrated up to simvastatin 80 mg), the incidence of myopathy was 0,2 % for ezetimibe/simvastatin and 0,1 % for simvastatin. The incidence of

rhabdomyolysis was 0,1 % for ezetimibe/simvastatin and 0,2 % for simvastatin. The incidence of consecutive elevations of transaminases (≥ 3 X ULN) was 2,5 % for ezetimibe/simvastatin and 2,3 % for simvastatin (see section 4.4). Gallbladder-related adverse effects were reported in 3,1 % vs 3,5 % of patients allocated to ezetimibe/simvastatin and simvastatin, respectively. The incidence of cholecystectomy hospitalisations was 1,5 % in both treatment groups. Cancer (defined as any new malignancy) was diagnosed in 9,4 % vs 9,5 %, respectively.

Patients with chronic kidney disease

In this patient group, the incidence of myopathy/rhabdomyolysis was 0,2 % in patients treated with MIBEZIT combined with simvastatin and 0,1 % in patients treated with placebo. Consecutive elevations of transaminases (> 3X ULN) occurred in 0,7 % of patients treated with MIBEZIT combined with simvastatin compared with 0,6 % of patients treated with placebo (see section 4.4).

Laboratory values

The incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was observed to be similar between ezetimibe (0,5 %) and placebo (0,3 %). In co-administration, the incidence was 1,3 % for patients treated with ezetimibe co-administered with a statin and 0,4 % for patients treated with a statin alone (see section 4.4).

CPK > 10 X ULN was reported for 0,2 % patients administered ezetimibe alone vs 0,1 % patients administered placebo, and for 0,1 % patients co-administered ezetimibe and a statin vs 0,4 % patients administered a statin alone (see section 4.4).

Reporting of suspected adverse reactions

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

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. In animals, no toxicity was observed after single oral doses of 5000 mg /kg of ezetimibe in rats and mice and 3000 mg /kg in dogs.

A few cases of overdosage with ezetimibe have been reported; most have not been associated with adverse experiences. In the event of an overdose, symptomatic and supportive measures should be employed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 7.5 Serum-cholesterol reducers

Pharmacotherapeutic group: Pharmacotherapeutic group: Other lipid modifying agents,

ATC code: C10A X09

Mechanism of action

Pharmacodynamic effects

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

In human studies, ezetimibe inhibited the intestinal absorption of cholesterol and related plant sterols.

Ezetimibe in experimental animals inhibited the absorption of [14C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat-soluble vitamins A and D.

5.2 Pharmacokinetic properties

Absorption

After oral administration, ezetimibe is 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 10 mg tablets. Medicine 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 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 14C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) 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

Elderly patients

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).

Hepatic insufficiency

After a single 10 mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1,7-fold in patients with mild hepatic insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. In a 14 day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (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. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score greater than 9) hepatic insufficiency, ezetimibe is contra-indicated in these patients.

Renal insufficiency

After a single 10 mg dose of ezetimibe in patients with severe renal disease (n equal to 8; mean creatinine clearance (CrCl) less than or equal to 30 ml/min/ 1,73 m^2), the mean AUC for total ezetimibe was increased approximately 1,5-fold, compared to healthy subjects (n equal to 9).
An additional patient in this study (post-renal transplant and receiving multiple medications, including cyclosporine) had a 12-fold greater exposure to total ezetimibe (see section 4.4).

Gender

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

Race

Based on a meta-analysis of pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium (E468)

Lactose monohydrate

Magnesium stearate (E470b)

Povidone k-30 (E1201)

Polysorbate 80 (E433)

Sodium lauryl sulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters and Bottles: 3 years

6.4 Special precautions for storage

Store at or below 25 ºC.

Blisters: Store in the original package in order to protect from moisture.

Bottles: Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

MIBEZIT is packed in Al-Al blister packs or Al-PVC blister packs and into cardboard cartons in pack sizes of 14's, 28's or 30's.

[PRODUCT NAME} is packed in white HDPE bottles with a white child resistant cap in pack sizes of 30's or 100's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER

MIBEZIT: 54/7.5/0365.364

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 September 2022

10. DATE OF REVISION OF THE TEXT