SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TOLEZE 10 10 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of ezetimibe.

Excipient(s) with known effect:

- contains sugar (lactose monohydrate): 63 mg per tablet.

For full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Tablets.

White to off white capsule shape tablets (about 8 mm x 4 mm) debossed with '713' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypercholesterolaemia

TOLEZE 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)

TOLEZE 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

Posology

The patient should be on an appropriate lipid-lowering diet and weight loss programme where indicated and should continue on this diet during treatment with **TOLEZE 10**.

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

Elderly

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

Paediatric population
Children 10 years of age or older: No dosage adjustment is required (see **section 5.2**).
Children under 10 years of age: No clinical data on safety and efficacy of **TOLEZE 10** in children under 10 years of age are available.
Treatment with **TOLEZE 10** is contraindicated (see **section 4.3**).

Use in hepatic impairment
No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with **TOLEZE 10** is contra-indicated in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction due to unknown effects (see **section 4.3** and **section 5.2**).

Co-administration with bile acid sequestrants
Dosing of **TOLEZE 10** should occur either 2 or more hours before or 4 or more hours after administration of a bile acid sequestrant.

Method of administration
Route of administration is oral.

4.3 Contraindications
- Hypersensitivity to the active substance(s) or to any of the excipients listed in **section 6.1**.
- Pregnancy, as no clinical data on exposed pregnancies is available (see **section 4.6**).
- Lactation, as it is not known whether ezetimibe is excreted into human breast milk (see **section 4.6**).
- Children below the age of 10 years (see **section 4.2** and **section 4.4**).
- Moderate to severe hepatic impairment (Child Pugh score 7 or more) (see **section 4.2**)

When **TOLEZE 10** is co-administered with a statin, please refer to the professional information for that particular medicinal product.

4.4 Special warnings and precautions for use
When **TOLEZE 10** is co-administered with a statin, please refer to the professional information for that particular medicinal product.

Liver Enzymes
In controlled co-administration trials in patients receiving ezetimibe, as contained in **TOLEZE 10**, with a statin, consecutive transaminase elevations (≥ 3 times the upper limit of normal [ULN]) have been observed. When **TOLEZE 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.

Skeletal Muscle

In post-marketing experience with **TOLEZE 10**, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with **TOLEZE 10**. However, rhabdomyolysis has been reported with **TOLEZE 10** monotherapy and with the addition of **TOLEZE 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, **TOLEZE 10**, any statin, and any of these other medicines that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with **TOLEZE 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, **TOLEZE 10** is contraindicated (see **section 4.3**).

Paediatric population

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

Fibrates

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

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

Ciclosporin

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

Anticoagulants

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

Statins

No clinically significant pharmacokinetic interactions were seen when **TOLEZE 10** was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin or rosuvastatin.

Excipient

TOLEZE 10 contains lactose.

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

4.5 Interactions 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 drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

In interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl oestradiol 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) approximately 55 %. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding **TOLEZE 10** to cholestyramine may be lessened by this interaction (see **section 4.2**).

Fibrates

In patients receiving fenofibrate and **TOLEZE 10**, medical practitioners should be aware of the possible risk of cholelithiasis and gallbladder disease (see **section 4.4** and **section 4.8**). If cholelithiasis is suspected in a patient receiving **TOLEZE 10** 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 **TOLEZE 10** with other fibrates has not been studied.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe sometimes increased cholesterol in the gallbladder bile but not in all species (see **section 5.3**). A lithogenic risk associated with the therapeutic use of **TOLEZE 10** cannot be ruled out. Co-administration of **TOLEZE 10** with fibrates (other than fenofibrate) is not recommended.

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 **TOLEZE 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 (n = 17). In a different study, a renal transplant patient with severe renal impairment 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 **TOLEZE 10** in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving **TOLEZE 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 International Normalised Ratio (INR) in patients who had **TOLEZE 10** added to warfarin or fluindione. If **TOLEZE 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

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

Pregnancy

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

Breastfeeding

TOLEZE 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.

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

a. Summary of the safety profile

In clinical studies of up to 112 weeks duration, ezetimibe 10 mg daily was administered alone in 2396 patients, with a statin in 11, 308 patients or with fenofibrate in 185 patients. Adverse reactions were usually mild and transient. The overall incidence of side effects was similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between ezetimibe and placebo.
Clinical studies were not performed with **TOLEZE 10**.

b. Tabulated summary of adverse reactions

Ezetimibe administered alone or co-administered with a statin:
The following adverse reactions were observed in patients treated with ezetimibe (N=2396) and at a greater incidence than placebo (N=1159) or in patients treated with ezetimibe co-administered with a statin (N=11308) and at a greater incidence than statin administered alone (N=9361). Post-marketing Adverse reactions were derived from reports containing ezetimibe either administered alone or with a statin.

Ezetimibe monotherapy		
System organ class	**Adverse reactions**	**Frequency**
Metabolism and nutrition disorders	decreased appetite	Less frequent
Vascular disorders	hot flush; hypertension	Less frequent
Respiratory, thoracic and mediastinal disorders	cough	Less frequent
Gastrointestinal disorders	abdominal pain; diarrhoea; flatulence	Frequent
	dyspepsia; gastro-oesophageal reflux disease; nausea	Less frequent
Musculoskeletal and connective tissue disorders	arthralgia; muscle spasms; neck pain	Less frequent
General disorders and administration site condition	fatigue, headache	Frequent
	chest pain, pain	Less frequent
Investigations	ALT and/or AST increased; blood CPK increased; gamma-glutamyltransferase increased; liver function test abnormal	Less frequent

Additional adverse reactions with Ezetimibe co-administered with a statin		
System organ class	**Adverse reactions**	**Frequency**
Nervous system disorders	headache	Frequent
	paraesthesia	Less frequent
Gastrointestinal disorders	abdominal pain; constipation; dry mouth; flatulence; gastritis; nausea	Less frequent
Skin and subcutaneous tissue disorders	pruritus; rash; urticaria	Less frequent
Musculoskeletal and connective tissue disorders	myalgia	Frequent
	back pain; muscular weakness; pain in extremity	Less frequent
General disorders and administration site condition	asthenia; fatigue; oedema peripheral	Less frequent
Investigations	ALT and/or AST increased	Frequent

Post-marketing Experience (with or without a statin)		
System organ class	**Adverse reactions**	**Frequency**
Blood and lymphatic system disorders	thrombocytopaenia	Frequency not known
Immune system disorders	hypersensitivity, including rash, urticaria, anaphylaxis and angioedema.	Frequency not known
Psychiatric disorders	depression	Frequency not known
Nervous system disorders	dizziness; paraesthesia	Frequency not known
Respiratory, thoracic and mediastinal disorders	dyspnoea	Frequency not known
Gastrointestinal disorders	constipation; nausea; pancreatitis;	Frequency not known
Hepatobiliary disorders	hepatitis; cholelithiasis; cholecystitis	Frequency not known
Skin and subcutaneous tissue disorders	erythema multiforme	Frequency not known
Musculoskeletal and connective tissue disorder	myalgia; myopathy/rhabdomyolysis (see **section 4.4**)	Frequency not known

General disorders and administration site conditions	asthenia	Frequency not known
Investigations	increased transaminases; increased CPK	Frequency not known

c. Description of selected adverse reactions

Ezetimibe co-administered with fenofibrate:
Gastrointestinal disorders: abdominal pain (common).
In a multicentre, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidaemia, 625 patients were treated for up to 12 weeks and 576 patients for up to 1 year. In this study, 172 patients treated with ezetimibe and fenofibrate completed 12 weeks of therapy, and 230 patients treated with ezetimibe and fenofibrate (including 109 who received ezetimibe alone for the first 12 weeks) completed 1 year of therapy. This study was not designed to compare treatment groups for infrequent events. Incidence rates (95 % CI) for clinically important elevations (> 3 X ULN, consecutive) in serum transaminases were 4,5 % (1,9; 8,8) and 2,7 % (1,2; 5,4) for fenofibrate monotherapy and ezetimibe co-administered with fenofibrate, respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0,6 % (0,0; 3,1) and 1,7 % (0,6; 4,0) for fenofibrate monotherapy and ezetimibe co-administered with fenofibrate, respectively (see **section 4.4** and **section 4.5**).

d. Paediatric population (6 to 17 years of age)

In a study involving paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia (n=138), elevations of ALT and/or AST (≥ 3 X ULN, consecutive) were observed in 1,1 % (1 patient) of the ezetimibe patients compared to 0 % in the placebo group. There were no elevations of CPK (≥ 10 X ULN).
No cases of myopathy were reported.
In a separate study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n = 248), elevations of ALT and/or AST (≥ 3 X ULN, consecutive) were observed in 3 % (4 patients) of the ezetimibe/simvastatin patients compared to 2 % (2 patients) in the simvastatin monotherapy group; these figures were respectively 2 % (2 patients) and 0 % for elevation of CPK (≥ 10 X ULN). No cases of myopathy were reported.
These trials were not suited for comparison of rare adverse drug reactions.

e. Other special population(s)

Patients with Coronary Heart Disease and ACS Event History
In the IMPROVE-IT study (see **section 5.1**), involving 18,144 patients treated with either ezetimibe/simvastatin 10/40 mg (n=9067; of whom 6 % were uptitrated to ezetimibe/simvastatin 10/80 mg) or simvastatin 40 mg (n = 9077; of whom 27 % were uptitrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6,0 years.

Discontinuation rates due to adverse experiences were 10,6 % for patients treated with ezetimibe/simvastatin and 10,1 % for patients treated with simvastatin. The incidence of myopathy was 0,2 % for ezetimibe/simvastatin and 0,1 % for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN or two consecutive observations of CK ≥ 5 and < 10 times ULN. The incidence of rhabdomyolysis was 0,1 % for ezetimibe/simvastatin and 0,2 % for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN with evidence of renal injury, ≥ 5 times ULN and < 10 times ULN on two consecutive occasions with evidence of renal injury or CK ≥ 10,000 IU/L without evidence of renal injury. 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 during the trial in 9,4 % vs 9,5 %, respectively.

Patients with Chronic Kidney Disease
In the Study of Heart and Renal Protection (SHARP) (see **section 5.1**), involving over 9000 patients treated with a fixed dose combination of ezetimibe 10 mg with simvastatin 20 mg daily (n = 4650) or placebo (n = 4620), the safety profiles were comparable during a median follow-up period of 4,9 years. In this trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse events were comparable (10,4 % in patients treated with ezetimibe combined with simvastatin, 9,8 % in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was 0,2 % in patients treated with ezetimibe combined with simvastatin and 0,1 % in patients treated with placebo. Consecutive elevations of transaminases (> 3 X ULN) occurred in 0,7 % of patients treated with ezetimibe combined with simvastatin compared with 0,6 % of patients treated with placebo (see **section 4.4**). In this trial, there were no statistically significant increases in the incidence of pre-specified adverse events, including cancer (9,4 % for ezetimibe combined with simvastatin, 9,5 % for placebo), hepatitis, cholecystectomy or complications of gallstones or pancreatitis.

Laboratory values
In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was similar between ezetimibe (0,5 %) and placebo (0,3 %). In co-administration trials, 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. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see **section 4.4**).
In clinical trials, CPK > 10 X ULN was reported for 4 of 1674 (0,2 %) patients administered ezetimibe alone vs 1 of 786 (0,1 %) patients administered placebo, and for 1 of 917 (0,1 %) patients co-administered ezetimibe and a statin vs 4 of 929 (0,4 %) patients administered a

statin alone. There was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or 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

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

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category and class: A.7.5 Serum-cholesterol reducers

Mechanism of action
Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols.
Pharmacodynamic effects
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 oestradiol, or fat-soluble vitamins A and D.

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 when administered as ezetimibe 10-mg tablets.
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 drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug 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 pharmacokinetics of ezetimibe are similar between children ≥ 10 years and adults. Pharmacokinetic data in the paediatric population < 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, ezetimibe is contraindicated in these patients (see **section 4.3**).

Renal impairment
After a single 10-mg dose of ezetimibe in patients with severe renal disease (n = 8; 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 (n = 9). 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 medications, 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 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 the African and Caucasian populations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Crospovidone
Hypromellose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.
Blisters: Do not remove the blister from the carton until required for use.
Bottles: Store in the original container until required for use.

6.5 Nature and contents of container

Blisters:
28’s or 30’s.
Push through blister: Clear PVC/ Aclar (polychloro-trifluoro-ethylene homopolymer) foil with plain, push through aluminium foil.
Peelable blister: Clear PVC/ Aclar (polychloro-trifluoro-ethylene homopolymer) foil with paper/ PET/ Aluminium peelable foil.
HDPE Bottles:
30’s or 28’s pack size: 40 cc HDPE bottle with a child resistant closure, silica gel dessicant and a 9 g absorbent rayon coil.
100’s pack size: 50 cc HDPE bottle silica gel dessicant and a 9 g absorbent rayon coil.

1000's pack size: 200 cc HDPE bottle silica gel dessicant and a 9 g absorbent rayon coil.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements.
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. MARKETING AUTHORISATION NUMBER(S)

54/7.5/0617

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 November 2020

10. DATE OF REVISION OF THE TEXT

26 October 2021