PROFESSIONAL INFORMATION

TRYZETOR

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TRYZETOR 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg ezetimibe.

Contains sugar (lactose monohydrate 78,25 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to off white, capsule shaped, flat faced, beveled edge tablet, debossed with “E” on one side and “10” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypercholesterolaemia

TRYZETOR, 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)

TRYZETOR, 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 TRYZETOR.

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

TRYZETOR 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 TRYZETOR 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 TRYZETOR 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 TRYZETOR 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 TRYZETOR (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.
- TRYZETOR 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 TRYZETOR 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 TRYZETOR with a statin, consecutive transaminase elevations (≥ 3 times the upper limit of normal (ULN)) have been observed. When TRYZETOR 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 TRYZETOR, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with

TRYZETOR. However, rhabdomyolysis has been reported with TRYZETOR monotherapy and with the addition of TRYZETOR 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, TRYZETOR, any statin, and any of these other medicines that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with TRYZETOR 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, TRYZETOR is contraindicated (see section 4.3 and 5.2).

Paediatric population

The safety and efficacy of TRYZETOR 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 TRYZETOR 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 TRYZETOR in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Fibrates

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

Fenofibrate

If cholelithiasis is suspected in a patient receiving TRYZETOR and fenofibrate, gallbladder

investigations are indicated and this therapy should be discontinued (see sections 1.1 and 4.8). Alternative lipid-lowering therapy should be considered.

Ciclosporin

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

Anticoagulants

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

Lactose monohydrate

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

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 (ethinylestradiol 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. The 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 TRYZETOR to cholestyramine may be lessened by this interaction (see section 4.2).

Fibrates

In patients receiving fenofibrate and TRYZETOR, 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 TRYZETOR 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 TRYZETOR 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 TRYZETOR 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 TRYZETOR 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 13,2mL/min/1,73m^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 TRYZETOR in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving TRYZETOR 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 TRYZETOR added to warfarin or fluindione. If TRYZETOR 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

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

Pregnancy

No clinical data are available on the use of TRYZETOR during pregnancy.

Lactation

TRYZETOR 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

TRYZETOR when administered alone

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: Less frequent:	abdominal pain, diarrhoea, flatulence dyspepsia, gastroesophageal reflux disease, nausea
Musculoskeletal, connective tissue and bone disorders	Frequent: Less frequent	arthralgia, back pain muscle spasms, neck pain
General disorders and administration site conditions	Frequent: Less frequent:	headache, fatigue 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

TRYZETOR when administered with a statin

Infections and infestations	Frequent:	pharyngitis, sinusitis, upper respiratory tract infection

Nervous system disorders	Frequent: Less frequent	headache, dizziness paraesthesia
Gastrointestinal disorders	Frequent: Less frequent	abdominal pain, constipation, diarrhoea, flatulence, nausea dry mouth, gastritis
Skin and subcutaneous tissue disorders	Less frequent:	pruritus, rash, urticaria
Musculoskeletal, connective tissue and bone disorders	Frequent: Less frequent:	myalgia, arthralgia, back pain muscular weakness, pain in extremity
General disorders and administration site conditions	Frequent: Less frequent:	chest pain, fatigue asthenia, peripheral oedema
Investigations	Frequent:	increased ALT and/or AST

TRYZETOR when administered with fenofibrate

Gastrointestinal disorders	Frequent:	abdominal pain

Post-marketing data

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	Frequency unknown:	dyspnoea

mediastinal disorders		
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 Tryzetor is important. It allows continued monitoring of the benefit/risk balance of TRYZETOR. Healthcare 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.

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: A7.5 Serum-cholesterol reducers. Pharmacotherapeutic group: Other lipid modifying agents.

ATC code: C10A X09.

Mechanism of action

Ezetimibe inhibits 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 [14C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinylestradiol, 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 (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) 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 14C-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, TRYZETOR 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

TRYZETOR. 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

Crospovidone

Lactose monohydrate

Povidone

Silicon colloidal anhydrous

Sodium lauryl sulphate

Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blisters in carton until required for use.

Keep bottle tightly closed.

6.5 Nature and contents of container

TRYZETOR is packed in:

- Clear PVC Aclar film, aluminium foil blister pack of 14 tablets in a pack size of 28 tablets in a carton
- Cold form Alu-Alu, aluminium foil blister pack of 15 tablets in a pack of 30 tablets in a carton
- Cold form dessicant coated aluminium foil blister of 15 tablets in a pack size of 30 tablets in a carton
- White, opaque, round HDPE bottle with child resistant closure, with aluminium foil heat seal liner, containing a dessicant sachet. Pack size of 30 tablets
- White, opaque, round HDPE bottle with child resistant closure, with aluminium foil heat seal liner, containing a molecular sieve sachet. Pack size of 30 tablets.

Not all pack types and sizes are marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pharma Dynamics (Pty) Ltd

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8. REGISTRATION NUMBER

A52/7.5/0169

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT