PROFESSIONAL INFORMATION

TRYZETOR PLUS RANGE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TRYZETOR PLUS 10/10 mg tablets

TRYZETOR PLUS 10/20 mg tablets

TRYZETOR PLUS 10/40 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TRYZETOR PLUS 10/10 mg tablet contains 10 mg ezetimibe and 10 mg simvastatin.

Contains sugar (51,63 mg lactose monohydrate).

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

Contains sugar (113,26 mg lactose monohydrate).

Each TRYZETOR PLUS 10/40 mg tablet contains 10 mg ezetimibe and 40 mg simvastatin.

Contains sugar (236,52 mg lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

TRYZETOR PLUS 10/10 mg: Light tan, mottled, round about 6 mm, biconvex tablets. Marking 511 on one side.

TRYZETOR PLUS 10/20 mg: Light tan, mottled, round about 8 mm, biconvex tablets. Marking 512 on one side.

TRYZETOR PLUS 10/40 mg: Light tan, mottled, round about 10 mm, biconvex tablets. Marking 513 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia

TRYZETOR PLUS is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG) and non-high-density lipoprotein cholesterol (non-HDL-C) and to moderately increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

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

4.2 Posology and method of administration

Posology

The patient should be placed on a standard cholesterol lowering diet before receiving TRYZETOR PLUS and should continue on this diet during treatment with TRYZETOR PLUS. The dosage should be individualised according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response.

Hypercholesterolaemia

The dosage range is 10/10 mg/day up to 10/40 mg/day. The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55 %) may be started at 10/40 mg/day. After initiation or titration of TRYZETOR PLUS, lipid levels may be analysed after 2 weeks and dosage adjusted if needed.

Dosage in patients with homozygous familial hypercholesterolaemia

The recommended dosage for patients with homozygous familial hypercholesterolaemia is TRYZETOR PLUS 10/40 mg/day in the evening. TRYZETOR PLUS should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Special populations

Use in the elderly

No dosage adjustment is required for elderly patients.

Use in hepatic impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6). Treatment with TRYZETOR PLUS is contraindicated in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score greater than 9) liver dysfunction as safety and efficacy have not been demonstrated (see sections 4.3 and 4.4).

Use in renal impairment

No dosage adjustment is required for patients with moderate renal insufficiency. If treatment in patients with severe renal insufficiency (creatinine clearance less than or equal to 30 mL/min) is deemed necessary, dosages above 10/10 mg/day should be implemented cautiously (see section 5.2).

Paediatric population

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

Co-administration with other medicines

Dosing of TRYZETOR PLUS should occur either 2 or more hours before or 4 or more hours after

administration of a bile acid sequestrant.

In patients taking ciclosporin, danazol or greater than or equal to 1 g/day of niacin concomitantly with TRYZETOR PLUS, the dose of TRYZETOR PLUS should not exceed 10/10 mg/day (see sections 4.4 and 4.5).

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

Method of administration

TRYZETOR PLUS is for oral use and should be taken as a single daily dose in the evening, with or without food.

4.3 Contraindications

- hypersensitivity to ezetimibe, simvastatin or to any of the ingredients of TRYZETOR PLUS
- active liver disease or unexplained persistent elevations of serum transaminases; moderate to severe hepatic impairment
- pregnancy and lactation. (see section 4.6)
- children, as safety and efficacy have not been demonstrated
- concomitant administration of potent CYP3A4 inhibitors (agents that increase AUC approximately 5-fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, nefazodone, and medicines containing cobicistat) (see sections 4.4 and 4.5)
- concomitant administration of gemfibrozil, ciclosporin, or danazol (see sections 4.4 and 4.5)
- in patients with HoFH, concomitant administration of lomitapide with doses > 10/40 mg TRYZETOR PLUS (see sections 4.2, 4.4 and 4.5).

4.4 Special warnings and precautions for use

The dose of TRYZETOR PLUS should not exceed 10/10 mg daily in patients receiving concomitant medicine with ciclosporin, danazol or ≥ 1 g/day of niacin.

The combined use of TRYZETOR PLUS with these medicines should be avoided (see section 4.5).

Ciclosporin concentrations should be monitored in patients receiving TRYZETOR PLUS and ciclosporin (see section 4.5).

Potent CYP3A4 inhibitors

Use of TRYZETOR PLUS concomitantly with potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors or nefazodone) should be avoided (see section 4.3).

If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with TRYZETOR PLUS should be suspended during the course of treatment.

Concomitant use with other medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided.

Fibrates (especially gemfibrozil)

There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates, especially gemfibrozil. The safety and effectiveness of ezetimibe administered with fibrates have not been formally studied. Therefore, the concomitant use of TRYZETOR PLUS and fibrates should be avoided (see sections 4.3 and 4.5).

Amiodarone, verapamil

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

Myopathy/rhabdomyolysis

All patients starting therapy with TRYZETOR PLUS, or whose dose of TRYZETOR PLUS is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. TRYZETOR PLUS should be discontinued immediately if myopathy is diagnosed or suspected.

Caution should be exercised in patients with predisposing factors for rhabdomyolysis. In order to establish a reference baseline value, a creatine kinase (CK) level should be measured before starting treatment in the following situations:

- elderly (age ≥ 65 years)
- female gender
- renal impairment
- uncontrolled hypothyroidism
- personal or familial history of hereditary muscular disorders
- previous history of muscular toxicity with a statin or fibrate
- alcohol abuse.

If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with any statin-containing product (such as TRYZETOR PLUS) should only be initiated with caution. If CK levels are significantly elevated at baseline (> 5 X ULN), treatment should not be started. Simvastatin may cause myopathy manifested as muscle pain, tenderness or weakness with CK above 10 times the ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

The presence of symptoms, and/or a CK level greater than 10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from simvastatin treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients

starting TRYZETOR PLUS treatment or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Creatine kinase measurement

Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 X ULN), levels should be remeasured within 5 to 7 days later to confirm the results.

Cases of myopathy and rhabdomyolysis have been reported in ezetimibe treatment. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. However, rhabdomyolysis has been reported with ezetimibe monotherapy and with the addition of ezetimibe to other medicines known to be associated with increased risk of rhabdomyolysis.

The risk of myopathy/rhabdomyolysis is increased by use of TRYZETOR PLUS with the following:

Potent inhibitors of CYP3A4

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

Other medicines

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

Acipimox is structurally related to niacin. Although acipimox was not studied, the risk for muscle related toxic effects may be similar to niacin.

Ciclosporin or danazol: particularly with higher doses of TRYZETOR PLUS (see section 4.5).

Diltiazem: The risk of myopathy in patients taking simvastatin 40 mg with diltiazem is similar to that in patients taking simvastatin 40 mg without diltiazem (see section 4.5).

Fusidic acid: Patients on fusidic acid treated concomitantly with TRYZETOR PLUS may have an increased risk of myopathy and rhabdomyolysis (see section 4.5). Patients should be closely monitored; temporary suspension of TRYZETOR PLUS treatment may be considered.
For patients with HoFH, this risk may be increased by concomitant use of lomitapide with TRYZETOR PLUS (see section 4.5). Patients should be closely monitored; temporary suspension of TRYZETOR PLUS treatment may be considered.

Many patients who developed rhabdomyolysis on therapy with simvastatin had complicated medical histories, including renal insufficiency, usually as a consequence of long-standing diabetes mellitus. Such patients taking TRYZETOR PLUS need closer monitoring. Therapy with TRYZETOR PLUS should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Daptomycin: Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. simvastatin and ezetimibe/simvastatin) co-administered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either agent can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to temporarily suspend TRYZETOR PLUS in patients taking daptomycin. Consult the prescribing information of Daptomycin to obtain further information about this potential interaction with HMG-CoA reductase inhibitors (e.g. simvastatin and ezetimibe/simvastatin) and for further guidance related to monitoring (see section 4.5).

Reduced function of transport proteins

Reduced function of hepatic OATP transport proteins can increase the systemic exposure of simvastatin acid and increase the risk of myopathy and rhabdomyolysis. Reduced function can

occur as the result of inhibition by interacting medicines (e.g. ciclosporin) or in patients who are carriers of the SLCO1B1 c.521T>C genotype.

Patients carrying the SLCO1B1 gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin acid and increased risk of myopathy.

Simvastatin (as contained in TRYZETOR PLUS) is a substrate of the breast cancer resistant protein (BCRP) efflux transporter. Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of TRYZETOR PLUS should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with simvastatin has not been studied; however, **the dose of TRYZETOR PLUS should not exceed 10/20 mg daily in patients receiving TRYZETOR PLUS concomitantly with medicines containing elbasvir or grazoprevir** (see section 4.5).

Anticoagulants

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

Liver enzymes

In controlled co-administration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (greater than or equal to 3 times the ULN) have been observed (see section 4.8).

It is recommended that liver function tests be performed before treatment with TRYZETOR PLUS begins and thereafter when clinically indicated. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of

progression, particularly if they rise to 3 times the ULN and are persistent, TRYZETOR PLUS should be discontinued. Note that alanine transferase (ALT) may emanate from muscle, therefore ALT rising with CK may indicate myopathy.

There have been reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with TRYZETOR PLUS, promptly interrupt therapy. If an alternate aetiology is not found, do not restart TRYZETOR PLUS.

TRYZETOR PLUS should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of TRYZETOR PLUS (see section 4.3).

Skeletal muscle effects

Risk of myasthenia gravis and ocular myasthenia.

Hepatic impairment

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

Diabetes mellitus

Some evidence suggests that statins as a class raise blood glucose and, in some patients at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping TRYZETOR PLUS treatment. Patients at risk (fasting glucose 5,6 to 6,9 mmol/L, BMI > 30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically.

Interstitial lung disease

Cases of interstitial lung disease have been reported with some statins, including simvastatin (as contained in TRYZETOR PLUS), especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, TRYZETOR PLUS therapy should be discontinued.

Porphyria

Simvastatin has been classified as probably porphyrinogenic and should therefore only be prescribed for compelling reasons and precautions should be considered in all patients.

Paediatric population

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

Ezetimibe has not been studied in patients younger than 10 years of age or in pre-menarche girls (see sections 4.2 and 4.5).

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.

Lactose

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

4.5 Interaction with other medicines and other forms of interaction

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with simvastatin.

TRYZETOR PLUS is bioequivalent to co-administered ezetimibe and simvastatin.

CYP3A4 interactions

No clinically significant pharmacokinetic interactions have been observed between ezetimibe and medicines known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9 and 3A4, or N-acetyltransferase.

Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity, therefore it is not expected to affect the plasma concentrations of other medicines metabolised by CYP3A4.

Pharmacodynamic interactions

Interactions with lipid-lowering medicinal products that can cause myopathy when given alone:

The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration of simvastatin with fibrates. Additionally, there is a pharmacokinetic interaction of simvastatin with gemfibrozil resulting in increased simvastatin plasma levels (see below *Pharmacokinetic interactions* and sections 4.3 and 4.4). Cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (see section 4.4). Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of TRYZETOR PLUS with fibrates is not recommended (see section 4.4).

Pharmacokinetic Interactions

Prescribing recommendations for interacting agents are summarised in the table below:

Medicine Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting medicines	**Prescribing recommendations**
Potent CYP3A4 inhibitors, e.g. Itraconazole* Ketoconazole*	*If treatment is unavoidable, then TRYZETOR PLUS should be

Posaconazole Voriconazole Erythromycin* Clarithromycin* Telithromycin* HIV protease inhibitors (e.g. nelfinavir) Boceprevir Telaprevir Nefazodone Cobicistat Ciclosporin Danazol Gemfibrozil	discontinued. All other potent CYP3A4 inhibitors should be avoided.
Other fibrates Fusidic acid	Not recommended with TRYZETOR PLUS
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with TRYZETOR PLUS
Amiodarone Amlodipine Verapamil Diltiazem Niacin (≥ 1 g/day) Elbasvir Grazoprevir	Do not exceed 10/20 mg TRYZETOR PLUS daily
Lomitapide Daptomycin	For patients with HoFH, do not exceed 10/40 mg TRYZETOR PLUS daily

Grapefruit juice	Avoid grapefruit juice when taking TRYZETOR PLUS

EZETIMIBE:

Antacids

Concomitant antacid administration with TRYZETOR PLUS decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

Cholestyramine

Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) by approximately 55 %. The incremental LDL-C reduction due to adding TRYZETOR PLUS to cholestyramine may be lessened by this interaction.

Fibrates

Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1,5 and 1,7-fold respectively, however these increases are not considered clinically significant. The safety and effectiveness of TRYZETOR PLUS administered with fibrates have not been established. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of TRYZETOR PLUS with fibrates is not recommended until use in patients is studied.

SIMVASTATIN:

Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity, therefore it is not expected to affect the plasma concentrations of other medicines metabolised by CYP3A4.

The following potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of the simvastatin component of TRYZETOR PLUS (see sections 4.3 and 4.4): Itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors and nefazodone.

Fluconazole

Cases of rhabdomyolysis associated with concomitant administration of simvastatin and fluconazole have been reported .

Ciclosporin or danazol

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin or danazol, particularly with higher doses of TRYZETOR PLUS (see sections 4.3 and 4.4).
In a study of 8 post-renal transplant patients with creatinine clearance of greater than 50 mL/min on a stable dose of ciclosporin, a single 10 mg dose of ezetimibe resulted in a 3,4-fold (range 2,3 to 7,9-fold) increase in the mean AUC for total ezetimibe compared to healthy patients. In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13,2 mL/min/1,73 m^2) receiving multiple medicines, including ciclosporin, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects. In a two-period crossover study in 12 healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of ciclosporin on day 7 resulted in a mean 15 % increase in ciclosporin, AUC (range 10 % decrease to 51 % increase) compared to a single 100 mg dose of ciclosporin alone (see section 4.4).

Fusidic acid

Patients on fusidic acid treated concomitantly with TRYZETOR PLUS may have an increased risk of myopathy and rhabdomyolysis (see section 4.4). The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. Co-administration of fusidic acid and TRYZETOR PLUS may cause increased plasma concentrations of both medicines.

If treatment with systemic fusidic acid is necessary, TRYZETOR PLUS treatment should be discontinued throughout the duration of the fusidic acid treatment.

Amiodarone or verapamil

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of TRYZETOR PLUS, therefore, the dose of TRYZETOR PLUS should not exceed 10/20 mg daily in patients receiving concomitant medicine with amiodarone (see section 4.4).

Diltiazem

The dose of TRYZETOR PLUS should not exceed 10/20 mg daily in patients receiving concomitant medicine with diltiazem (see section 4.4).

Amlodipine

Patients on amlodipine treated concomitantly with simvastatin (as contained in TRYZETOR PLUS) have an increased risk of myopathy. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1,6-fold increase in exposure of simvastatin acid. Therefore, the dose of TRYZETOR PLUS should not exceed 10/20 mg daily in patients receiving concomitant medicine with amlodipine.

Lomitapide

The risk of myopathy and rhabdomyolysis may be increased by concomitant administration of lomitapide with simvastatin (see sections 4.3 and 4.4). Therefore, in patients with HoFH, the dose of TRYZETOR PLUS must not exceed 10/40 mg daily in patients receiving concomitant medication with lomitapide.

Moderate inhibitors of CYP3A4

Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4

concomitantly with TRYZETOR PLUS, particularly higher TRYZETOR PLUS doses, may have an increased risk of myopathy (see section 4.4).

Inhibitors of the transport protein OATP1B1

Simvastatin acid is a substrate of the transport protein OATP1B1. Concomitant administration of medicines that are inhibitors of the transport protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and an increased risk of myopathy (see section 4.4).

Inhibitors of breast cancer resistant protein (BCRP)

Concomitant administration of medicines that are inhibitors of BCRP, including products containing elbasvir or grazoprevir, may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy (see section 4.4).

Grapefruit juice

Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 litre daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 mL of grapefruit juice in the morning and administration of simvastatin in the evening also resulted in a 1,9-fold increase. Intake of grapefruit juice during treatment with TRYZETOR PLUS should therefore be avoided.

Colchicine

There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin, in patients with renal impairment. Close clinical monitoring of such patients taking this combination is advised.

Rifampicin

Because rifampicin is a potent CYP3A4 inducer, patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis) may experience loss of efficacy of simvastatin. In a pharmacokinetic

study in normal volunteers, the area under the plasma concentration curve (AUC) for simvastatin acid was decreased by 93 % with concomitant administration of rifampicin.

Niacin

Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (see section 4.4).

Daptomycin

The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors (e.g. simvastatin and ezetimibe/simvastatin) and daptomycin (see section 4.4).

Effect of TRYZETOR PLUS on the pharmacokinetics of other products

Anticoagulants

EZETIMIBE:

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of healthy adult males. However, there have been post-marketing reports of increased International Normalized Ratio in patients who had ezetimibe added to warfarin or fluindione (see section 4.4). The effect of TRYZETOR PLUS on prothrombin time has not been studied.

SIMVASTATIN:

In two clinical studies, one in healthy subjects and the other in hypercholesterolaemic patients, simvastatin 20 - 40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalised Ratio (INR), increased from a baseline of 1,7 to 1,8 and from 2,6 to 3,4 in the volunteer and patient studies, respectively. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting TRYZETOR PLUS and frequently enough during early therapy to ensure that no significant alteration of prothrombin

time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of TRYZETOR PLUS is changed or discontinued, the same procedure should be repeated.

Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

TRYZETOR PLUS is contraindicated during pregnancy (see section 4.3.).

No controlled clinical trials with simvastatin have been conducted in pregnant women. Reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. The safety of TRYZETOR PLUS in pregnant women has not been established.

Maternal treatment with TRYZETOR PLUS may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. For this reason, TRYZETOR PLUS should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with TRYZETOR PLUS should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

No clinical data on exposed pregnancies are available for ezetimibe.

Breastfeeding

TRYZETOR PLUS is contraindicated during lactation (see section 4.3.).

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether the active ingredients of TRYZETOR PLUS are excreted into human breast milk; therefore, women who are nursing should not take TRYZETOR PLUS.

Fertility

No clinical trial data are available on the effects of ezetimibe or simvastatin on human fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on 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 when taking TRYZETOR PLUS.

4.8 Undesirable effects

a. Summary of the safety profile

The most common adverse effects include headache, abdominal pain and diarrhoea.

The commonest adverse effect with simvastatin is gastrointestinal disturbances.

b. Tabulated summary of adverse reactions

Adverse effects with TRYZETOR PLUS

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequency unknown	Thrombocytopenia, anaemia
Immune system disorders	Frequency unknown	Hypersensitivity, anaphylaxis, hypersensitivity syndrome
Metabolism and nutrition disorders	Less frequent Frequency unknown	Decreased weight Decreased appetite

Psychiatric disorders	Less frequent Frequency unknown	Sleep disorder, insomnia Depression, memory loss, forgetfulness, amnesia, memory impairment, confusion, sleep disturbances, nightmares
Nervous system disorders	Frequent Less frequent Frequency unknown	Headache Dizziness, paraesthesia Peripheral neuropathy, memory impairment
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Cough, dyspnoea, interstitial lung disease
Vascular disorders	Frequency unknown	Hot flush, hypertension
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Flatulence Abdominal pain, abdominal discomfort, upper abdominal pain, dyspepsia, nausea, vomiting, abdominal distension, diarrhoea, dry mouth, gastroesophageal reflux disease Constipation, pancreatitis, gastritis
Hepato-biliary disorders	Frequency unknown	Hepatitis, jaundice, fatal and non-fatal hepatic failure, cholelithiasis, cholecystitis

Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Pruritus, rash, urticaria Alopecia, erythema multiforme, angioedema
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent Frequency unknown	Myalgia, pain in limb Arthralgia, muscle spasms, muscular weakness, musculoskeletal pain and discomfort, neck pain, pain in extremity, back pain Muscle cramps, myopathy, myositis, rhabdomyolysis (with or without renal failure), tendinopathy, tendon rupture, immune-mediated necrotising myopathy
Reproductive system and breast disorders	Frequency unknown	Erectile dysfunction, sexual dysfunction
General disorders and administrative site conditions	Less frequent Frequency unknown	Asthenia, fatigue, malaise, peripheral oedema, chest pain Pain

Investigations	Frequent Less frequent Frequency unknown	Increased ALT and/or aspartate aminotransferase (AST); increased blood creatinine kinase (CK) Increased blood bilirubin blood uric acid, gamma-glutamyl transferase and international normalised ratio, protein present in the urine Elevated alkaline phosphatase, abnormal liver function test results, increases in HbA1c and fasting serum glucose levels, diabetes mellitus

Adverse effects with Ezetimibe

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Frequent	Viral infection, pharyngitis, sinusitis, upper respiratory tract infection
Immune system disorders	Less frequent	Hypersensitivity reactions, anaphylaxis and angioedema
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Psychiatric disorders	Less frequent	Depression

Nervous system disorders	Frequent Less frequent	Headache Dizziness, paraesthesia
Respiratory, thoracic and mediastinal disorders	Frequent	Coughing
Gastrointestinal disorders	Frequent Less frequent	Abdominal pain and diarrhoea Nausea, pancreatitis
Hepato-biliary disorders	Less frequent Frequency unknown	Hepatitis, cholelithiasis, cholecystitis Raised liver enzymes
Skin and subcutaneous tissue disorders	Less frequent	Rash and urticaria, erythema mulitforme
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Back pain, myalgia Arthralgia, myopathy/rhabdomyolysis (see section 4.4)
General disorders and administrative site conditions	Frequent	Fatigue, chest pain
Investigations	Less frequent	Increased creatine phosphokinase (CPK), elevations of liver transaminases

Adverse effects with Simvastatin:

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Anaemia, thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity syndrome (including angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, increased erythrocyte sedimentation rate, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea, malaise)
Psychiatric disorders	Less frequent Frequency unknown	Insomnia Reversible cognitive impairment, depression
Nervous system disorders	Less frequent Frequency unknown	Dizziness, paraesthesia, peripheral neuropathy, memory impairment, headache Myasthenia gravis
Eye disorders	Frequency unknown	Ocular myasthenia

Respiratory, thoracic and mediastinal disorders	Frequency unknown	Dyspnoea, interstitial lung disease
Gastrointestinal disorders	Frequent Less frequent	Gastrointestinal disturbances Constipation, abdominal pain, dyspepsia, diarrhoea, nausea, vomiting and pancreatitis
Hepato-biliary disorders	Less frequent	Hepatitis/jaundice, hepatic failure
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Alopecia, pruritus and rash Amyopathic dermatomyositis, vesiculobullous eruptions
Musculoskeletal, connective tissue and bone disorders	Less frequent	Muscle cramps, myopathy, rhabdomyolysis, dermatomyositis, polymyositis, myasthenia gravis
Renal and urinary disorders	Frequency unknown	Proteinuria, renal failure
Reproductive system and breast disorders	Frequency unknown	Sexual dysfunction, erectile dysfunction, impotence, decreased libido, testicular pain
General disorders and administrative site conditions	Frequency unknown	Asthenia
Investigations	Frequency unknown	Hyperglycaemia, diabetes mellitus

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows for continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by using either of the following links: https://www.sahpra.org.za/Publications.Index/8 or http://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/. An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to healthy subjects for up to 14 days, or 40 mg/day to patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Simvastatin

A few cases of overdosage have been reported; the maximum dose taken was 3,6 g. All patients recovered without sequelae.

Management of overdose

No specific treatment of overdosage with TRYZETOR PLUS can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed. Co-administration of ezetimibe (1 000 mg/kg) and simvastatin (1 000 mg/kg) was well-tolerated in acute, oral toxicity studies in mice and rats. No clinical signs of toxicity were observed in these animals. The estimated oral LD_{50} for both species was ezetimibe greater than or equal to 1 000 mg/kg and simvastatin greater than or equal to 1 000 mg/kg.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors in combination with other lipid modifying agents

ATC code: C10BA02

Pharmacological classification: A 7.5 Serum-cholesterol reducers

Mechanism of action

Ezetimibe

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

Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver.

Ezetimibe in animals inhibits the absorption of [^{14}C]–cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinylestradiol, or the fat-soluble vitamins A and D.

Simvastatin

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active beta-hydroxy acid form which inhibits HMG-CoA reductase (3-hydroxy-3-methylglutaryl-CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also decreases during treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes, the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

5.2 Pharmacokinetic properties

No clinically significant pharmacokinetic interaction is seen when ezetimibe is co-administered with simvastatin.

Absorption:

TRYZETOR PLUS

TRYZETOR PLUS is bioequivalent to co-administered ezetimibe and simvastatin.

Ezetimibe

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (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) has no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10 mg tablets.

Simvastatin

The availability of the beta-hydroxy acid to the systemic circulation following an oral dose of simvastatin is less than 5 % of the dose, consistent with extensive hepatic first-pass extraction. The major metabolites of simvastatin present in human plasma are the beta-hydroxy acid and four additional active metabolites.
Relative to the fasting state, the plasma profiles of both active and total inhibitors are not affected when simvastatin is administered immediately before a test meal.

Distribution:

Ezetimibe

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

respectively.

Simvastatin

Both simvastatin and the beta-hydroxy acid are bound to human plasma proteins (95 %).

The pharmacokinetics of single and multiple doses of simvastatin show that no accumulation of simvastatin occurs after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurs 1,3 to 2,4 hours post-dose.

Biotransformation:

Ezetimibe

Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) is observed in all animal species evaluated.

Ezetimibe and ezetimibe-glucuronide are the major active ingredient-derived compounds detected in plasma, constituting approximately 10 - 20 % and 80 - 90 % of the total active ingredient in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Simvastatin

Simvastatin is an inactive lactone which is readily hydrolysed *in vivo* to the corresponding beta-hydroxy acid; a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

Simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is its primary site of action, with subsequent excretion of simvastatin equivalents in the bile. Consequently, availability of active simvastatin to the systematic circulation is low.

Elimination:

Ezetimibe

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

Simvastatin

Following an oral dose of radioactive simvastatin, 13 % of the radioactivity is excreted in the urine and 60 % in the faeces within 96 hours. The amount recovered in the faeces represents absorbed simvastatin equivalents excreted in bile as well as unabsorbed simvastatin. Following an intravenous injection of the beta-hydroxy acid metabolite an average of only 0,3 % of the IV dose is excreted in urine as inhibitors.

Pharmacokinetics in special patient groups

Geriatric patients

Ezetimibe:

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

Simvastatin:

In a study including 16 elderly patients between 70 - 78 years of age who receive simvastatin 40 mg/day, exhibit an increase in mean plasma levels of HMG-CoA reductase inhibitory activity of approximately 45 % compared with patients between 18 to 30 years of age.

Renal insufficiency

Ezetimibe:

After a single 10 mg dose of ezetimibe as monotherapy in patients with severe renal disease (mean

creatinine clearance (CrCl) less than or equal to 30 mL/min), the mean AUC for total ezetimibe is increased approximately 1,5-fold, compared to healthy subjects.

One patient (post-renal transplant and receiving multiple medications, including ciclosporin) showed a 12-fold greater exposure to total ezetimibe.

Simvastatin

In a study of patients with severe renal insufficiency (creatinine clearance less than 30 mL/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor are approximately 2-fold higher than those in healthy patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic acid

Butylhydroxyanisole (BHA)

Citric acid anhydrous (pH-adjuster)

Croscarmellose sodium

Hypromellose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Pigment blend PB-220001 Yellow (lactose monohydrate, iron oxide (yellow, red, black)

Propyl gallate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Blister strip: Store at or below 30 °C.

Store in a cool, dry place.

Do not take tablets from the blisters until time for administration.

Keep blisters in carton until required for use.

6.5 Nature and contents of container

TRYZETOR PLUS is packed in:

- Blister strips with aluminium foil base and PVC lidding, containing 30 tablets in a carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

TRYZETOR PLUS 10/10 mg: A51/7.5/1007

TRYZETOR PLUS 10/20 mg: A51/7.5/1008

TRYZETOR PLUS 10/40 mg: A51/7.5/1009

9. DATE OF FIRST AUTHORISATION

February 2021

10. DATE OF REVISION OF THE TEXT

August 2023

MOZAMBIQUE

TRYZETOR PLUS 10/10 mg: C6915
TRYZETOR PLUS 10/20 mg: C6916
TRYZETOR PLUS 10/40 mg: C6917