TRYZETOR PLUS

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 ezetimibe 10 mg and simvastatin 10 mg.
Contains sugar (51,63 mg lactose monohydrate).
Each TRYZETOR PLUS 10/20 mg tablet contains ezetimibe 10 mg and simvastatin 20 mg.
Contains sugar (113,26 mg lactose monohydrate).
Each TRYZETOR PLUS 10/40 mg tablet contains ezetimibe 10 mg and simvastatin 40 mg.
Contains sugar (236,52 mg lactose monohydrate).
Essentially 'sodium free'.

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

Reduction in the risk of cardiovascular events
TRYZETOR PLUS is indicated to reduce the risk of cardiovascular events in patients with coronary artery heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

Benefits have been shown for this group of patients when their low-density lipoprotein cholesterol (LDL-C) was above 1,2 mmol/L.

No statistically significant benefit was demonstrated for risk reduction of stroke, hospitalisation for unstable angina pectoris and for coronary artery revascularisation procedures.

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 10/80 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.

Patients with coronary heart disease and ACS event history
The starting dose is 10/40 mg once a day in the evening.
An 10/80 mg dose is only recommended in patients who have not achieved a suitable reduction in LDL-C, in which case, the patient should be changed to an alternately available product.

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.
In patients taking lomitapide concomitantly with TRYZETOR PLUS, the dose of TRYZETOR PLUS should not exceed 10/40 mg/day (see sections 4.4 Myopathy/rhabdomyolysis and 4.5).

Special populations
Use in the elderly
No dosage adjustment is required for elderly patients.
Because advanced age (≥ 65 years) is a predisposing factor for myopathy, TRYZETOR PLUS should be prescribed with caution in the elderly.
In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥ 65 years of age had an increased risk of myopathy compared to patients < 65 years of age.

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, verapamil or diltiazem, or products containing elbasvir or grazoprevir concomitantly with TRYZETOR PLUS, the dose of TRYZETOR PLUS should not exceed 10/20 mg/day (see sections 4.4 and 4.5).

In patients taking amlodipine concomitantly with TRYZETOR PLUS, the dose of TRYZETOR PLUS should not exceed 10/40 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.

Missed dose
Medical practitioners should advise patients who forget to take TRYZETOR PLUS to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

TRYZETOR PLUS is contraindicated in:
- hypersensitivity to ezetimibe, simvastatin or to any of the ingredients of TRYZETOR PLUS (see section 6.1)
- 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 (area under the curve) approximately 5-fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV (human immunodeficiency virus) 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).

Other 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, except fenofibrate, have not been formally studied. Therefore, the concomitant use of TRYZETOR PLUS and fibrates, except fenofibrate, should be avoided. Concomitant use of gemfibrozil is contraindicated (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 upper limit of normal (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 hydroxymethylglutaryl-coenzyme A (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 - 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:
Contraindicated medicines
Potent inhibitors of CYP3A4
Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses, including itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone or medicines containing cobicistat, is contraindicated (see section 4.3).
If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with TRYZETOR PLUS should be suspended during the course of treatment (see sections 4.3, 4.5 and 5.2).

Gemfibrozil, ciclosporin or danazol
Concomitant use with TRYZETOR PLUS is contraindicated (see sections 4.3 and 4.5).

Other medicines
Niacin (1 g or more per day): Concomitant use of simvastatin and lipid modifying doses (greater than or equal to 1 g/day) of niacin, has resulted in cases of myopathy/rhabdomyolysis being reported. Co-administration of TRYZETOR PLUS with lipid-modifying doses of niacin (≥ 1 g/day) in Asian patients is not recommended (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.

Amlodipine: The dose of TRYZETOR PLUS should not exceed 10/40 mg in patients receiving concomitant amlodipine therapy.

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 organic anion transporting polypeptide (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 SLC01B1 c.521T>C genotype.

Patients carrying the SLC01B1 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 aminotransferase (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.
Statins have been reported to either induce new onset, or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8), should these conditions occur, TRYZETOR PLUS should be discontinued. There have been reports of recurrences of these conditions when the same or a different statin was (re-) administered.

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 - 6,9 mmol/L, BMI > 30 kg/m², 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 the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TRYZETOR PLUS.

Sodium
TRYZETOR PLUS contains less than 1 mmol (0,023 g) sodium per tablet, that is to say essentially 'sodium free'.

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* Posaconazole Voriconazole Erythromycin* Clarithromycin* Telithromycin* HIV protease inhibitors (e.g. nelfinavir) Boceprevir Telaprevir Nefazodone Cobicistat Ciclosporin Danazol Gemfibrozil	*If treatment is unavoidable, then TRYZETOR PLUS should be 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:
Gemfibrozil
In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1,7-fold. Co-administration with TRYZETOR PLUS is contraindicated. No clinical data are available (see sections 4.3 and 4.4).

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 - 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 m²) 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).

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 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. Concomitant use of medicines labelled as having a potent inhibitory effect on CYP3A4 (e.g. itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone and medicines containing cobicistat is contraindicated (see sections 4.3 and 4.4).

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

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 - 1,8 and from 2,6 - 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 list of adverse effects
Adverse effects with TRYZETOR PLUS

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	*Frequency unknown*	Thrombocytopaenia, anaemia
Immune system disorders	*Frequency unknown*	Hypersensitivity, anaphylaxis, hypersensitivity syndrome
Metabolism and nutrition disorders	*Less frequent*	Decreased weight
	Frequency unknown	Decreased appetite
Psychiatric disorders	*Less frequent*	Sleep disorder, insomnia
	Frequency unknown	Depression, memory loss, forgetfulness, amnesia, memory impairment, confusion, sleep disturbances, nightmares
Nervous system disorders	*Frequent*	Headache
	Less frequent	Dizziness, paraesthesia
	Frequency unknown	Peripheral neuropathy, memory impairment
Eye disorders	*Less frequent*	Vision blurred, visual impairment
Vascular disorders	*Frequency unknown*	Hot flush, hypertension
Respiratory, thoracic and mediastinal disorders	*Frequency unknown*	Cough, dyspnoea, interstitial lung disease
Gastrointestinal disorders	*Frequent*	Flatulence
	Less frequent	Abdominal pain, abdominal discomfort, upper abdominal pain, dyspepsia, nausea, vomiting, abdominal distension, diarrhoea, dry mouth, gastroesophageal reflux disease
	Frequency unknown	Constipation, pancreatitis, gastritis
Hepatobiliary disorders	*Frequency unknown*	Hepatitis, jaundice, fatal and non-fatal hepatic failure, cholelithiasis, cholecystitis
Skin and subcutaneous tissue disorders	*Less frequent*	Pruritus, rash, urticaria, lichenoid drug eruptions
	Frequency unknown	Alopecia, erythema multiforme, angioedema
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Myalgia, pain in limb
	Less frequent	Arthralgia, muscle spasms, muscular weakness, musculoskeletal pain and discomfort, neck pain, pain in extremity, back pain, muscle rupture
	Frequency unknown	Muscle cramps, myopathy, myositis, rhabdomyolysis (with or without renal failure), tendinopathy, tendon rupture, immune-mediated necrotising myopathy
Reproductive system and breast disorders	*Less frequent*	Gynaecomastia
	Frequency unknown	Erectile dysfunction, sexual dysfunction
General disorders and administrative site conditions	*Less frequent*	Asthenia, fatigue, malaise, peripheral oedema, chest pain
	Frequency unknown	Pain
Investigations	*Frequent*	Increased ALT and/or aspartate aminotransferase (AST); increased blood creatinine kinase (CK)
	Less frequent	Increased blood bilirubin blood uric acid, gamma-glutamyl transferase and international normalised ratio, protein present in the urine, weight decreased
	Frequency unknown	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
Blood and lymphatic system disorders	*Frequency unknown*	Thrombocytopaenia*
Immune system disorders	*Frequency unknown*	Hypersensitivity reactions*, anaphylaxis* and angioedema*
Metabolism and nutrition disorders	*Less frequent*	Decreased appetite
Psychiatric disorders	*Frequency unknown*	Depression*
Nervous system disorders	*Frequent*	Headache
	Less frequent	Dizziness, paraesthesia
Vascular disorders	*Less frequent*	Hot flush, hypertension
Respiratory, thoracic and mediastinal disorders	*Frequent*	Coughing
Gastrointestinal disorders	*Frequent*	Abdominal pain and diarrhoea
	Less frequent	Nausea
	Frequency unknown	Constipation*, pancreatitis*
Hepatobiliary disorders	*Frequency unknown*	Hepatitis*/jaundice*, cholelithiasis*, cholecystitis*, raised liver enzymes*
Skin and subcutaneous tissue disorders	*Frequency unknown*	Rash*, urticaria*, erythema multiforme*
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Back pain, myalgia
	Less frequent	Arthralgia
	Frequency unknown	Myopathy/rhabdomyolysis* (see section 4.4)
General disorders and administrative site conditions	*Frequent*	Fatigue, chest pain
	Less frequent	Pain
Investigations	*Less frequent*	Increased creatine phosphokinase (CPK), elevations of liver transaminases

*Post marketing

Adverse effects with simvastatin:

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	*Less frequent*	Thrombocytopaenia
	Frequency unknown	Anaemia*
Immune system disorders	*Less frequent*	Hypersensitivity syndrome (including angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopaenia, eosinophilia, increased erythrocyte sedimentation rate, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea, malaise)
Psychiatric disorders	*Less frequent*	Insomnia
	Frequency unknown	Reversible cognitive impairment, depression
Nervous system disorders	*Less frequent*	Dizziness, paraesthesia, memory impairment, headache
	Frequency unknown	Myasthenia gravis*, peripheral neuropathy*
Eye disorders	*Frequency unknown*	Ocular myasthenia*
Respiratory, thoracic and mediastinal disorders	*Frequency unknown*	Dyspnoea*, interstitial lung disease*
Gastrointestinal disorders	*Frequent*	Gastrointestinal disturbances
	Less frequent	Constipation, abdominal pain, dyspepsia, diarrhoea, nausea, vomiting and pancreatitis
Hepatobiliary disorders	*Frequency unknown*	Hepatitis/jaundice*, fatal and non-fatal hepatic failure*
Skin and subcutaneous tissue disorders	*Less frequent*	Pruritus and rash
	Frequency unknown	Amyopathic dermatomyositis, vesiculobullous eruptions, alopecia*, lichen planus*
Musculoskeletal, connective tissue and bone disorders	*Less frequent*	Myopathy, rhabdomyolysis, dermatomyositis, polymyositis, myasthenia gravis
	Frequency unknown	Muscle cramps*
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

* Post marketing.

There have been reports of immune-mediated necrotising myopathy (IMNM), an autoimmune myopathy associated with statin use. IMNM is characterised by: proximal muscle weakness and elevated serum creatine kinase, which persists despite discontinuation of statin treatment; muscle biopsy showing necrotising myopathy without significant inflammation; improvement with immunosuppressive agents (see section 4.4 Myopathy/rhabdomyolysis).

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. 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 LD50 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 [14C]–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 - 2 hours for ezetimibe-glucuronide and 4 - 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 - 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 14C-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 - 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 - 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.

Paediatric population
The absorption and metabolism of ezetimibe are similar between children and adolescents (10 - 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population < 10 years of age are not available.

5.3 Preclinical safety data

Not applicable.

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

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, 7945
Cape Town, South Africa
Tel: +27 21 707 7000
or 0860-PHARMA (742 762)

8. REGISTRATION NUMBERS

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

16 February 2021

10. DATE OF REVISION OF THE TEXT

29 January 2025

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

D6096

pharma dynamics

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

TRYZETOR PLUS 10/10 mg tablets
TRYZETOR PLUS 10/20mg tablets
TRYZETOR PLUS 10/40 mg tablets
Ezetimibe and simvastatin
TRYZETOR PLUS 10/10 mg contains sugar (lactose monohydrate 51,63 mg)
TRYZETOR PLUS 10/20 mg contains sugar (lactose monohydrate 113,26 mg)
TRYZETOR PLUS 10/40 mg contains sugar (lactose monohydrate 236,52 mg)
Essentially 'sodium free'.

Read all of this leaflet carefully before you start taking TRYZETOR PLUS
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist, nurse or other healthcare provider.
- TRYZETOR PLUS has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet
1. What TRYZETOR PLUS is and what it is used for
2. What you need to know before you take TRYZETOR PLUS
3. How to take TRYZETOR PLUS
4. Possible side effects
5. How to store TRYZETOR PLUS
6. Contents of the pack and other information

1. What TRYZETOR PLUS is and what it is used for
TRYZETOR PLUS contains ezetimibe which is part of a group of medicines called lipid modifying agents and simvastatin part of a group of medicines called serum-cholesterol reducers.

TRYZETOR PLUS is taken by patients who cannot control their cholesterol levels by diet alone. You should stay on a cholesterol-lowering diet while taking TRYZETOR PLUS.

TRYZETOR PLUS is used in addition to your cholesterol-lowering diet if you have:
a raised cholesterol level in your blood (primary hypercholesterolaemia [heterozygous familial and non-familial]) or elevated fat levels in your blood (mixed hyperlipidaemia):
- that is not well controlled with a statin alone
- for which you have used a statin and ezetimibe as separate tablets
- a hereditary illness (homozygous familial hypercholesterolaemia) that increases the cholesterol level in your blood. You may also receive other treatments.

2. What you need to know before you take TRYZETOR PLUS
Do not take TRYZETOR PLUS:
- if you are hypersensitive (allergic) to ezetimibe, simvastatin or any of the other ingredients of TRYZETOR PLUS (see section 6)
- if you have liver disease
- if you are pregnant or breastfeeding your baby
- if you are a child
- if you are taking medicine(s) with one or more than one of the following active ingredients:
  - itraconazole, ketoconazole, posaconazole, or voriconazole (used to treat fungal infections)
  - erythromycin, clarithromycin, or telithromycin (used to treat infections)
  - protease inhibitors such as indinavir, nelfinavir, ritonavir and saquinavir (human immunodeficiency virus (HIV) protease inhibitors are used to treat HIV infections)
  - boceprevir or telaprevir (used to treat hepatitis C virus infections)
  - nefazodone (used to treat depression)
  - cobicistat
  - gemfibrozil (used to lower cholesterol)
  - ciclosporin (often used in organ transplant patients)
  - danazol (a man-made hormone used to treat endometriosis, a condition in which the lining of the uterus grows outside the uterus)
- if you are taking or have taken, in the last 7 days, a medicine called fusidic acid (a medicine for bacterial infection) orally or by injection. The combination of fusidic acid and TRYZETOR PLUS can lead to serious muscle problems (rhabdomyolysis).

Do not take more than 10/40 mg TRYZETOR PLUS if you are taking lomitapide (used to treat a serious and rare genetic cholesterol condition).

Warnings and precautions
Take special care with TRYZETOR PLUS:
- if you have moderate to severe liver problems
- if you are taking medicines containing danazol (to treat endometriosis), niacin (nicotinic acid), acipimox (also used to lower cholesterol)
- if you are taking medicine containing ciclosporin (used in organ transplant patients), as your doctor will want to monitor your progress
- if you are taking medicine to treat fungal or bacterial infections (e.g. itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin)
- if you are taking medicine to treat HIV or medicine to treat depression (nefazodone)
- if you are taking fibrates, except fenofibrate (to lower cholesterol levels), especially gemfibrozil and bezafibrate
- if you are taking medicines to treat a heart condition (amiodarone or verapamil)
- if you experience any unexplained muscle pain, tenderness, or weakness contact your doctor immediately. This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage.
- the risk of muscle breakdown is greater at higher doses of TRYZETOR PLUS. The risk of muscle breakdown is also greater in certain patients:
  - if you have kidney problems
  - if you have thyroid problems
  - if you are female, or are an elderly patient (age ≥ 65 years)
  - if you have ever had muscle problems during treatment with cholesterol lowering medicines called "statins" (such as simvastatin, atorvastatin, and rosuvastatin)
  - if you or close family members have a hereditary muscle disorder
- if you drink large amounts of alcohol
- if you are taking any medicines that may increase the risk of myopathy and rhabdomyolysis (disease of the muscle tissue) – see Other medicines and TRYZETOR PLUS below
- if you are taking medicines to thin your blood (e.g. warfarin)
- if you have diabetes or at risk of developing diabetes
- if you have severe lung disease
- if you have porphyria (a rare hereditary blood disease).

Children
TRYZETOR PLUS is not recommended in children under the age of 10.

Other medicines and TRYZETOR PLUS
Always tell your healthcare provider if you are taking any other medicine. (This includes complementary or traditional medicines.)

Tell your doctor if you are taking, have recently taken or might take any other medicine(s) with any of the following active ingredients. Taking TRYZETOR PLUS with any of the following medicines can increase the risk of muscle problems (some of these have already been listed in the above section Do not take TRYZETOR PLUS).
- medicines with an active ingredient like itraconazole, ketoconazole, fluconazole, posaconazole, or voriconazole (used to treat fungal infections)
- fibrates with active ingredients like gemfibrozil and bezafibrate (used to lower cholesterol)
- ciclosporin (often used in organ transplant patients)
- danazol (used to treat endometriosis, a condition in which the lining of the uterus grows outside the uterus)
- amiodarone (used to treat an irregular heartbeat)
- verapamil, diltiazem, or amlodipine (used to treat high blood pressure, chest pain associated with heart disease, or other heart conditions)
- fusidic acid (to treat a bacterial infection)
- if you need to take oral fusidic acid, you will need to temporarily stop using this medicine. Your doctor will tell you when it is safe to restart TRYZETOR PLUS. Taking TRYZETOR PLUS with fusidic acid may lead to muscle weakness, tenderness or pain (rhabdomyolysis). See more information regarding rhabdomyolysis in section 4
- HIV protease inhibitors such as indinavir, nelfinavir, ritonavir, and saquinavir (used to treat acquired immunodeficiency syndrome (AIDS))
- hepatitis C antiviral agents such as boceprevir, telaprevir, elbasvir, or grazoprevir (used to treat hepatitis C virus infection)
- nefazodone (used to treat depression)
- medicines with the active ingredient cobicistat
- erythromycin, clarithromycin, daptomycin or telithromycin (used to treat bacterial infections)
- cholestyramine (also used to lower cholesterol), because it affects the way TRYZETOR PLUS works
- medicines with an active ingredient to prevent blood clots, such as warfarin, fluindione (anticoagulants)
- lomitapide (used to treat a serious and rare genetic cholesterol condition)
- grapefruit juice (may increase your risk of experiencing muscle problems)
- colchicine (used to treat gout)
- rifampicin (used to treat tuberculosis)
- large amounts (1 gram or more each day) of niacin or nicotinic acid (also used to lower cholesterol).

TRYZETOR PLUS with food and drink
TRYZETOR PLUS can be taken with or without food. Grapefruit juice contains one or more components that alter the metabolism of some medicines, including TRYZETOR PLUS. Consuming grapefruit juice should be avoided as it may increase your risk of muscle problems.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before taking TRYZETOR PLUS.
Do not take TRYZETOR PLUS if you are pregnant, trying to get pregnant or are breastfeeding your baby (see Do not take TRYZETOR PLUS).

Driving and using machines
TRYZETOR PLUS can cause dizziness.
It is not always possible to predict to what extent TRYZETOR PLUS may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which TRYZETOR PLUS affects them.

TRYZETOR PLUS contains lactose monohydrate
TRYZETOR PLUS contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking TRYZETOR PLUS.

TRYZETOR PLUS contains sodium
TRYZETOR PLUS contains less than 1 mmol (0,023 g) sodium per tablet, that is to say essentially 'sodium free'.

3. How to take TRYZETOR PLUS
Do not share medicines prescribed for you with any other person.
Always take TRYZETOR PLUS exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Before starting, and during treatment with TRYZETOR PLUS, you should be on a diet to lower your cholesterol.

Adults:
The usual starting dose, depending on your condition, is one TRYZETOR PLUS 10/20 mg tablet per day.
One tablet is to be taken in the evening, either with or without food. The dosage range is 10/10 mg to 10/80 mg per day.

If your doctor has prescribed TRYZETOR PLUS with a bile acid sequestrant such as cholestyramine (a medicine to lower cholesterol), TRYZETOR PLUS should be taken at least 2 hours before or 4 hours after taking the bile acid sequestrant.

Children:
TRYZETOR PLUS is not for use in children (see Do not take TRYZETOR PLUS).

Your doctor will tell you how long your treatment with TRYZETOR PLUS will last. Do not stop treatment early because cholesterol levels may increase again.
If you have the impression that the effect of TRYZETOR PLUS is too strong or too weak, tell your doctor or pharmacist.

If you take more TRYZETOR PLUS than you should
In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to take TRYZETOR PLUS
If you forget to take TRYZETOR PLUS, take a dose as soon as you remember, then continue to take TRYZETOR PLUS at the usual times. Do not take a double dose to make up for forgotten individual doses.

If you stop taking TRYZETOR PLUS
If you stop taking TRYZETOR PLUS without consulting your doctor, your cholesterol levels may rise again.

4. Possible side effects
TRYZETOR PLUS can have side effects.
Not all side effects reported for TRYZETOR PLUS are included in this leaflet. Should your general health worsen, or if you experience any untoward effects while using TRYZETOR PLUS, please consult your doctor, pharmacist or other healthcare professional for advice.

If any of the following happens, stop using TRYZETOR PLUS and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing
- rash or itching
- pain or inflammation of the joints, unusual bruising, skin eruptions and swelling, skin sensitivity to the sun, fever, flushing, feeling unwell.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to TRYZETOR PLUS. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
- muscle breakdown (with symptoms such as muscle pain, tenderness, weakness, swollen muscles, tendon rupture/tear, kidney disorder with reddish-brown urine
- liver problems (you may experience jaundice – yellowing of the skin and eyes - stomach pain and swelling, dark coloured urine)
- an increase in blood sugar which could lead to problems if you are a diabetic (your diabetic medicine may need to be adjusted).

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:
Frequent side effects:
- headache
- cough
- viral infections, sore throat (pharyngitis), sinusitis, chest infections
- flatulence
- muscle pain, back pain
- extreme tiredness, chest pain
- elevations in laboratory blood tests of liver (transaminases) and/or muscle (creatine kinase (CK)) function.

Less frequent side effects:
- weight loss
- sleep disorder, trouble sleeping
- dizziness, pins and needles
- blurred vision, vision problems
- gastrointestinal problems such as wind, discomfort or bloating, indigestion or heartburn, nausea, vomiting, dry mouth, stomach pain/disturbances, diarrhoea
- itchy or red skin, rash, hair loss, skin or mouth lesions that have a pink-red centre surrounded by a pale ring border and an outer pink-red ring (erythema multiforme)
- pain in the joints or neck, back pain, muscle pain and weakness with skin rash, muscle cramps, muscle spasm, inflammation of the muscle, weakness in the arm and leg muscles, double vision and difficulties with speech and chewing (myasthenia gravis)
- abnormal lack of energy, feeling generally unwell, swelling of the hands or feet, chest pain
- gynaecomastia (breast enlargement in men)
- alterations in some laboratory blood tests for liver function.

The following side effects have been reported but the frequency for them to occur is not known:
- low red blood cell count (anaemia); reduction in blood cell counts, which may cause bruising/bleeding (thrombocytopaenia), increased blood clotting time (longer than normal bleeding)
- difficulty breathing, chest infection, cough
- constipation, gastritis, inflammation of the pancreas often with severe abdominal pain, pain that worsens with deep breathing or pain that travels to the right shoulder or back
- decrease in appetite
- changes to the content of your urine which will be seen in a test performed by your doctor, kidney failure
- depression, trouble remembering, learning new things, concentrating, or making decisions, nightmares, sleep disturbances
- poor memory, weakness/numbness/pain (peripheral neuropathy)
- hot flush, high blood pressure
- gall stones, inflammation of the gall bladder
- erectile dysfunction, sexual dysfunction, decreased sex drive, testicular pain, impotence
- muscle weakness, impaired speech, difficulty swallowing and drooping of one or both eyelids or double vision (myasthenia gravis and ocular myasthenia).

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects
If you get side effects, talk to your doctor, pharmacist or nurse. You can also report any side effects to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
By reporting side effects, you can help provide more information on the safety of TRYZETOR PLUS. You can also send an email directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

5. How to store TRYZETOR PLUS
Store all medicines out of reach of children.
Blister strip: Store at or below 30 °C.
Store in a cool, dry place.
Do not take tablets from the blisters until time for use.
Keep blisters in carton until required for use.
Do not use after the expiry date stated on the carton.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information
What TRYZETOR PLUS contains:
The active substances are ezetimibe and simvastatin.
Each TRYZETOR PLUS 10/10 mg tablet contains ezetimibe 10 mg and simvastatin 10 mg.
Each TRYZETOR PLUS 10/20 mg tablet contains ezetimibe 10 mg and simvastatin 20 mg.
Each TRYZETOR PLUS 10/40 mg tablet contains ezetimibe 10 mg and simvastatin 40 mg.

TRYZETOR PLUS tablets contain sugar in the form of lactose monohydrate.

The other ingredients are 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.

What TRYZETOR PLUS looks like and contents of the pack
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.

TRYZETOR PLUS is packed in:
Blister strips with aluminium foil base and PVC lidding, containing 10 tablets; 30 tablets in a carton.

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Registration numbers
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

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

PASIËNTINLIGTINGSBLAD

SKEDULERINGSTATUS S4

TRYZETOR PLUS 10/10 mg tablette
TRYZETOR PLUS 10/20 mg tablette
TRYZETOR PLUS 10/40 mg tablette
Esetimieb en simvastatien
TRYZETOR PLUS 10/10 mg bevat suiker (laktosemonohidraat 51,63 mg)
TRYZETOR PLUS 10/20 mg bevat suiker (laktosemonohidraat 113,26 mg)
TRYZETOR PLUS 10/40 mg bevat suiker (laktosemonohidraat 236,52 mg)
Wesenlik 'natriumvry'.

Lees hierdie hele inligtingsblad deeglik deur, voordat u begin om TRYZETOR PLUS te neem
- Hou hierdie inligtingsblad. Dit mag nodig wees vir u om dit weer te lees.
- Indien u verdere vrae het, vra asseblief u dokter, apteker, verpleegkundige, of ander gesondheidsorgverskaffer.
- TRYZETOR PLUS is vir u persoonlik voorgeskryf en u moet nie u medisyne met ander mense deel nie. Dit mag skadelik wees vir hulle, selfs al is hulle simptome dieselfde as u eie.

Wat hierdie inligtingsblad bevat
1. Wat TRYZETOR PLUS is en waarvoor dit gebruik word
2. Wat u nodig het om te weet, voordat u TRYZETOR PLUS neem
3. Hoe om TRYZETOR PLUS te neem
4. Moontlike newe-effekte
5. Hoe om TRYZETOR PLUS te bewaar
6. Verpakkingsinhoud en ander inligting

1. Wat TRYZETOR PLUS is en waarvoor dit gebruik word
TRYZETOR PLUS bevat esetimieb, wat deel is van 'n groep medisyne wat lipied wysigers genoem word en simvastatien, wat deel is van 'n groep medisyne wat serum-cholesterol verlagers, genoem word.

TRYZETOR PLUS word deur pasiënte, wie nie hulle cholesterolvlakke deur dieet alleen kan beheer nie, geneem. U moet 'n cholesterol-verlagende dieet volhou, terwyl u TRYZETOR PLUS neem.

TRYZETOR PLUS word, aanvullend tot u cholesterol-verlagende dieet, onder die volgende omstandighede gebruik:
'n verhoging in bloedcholesterolvlakke (primêre hipercholesterolemie [heterosigotiese familiële en nie-familiële]), of verhoging in die vetvlakke in u bloed (gemengde hiperlipidemie):
- wat nie goed deur 'n statien alleen beheer word nie
- waarvoor u 'n statien en esetimieb as afsonderlike tablette geneem het
- 'n oorerflike siekte (homosigotiese familiële hipercholesterolemie), wat die cholesterolvlak in u bloed verhoog. U mag ook ander behandelings ontvang.

2. Wat u nodig het om te weet, voordat u TRYZETOR PLUS neem
Moet nie TRYZETOR PLUS neem:
- indien u hipersensitief (allergies) is vir esetimieb, of vir enige van die ander bestanddele van TRYZETOR PLUS nie (sien afdeling 6)
- indien u 'n lewersiekte het nie
- indien u swanger is, of u baba borsvoed nie
- indien u 'n kind is nie
- indien u medisyne, wat een of meer, van die volgende aktiewe bestanddele bevat, neem nie:
  - itrakonasool, ketokonasool, posakonasool, of vorikonasool (gebruik om swaminfeksies te behandel)
  - eritromisien, klaritromisien, of telitromisien (gebruik om infeksies te behandel)
  - protease remmers, soos indinavir, nelfinavir, ritonavir en sakinavir (menslike immuniteitsgebreksvirus (MIV) protease remmers, wat gebruik word om MIV infeksies te behandel)
  - boseprevir, of telaprevir (gebruik om hepatitis C virusinfeksies te behandel)
  - nefasodoon (gebruik om depressie te behandel)
  - kobisistat
  - gemfibrosil (gebruik om cholesterol te verlaag)
  - siklosporien (dikwels by orgaanoorplantingspasiënte gebruik)
  - danasol ('n mensgemaakte hormoon, wat gebruik word om endometriose te behandel, 'n toestand waar die wand van die uterus, aan die buitekant van die uterus groei)
- indien u tans, of tydens die vorige 7 dae, 'n medisyne wat fusidiensuur genoem word ('n medisyne wat aangedui word vir bakteriële infeksie), mondeliks, of deur middel van 'n inspuiting, neem, of geneem het. Die kombinasie van fusidiensuur en TRYZETOR PLUS kan lei tot ernstige spierprobleme (rabdomiolise).

Moet nie meer as 10/40 mg TRYZETOR PLUS neem, indien u lomitapied neem nie (gebruik om 'n ernstige en skaars genetiese cholesteroltoestand te behandel).

Waarskuwings en voorsorgmaatreëls
Neem spesiale sorg met TRYZETOR PLUS:
- indien u matig, tot erge lewerprobleme het
- indien u medisyne, wat danasol bevat (om endometriose te behandel), niasien (nikotiensuur), asipimoks (ook gebruik om cholesterol te verlaag), neem
- indien u medisyne neem, wat siklosporien bevat (gebruik deur orgaanoorplantingspasiënte), aangesien u dokter, u vordering sal wil monitor
- indien u medisyne neem om swam- of bakteriële infeksies te behandel (bv. itrakonasool, ketokonasool, eritromisien, klaritromisien, telitromisien)
- indien u medisyne neem om MIV te behandel, of medisyne neem wat depressie behandel (nefasodoon)
- indien u fibrate (om cholesterol te verlaag) neem, veral gemfibrosil en besafibraat
- indien u medisyne neem om 'n harttoestand te behandel (amiodaroon, of verapamiel)
- indien u enige onverklaarbare spierpyn, gevoeligheid, of swakheid ervaar, kontak u dokter onmiddellik. Dit is omdat in skaars gevalle, spierprobleme ernstig mag wees, en spierafbraak insluit, wat tot nierskade mag lei.
- die risiko vir spierafbraak is groter, teen hoër dosisse TRYZETOR PLUS. Die risiko vir spierafbraak, is ook groter by sekere pasiënte:
  - indien u nierprobleme het
  - indien u skildklierprobleme het
  - indien u 'n vrou, of 'n bejaarde pasiënt is (ouderdom ≥ 65 jaar)
  - indien u ooit spierprobleme, tydens behandeling met cholesterol-verlagende medisyne, wat "statiene" genoem word, (soos simvastatien, atorvastatien en rosuvastatien), ervaar het
  - indien u, of 'n nabye familielid, 'n oorerflike spierafwyking het
- indien u groot hoeveelhede alkohol gebruik
- indien u enige medisyne neem, wat die risiko vir miopatie en rabdomiolise verhoog (siekte van die spierweefsel) – sien Ander medisyne en TRYZETOR PLUS onder
- indien u medisyne neem, wat u bloed verdun (bv. warfarien)
- indien u diabetes het, of 'n risiko het om diabetes te ontwikkel
- indien u 'n ernstige longsiekte het
- indien u porfirie het ('n skaars, oorerflike bloedsiekte).

Kinders
TRYZETOR PLUS word nie vir kinders, jonger as 10 jaar oud, aanbeveel nie.

Ander medisyne en TRYZETOR PLUS
Vertel altyd u gesondheidsorgverskaffer, indien u enige ander medisyne neem (Hierdie sluit aanvullende, of tradisionele medisyne in).

Vertel u dokter indien tans, of onlangs moontlik enige ander medisyne, wat enige van die volgende aktiewe bestanddele bevat neem, of beplan om te neem. TRYZETOR PLUS, wat gebruik word saam met enige van die volgende medisyne, kan die risiko vir spierprobleme, verhoog (sommige hiervan is alreeds gelys in bogenoemde afdeling: Moet nie TRYZETOR PLUS neem)
- medisyne met 'n aktiewe bestanddeel soos itrakonasool, ketokonasool, flukonasool, posakonasool, of vorikonasool (gebruik om swaminfeksies te behandel)
- fibrate, met aktiewe bestanddele soos gemfibrosil en besafibraat (gebruik om cholesterol te verlaag)
- siklosporien (dikwels gebruik by orgaanoorplantingspasiënte)
- danasol (gebruik om endometriose, 'n toestand waar die wand van die uterus, aan die buitekant van die uterus groei, te behandel)
- amiodaroon (gebruik om 'n onreëlmatige hartklop te behandel)
- verapamiel, diltiasem, of amlodipien (gebruik om hoë bloeddruk, borspyn wat verband hou met hartsiekte, of ander harttoestande, te behandel)
- fusidiensuur (om 'n bakteriële infeksie te behandel)
- indien u orale fusidiensuur benodig, sal u die gebruik van hierdie medisyne tydelik moet staak. U dokter sal aandui wanneer dit veilig is om TRYZETOR PLUS behandeling te hervat. TRYZETOR PLUS, wat saam met fusidiensuur geneem word, mag lei tot spierswakheid, gevoeligheid, of pyn (rabdomiolise). Vir meer inligting aangaande rabdomiolise, sien afdeling 4
- MIV protease remmers, soos indinavir, nelfinavir, ritonavir en sakinavir (gebruik om verworwe immuniteitsgebreksindroom (VIGS) te behandel)
- hepatitis C antivirale middels, soos boseprevir, telaprevir, elbasvir, of grasoprevir (gebruik om hepatitis C virusinfeksie te behandel)
- nefasodoon (gebruik om depressie te behandel)
- medisyne wat die aktiewe bestanddeel, kobisistat bevat
- eritromisien, klaritromisien, daptomisien, of telitromisien (gebruik om bakteriële infeksies te behandel)
- cholestiramien (ook gebruik om cholesterol te verlaag), want dit beïnvloed die manier waarop TRYZETOR PLUS werk
- medisyne met 'n aktiewe bestanddeel wat bloedklonte verhoed, soos warfarien, fluïendioon (teenstolmiddels)
- lomitapied (gebruik om 'n ernstige en skaars genetiese cholesteroltoestand te behandel)
- pomelosap (mag u risiko om spierprobleme te ervaar, verhoog)
- kolgisien (gebruik om jig te behandel)
- rifampisien (gebruik om tuberkulose te behandel)
- groot hoeveelhede niasien, of nikotiensuur (1 gram of meer, elke dag) – ook gebruik om cholesterol te verlaag.

TRYZETOR PLUS saam met kos en drinkgoed
TRYZETOR PLUS kan saam met, of sonder kos geneem word. Pomelosap bevat een, of meer bestanddele, wat die metabolisme van sekere medisyne, (insluitend TRYZETOR PLUS), verander. Inname van pomelosap moet vermy word, aangesien dit u risiko vir spierprobleme mag verhoog.

Swangerskap, borsvoeding en fertiliteit
Indien u swanger is, of borsvoed, vermoed dat u swanger is, of 'n baba beplan, raadpleeg asseblief u dokter, apteker, of ander gesondheidsorgverskaffer vir advies, voordat u TRYZETOR PLUS neem.
U moet nie TRYZETOR PLUS neem, indien u swanger is, probeer om swanger te raak, of u baba borsvoed nie (sien Moet nie TRYZETOR PLUS neem).

Bestuur en die hantering van masjiene
TRYZETOR PLUS mag duiseligheid veroorsaak.
Dit is nie altyd moontlik om te voorspel tot watter mate TRYZETOR PLUS met die daaglikse aktiwiteite van 'n pasiënt sal inmeng nie. Pasiënte moet verseker dat u nie by bogenoemde aktiwiteite betrokke raak, totdat u weet hoe TRYZETOR PLUS hulle beïnvloed nie.

TRYZETOR PLUS bevat laktosemonohidraat
TRYZETOR PLUS bevat laktosemonohidraat. Indien u dokter aangedui het, dat u 'n onverdraagsaamheid teenoor sekere suikers toon, kontak u dokter, voordat u TRYZETOR PLUS neem.

TRYZETOR PLUS bevat natrium
TRYZETOR PLUS bevat minder as 1 mmol (0,023 g) natrium per tablet, dit wil sê wesenlik 'natriumvry'.

3. Hoe om TRYZETOR PLUS te neem
Moet nie medisyne wat vir u voorgeskryf is, met enige ander persoon deel nie. Neem TRYZETOR PLUS altyd presies soos deur u dokter aanbeveel is. U moet u dokter, of apteker raadpleeg, indien u onseker is.

U moet 'n dieet volg wat u cholesterolvlakke verlaag, voordat u begin om TRYZETOR PLUS neem en tydens die behandeling daarmee.

Volwassenes:
Die gewone aanvangsdosis, na gelang van u toestand, is een TRYZETOR PLUS 10/20 mg tablet per dag.
Een tablet moet in die aand, óf saam met, óf sonder kos, geneem word. Die dosisreeks is 10/10 mg - 10/80 mg per dag.

Indien u dokter TRYZETOR PLUS saam met 'n galsuur-sekwestreermiddel, soos cholestiramien ('n medisyne om cholesterol te verlaag), voorgeskryf het, moet u TRYZETOR PLUS ten minste 2 uur voor, of 4 uur na die galsuur-sekwestreermiddel, neem.

Kinders:
TRYZETOR PLUS word nie deur kinders gebruik nie (sien Moet nie TRYZETOR PLUS neem).

U dokter sal u vertel vir hoe lank u behandeling met TRYZETOR PLUS sal duur. Moet nie behandeling vroegtydig staak nie, aangesien u cholesterolvlakke weer mag verhoog. Indien u onder die indruk is, dat die werking van TRYZETOR PLUS té sterk, of té swak is, vertel u dokter, of apteker.

Indien u meer TRYZETOR PLUS neem as wat u behoort
In die geval van 'n oordosering, raadpleeg u dokter, of apteker. Indien beide nie beskikbaar is nie, kontak u naaste hospitaal, of gifbeheersentrum.

Indien u vergeet om TRYZETOR PLUS te neem
Indien u vergeet om TRYZETOR PLUS te neem, neem die dosis so gou as wat u onthou en gaan dan voort om TRYZETOR PLUS op die gewone, geskeduleerde tyd te neem. Moet nie 'n dubbeldosis neem, om op te maak vir die vergete, individuele doserings nie.

Indien u die gebruik van TRYZETOR PLUS staak
Indien u ophou om TRYZETOR PLUS te neem, sonder om u dokter te raadpleeg, mag u cholesterolvlakke weer verhoog.

4. Moontlike newe-effekte
TRYZETOR PLUS kan newe-effekte hê.
Nie alle newe-effekte wat vir TRYZETOR PLUS aangemeld is, word in hierdie inligtingsblad ingesluit nie. Sou u algemene gesondheid versleg, of indien u enige ongunstige effekte ervaar, terwyl u TRYZETOR PLUS neem, raadpleeg asseblief u dokter, apteker, of ander gesondheidsorgverskaffer vir advies.

Indien enige van die volgende gebeur, staak die gebruik van TRYZETOR PLUS en vertel u dokter onmiddellik, of gaan na die ongevalle-afdeling, by u naaste hospitaal:
- swelling van die hande, voete, enkels, gesig, lippe, mond, of keel, wat sluk, of asemhaling mag bemoeilik
- uitslag, of gejeuk
- pyn of inflammasie van die gewrigte, ongewone kneusing, veluitbarstings en swelling, velsensitiwiteit vir die son, koors, blosvorming, u voel ongesteld.

Hierdie is alles baie ernstige newe-effekte. Indien u dit ondervind, kon u 'n ernstige allergiese reaksie teenoor TRYZETOR PLUS ervaar het. U mag dringende mediese aandag, of hospitalisasie benodig.

Vertel u dokter onmiddellik, of gaan na die ongevalle-afdeling by u naaste hospitaal, indien u enige van die volgende opmerk:
- spierafbraak (met simptome soos spierpyn, gevoeligheid, swakheid, geswelde spiere, tendonruptuur/-skeur, nierversteuring met rooi-bruin urine
- lewerprobleme (u mag geelsug ervaar – vergeling van die vel en oë – maagpyn en swelling, donkerkleurige urine)
- 'n verhoging in bloedsuiker, wat kan lei tot probleme, indien u 'n diabeet is (dit mag nodig wees om u diabetiese medisyne aan te pas.

Hierdie is alles ernstige newe-effekte. U mag dringende mediese aandag benodig.

Vertel u dokter, indien u enige van die volgende opmerk:
Algemene newe-effekte:
- hoofpyn
- hoes
- virusinfeksies, seer keel (faringitis), sinusitis, borsinfeksies
- winderigheid
- spierpyn, rugpyn
- uiterste moegheid, borspyn
- verhoging in lewer (transaminase) laboratorium bloedtoetse en/of spier-(kreatienkinase (KK)) funksie.

Minder algemene newe-effekte:
- gewigsverlies
- slaapversteuring, slaapprobleme
- duiseligheid, spelde en naalde
- wasige sig, sigprobleme
- gastroïntestinale probleme, soos winderigheid, ongemak, of opgeblase gevoel, indigestie, of sooibrand, naarheid, braking, droë mond, maagpyn/-aandoenings, diarree
- jeukerige, rooi vel, uitslag, haarverlies, vel-, of mondletsels, met 'n pienk-rooi kern, omring deur 'n bleek ronde ring en 'n buitenste pienk-rooi ring (erythema multiforme)
- pyn in die gewrigte, of nek, rugpyn, spierpyn en swakheid, met veluitslag, spierkrampe, spierspasma, inflammasie van die spier, swakheid in die arm- en beenspiere, dubbelvisie en kou- en spraakprobleme (myasthenia gravis)
- abnormale energietekort, voel oor die algemeen ongesteld, swelling van die hande, of voete, borspyn
- ginekomastie (vergroting van borste by mans)
- veranderinge in sommige laboratorium bloedtoetse vir lewerfunksie.

Die volgende newe-effekte is aangemeld, maar die frekwensie van voorkoms is onbekend:
- lae rooibloedseltelling (anemie); afname in rooibloedseltellings, wat kneusing/bloeding (trombositopenie), mag veroorsaak, verhoging in bloedstollingstyd (bloei langer as wat normaal is)
- moeilike asemhaling, borsinfeksie, hoes
- hardlywigheid, gastritis, inflammasie van die pankreas, dikwels met erge buikpyn, wat vererger met diep asemhaling, of pyn wat versprei na die regterskouer of rug
- aptytverlies
- veranderinge in die urieninhoud, wat opgemerk word deur toetse, soos deur u dokter uitgevoer word, nierversaking
- depressie, probleme om te onthou, nuwe dinge te leer, te konsentreer, of besluite te neem, nagmerries, slaapsteurnisse
- slegte geheue, swakheid/gevoelloosheid/pyn (perifere neuropatie)
- warm gloed, hoë bloeddruk
- galstene, inflammasie van die galblaas
- erektiele wanfunksie, seksuele wanfunksie, afname in in seksdrang, testikulêre pyn, impotensie
- spierswakheid, belemmerde spraak, sluk moeilik en een of beide ooglede hang, of dubbelvisie (myasthenia gravis en okulêre miastenie).

Indien u enige newe-effekte opmerk, wat nie in hierdie inligtingsblad genoem word nie, raadpleeg asseblief u dokter, of apteker.

Aanmelding van newe-effekte
Indien u newe-effekte ervaar, praat met u dokter, apteker of verpleegkundige. U kan ook newe-effekte by SAHPRA via die Med Safety toepassing (Medsafety X SAHPRA) en eReporting platform (who-umc.org), wat op SAHPRA se webtuiste gevind kan word, aanmeld. Deur die aanmelding van newe-effekte, kan u help om meer inligting aangaande die veiligheid van TRYZETOR PLUS in te win. U kan ook 'n epos direk na die maatskappy stuur: pharmacovigilance@pharmadynamics.co.za om veiligheid van die produk te verseker.

5. Hoe om TRYZETOR PLUS te bewaar
Bewaar alle medisyne buite die bereik van kinders.
Stulpstrook: Bewaar teen of benede 30 °C.
Bewaar in 'n koel, droë plek.
Moet nie tablette vanuit die stulpstroke verwyder totdat dit tyd is om te gebruik nie.
Hou stulpstroke in die kartonhouer, totdat dit benodig word vir gebruik.
Moet nie gebruik na die vervaldatum, wat op die stulpstrook aangedui word nie.
Neem alle ongebruikte medisyne na u apteker terug.
Moet nie ongebruikte medisyne in afvoerpype, of rioolstelsels (bv. toilette) weggooi nie.

6. Verpakkingsinhoud en ander inligting
Wat TRYZETOR PLUS bevat:
Die aktiewe bestanddele is esetimieb en simvastatien.
Elke TRYZETOR PLUS 10/10 mg tablet bevat esetimieb 10 mg en simvastatien 10 mg.
Elke TRYZETOR PLUS 10/20 mg tablet bevat esetimieb 10 mg en simvastatien 20 mg.
Elke TRYZETOR PLUS 10/40 mg tablet bevat esetimieb 10 mg en simvastatien 40 mg.
TRYZETOR PLUS bevat suiker in die vorm van laktosemonohidraat.

Die ander bestanddele is askorbiensuur, butielhidroksie-anisool (BHA), hipromellose, kruisgekoppelde natriumkarmellose, laktosemonohidraat, magnesiumstearaat, mikrokristallyne sellulose, pigmentmengsel PB-220001 Geel (laktosemonohidraat, ysteroksied (geel, rooi, swart)), propielgallaat, watervrye sitroensuur (pH aanpassing).

Hoe TRYZETOR PLUS lyk en die verpakkingsinhoud
TRYZETOR PLUS 10/10 mg: Ligbruin, gevlekte, ronde, ongeveer 6 mm, bikonvekse tablette. Gemerk 511 aan een kant.
TRYZETOR PLUS 10/20 mg: Ligbruin, gevlekte, ronde, ongeveer 8 mm, bikonvekse tablette. Gemerk 512 aan een kant.
TRYZETOR PLUS 10/40 mg: Ligbruin, gevlekte, ronde, ongeveer 10 mm, bikonvekse tablette. Gemerk 513 aan een kant.

TRYZETOR PLUS word verpak in:
Stulpstroke met 'n aluminiumfoeliebasis en PVC bedekking, wat 10 tablette bevat: 30 tablette per kartonhouer.

Eienaar van die Registrasiesertifikaat
Pharma Dynamics (Edms.) Bpk.
1ste Vloer Grapevine House, Steenberg Office Park
Silverwood Close
Westlake, 7945
Kaapstad, Suid-Afrika
Tel: + 27 21 707 7000
of 0860-PHARMA (742 762)

Hierdie inligtingsblad was voorheen hersien
29 Januarie 2025

Registrasienommers
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

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

D6096