EZERO

Rosuvastatin/Ezetimibe 10mg/10mg & 20mg/10mg film-coated tablets

Description
Rosuvastatin/Ezetimibe tablets 10mg/10mg: Pink colored round shaped film-coated tablets debossed with "AL" on one side and plain on the other side
Rosuvastatin/Ezetimibe tablets 20mg/10mg: Pink colored round shaped film coated tablets plain on both sides

COMPOSITION
Rosuvastatin/Ezetimibe tablets 10mg/10mg
Each film coated tablet contains:
Rosuvastatin Calcium
Eq. to Rosuvastatin 10mg
Ezetimibe 10mg

Rosuvastatin/Ezetimibe tablets 20mg/10mg
Each film coated tablet contains:
Rosuvastatin Calcium
Eq. to Rosuvastatin 20mg
Ezetimibe 10mg

Excipients:
Rosuvastatin/Ezetimibe tablets 10mg/10mg: Pregelatinised starch, Microcrystalline cellulose, Meglumine, Calcium hydrogen phosphate dihydrate, Crospovidone, Colloidal anhydrous silica, Sodium stearyl fumarate, Mannitol, Butylated hydroxyanisole, Sodium lauryl sulphate, Croscarmellose sodium, Povidone K-30, Ferric oxide red, Magnesium stearate, Purified water, Ready for use mixture Opadry pink containing (03F540068)

Rosuvastatin/Ezetimibe tablets 20mg/10mg : Pregelatinised starch, Microcrystalline cellulose, Meglumine, Calcium hydrogen phosphate dihydrate, Crospovidone, Colloidal anhydrous silica, Sodium stearyl fumarate, Mannitol, Butylated hydroxyanisole, Sodium lauryl sulphate, Croscarmellose sodium, Povidone K-30, Ferric oxide red, Magnesium stearate, Purified water, Ready for use mixture Opadry pink containing (03F540068)

PHARMACEUTICAL FORM: film-coated tablets

INDICATIONS

ROSUVASTATIN/EZETIMIBE fixed dose combination is indicated as adjunct to diet for treatment of primary hypercholesterolemia as substitution therapy in adult patients adequately controlled with the individual substances given concurrently at the same dose level as in the fixed dose combination, but as separate products.
ROSUVASTATIN/ EZETIMIBE fixed dose combination should not be used as initial therapy.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology
The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with ROSUVASTATIN/EZETIMIBE.

The recommended daily dose is one film-coated tablet, with or without food.
Patient should use the strength corresponding to their previous treatment.

ROSUVASTATIN/EZETIMIBE is not suitable for initial therapy.

Treatment initiation or dose adjustment if necessary should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Co-administration with bile acid sequestrants

ROSUVASTATIN/EZETIMIBE should be taken either ⩾ 2 hours before or ⩾ 4 hours after administration of a bile acid sequestrant.

Paediatric population
The safety and efficacy of ROSUVASTATIN/EZETIMIBE in children below the age of 18 years has not yet been established.

Use in the elderly
A start dose of 5 mg Rosuvastatin is recommended in patients >70 years. The combination is not suitable for initial therapy. Treatment initiation or dose adjustment if necessary should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Dosage in patients with renal insufficiency
No dose adjustment is necessary in patients with mild to moderate renal impairment. The recommended start dose is Rosuvastatin 5 mg in patients with moderate renal impairment (creatinine clearance <60 ml/min). The fixed dose combination i s not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.
The use of Rosuvastatin in patients with severe renal impairment is contraindicated for all doses.

Dosage in patients with hepatic impairment
Treatment with ROSUVASTATIN/EZETIMIBE is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score >9) liver dysfunction.
ROSUVASTATIN/EZETIMIBE is contraindicated in patients with active liver disease.

Race
Increased systemic exposure of Rosuvastatin has been seen in Asian subjects.The recommended start dose is Rosuvastatin 5 mg fo r patients of Asian ancestry. The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.

Genetic polymorphisms
Specific types of genetic polymorphisms are known that can lead to increased Rosuvastatin exposure. For patients who are known to have such specific types of polymorphisms, a lower daily dose is recommended.

Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is Rosuvastatin 5 mg in patients with predisposing factors to myopathy. The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.

Concomitant therapy
Rosuvastatin is a substrate of various transporter proteins (e. g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when ROSUVASTATIN/EZETIMIBE is administered concomitantly with certain medicinal products that may increase the plasma concentration of Rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of riton avir with atazanavir, lopinavir, and/or tipranavir).

Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing ROSUVASTATIN/EZETIMIBE therapy. In situations where co-administration of these medicin al products with ROSUVASTATIN/EZETIMIBE is unavoidable, the benefit and the risk of concurrent treatment and Rosuvastatin dosing adjustments should be carefully considered.

Method of administration
For oral use.
ROSUVASTATIN/EZETIMIBE should be taken each day once at the same time of the day with or without food. The film-coated tablet should be swallowed whole with a drin k of water.

CONTRAINDICATIONS
- Hypersensitivity to the active substances (Rosuvastatin, Ezetimibe) or to any of the excipients used in the proposed formulation.
- Active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3x the upper limit of normal (ULN).
- Pregnancy, breast-feeding and women of childbearing potential not using appropriate contraceptive measures.
- Severe renal impairment (creatinine clearance <30 ml/mi n).
- Patients with myopathy.
- Patients receiving concomitant ciclosporin.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Skeletal Muscle Effects
Effects on skeletal muscle e.g. myalgia, myopathy, and, rarely rhabdomyolysis have been reported in Rosuvastatin-treated patients with all doses and in particular with doses >20 mg.

In post-marketing experience with Ezetimibe, cases of myopathy and rhabdomyolysis have been reported. However, rhabdomyolysis has been reported very rarely with Ezetimibe monotherapy and very rarely with the addition of Ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected base d on muscle symptoms or is confirmed by a creatine kinase level, Ezetimibe, any statin, and any of these agents known to be associated with increased risk of rhabdomyolysis, that the patient is taking concomitantly should be immediately discontinued. All patients starting should be told to report promptly any unexplained muscle pain, tenderness or weakness.

Liver effects
In controlled co-administration trials in patients receiving Ezetimibe with a statin, consecutive transaminase elevations (⩾ 3x the upper limit of normal [ULN]) have been observed. It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminase is greater than 3 times the upper limit of normal.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with ROSUVASTATIN/EZETIMIBE.

Due to the unknown effects of the increased exposure to Ezetimibe in patients with moderate or severe hepatic insufficiency, ROSUVASTATIN/EZETIMIBE is not recommended.

The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

Renal effects
Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of Rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease.

The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Creatine Kinase Measurement
Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase, which may confound interpretation of the results. If CK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5-7 days. If the repeat test confirms a baseline CK>5xULN, treatment should not be started.

Before treatment
ROSUVASTATIN/EZETIMIBE, as other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:
- Renal impairment
- Hypothyroidism
- Personal or family history of hereditary muscular disorders
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- Alcohol abuse
- Age >70 years
- Situations where an increase in plasma levels may occur
- Concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (>5xULN) treatment should not be started.

Whilst on treatment
Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK leve ls are <5xULN). Routine monitoring of CK levels in asymptomatic patients is not warranted.

There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including Rosuvastatin IMNM is clinically characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

EREG10025312000033; EREG10025312000034

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with Rosuvastatin and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolid antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of ROSUVASTATIN/EZETIMIBE and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of ROSUVASTATIN/EZETIMIBE with fibrates should be carefully weighed against the potential risks of such combinations.

ROSUVASTATIN/EZETIMIBE should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Fusidic acid
ROSUVASTATIN/EZETIMIBE must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.
Statin therapy may be re-introduced seven days after the last dose of fusidic acid.
In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of ROSUVASTATIN/EZETIMIBE and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Race
Rosuvastatin pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians.

Protease inhibitors
Increased systemic exposure to Rosuvastatin has been observed in subjects receiving Rosuvastatin, concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of ROSUVASTATIN/EZETIMIBE in HIV patients receiving protease inhibitors and the potential for increased Rosuvastatin, plasma concentrations when initiating and up titrating Rosuvastatin in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose is adjusted.

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. 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, statin therapy should be discontinued.

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 statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.
In the JUPITER study, the reported overall frequency of diabetes mellitus was 2.8% in Rosuvastatin and 2.3% in placebo, mostly in patients with fasting glucose 5.6 to 6.9 mmol/L.

Fibrates
The safety and efficacy of Ezetimibe administered with fibrates have not been established. If cholelithiasis is suspected in a patient receiving ROSUVASTATIN/EZETIMIBE and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued.

Anticoagulants
If ROSUVASTATIN/EZETIMIBE is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored.

Paediatric population
The safety and efficacy of ROSUVASTATIN/EZETIMIBE in children below the age of 18 years has not yet been established, therefore its use is not recommended in this age group.

Liver disease and alcohol
ROSUVASTATIN/EZETIMIBE should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

ADVERSE EVENTS

Summary of the safety profile

The adverse reactions seen with Rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4% of Rosuvastatin-treated patients were withdrawn due to adverse reactions.

In clinical studies of up to 112 weeks duration, Ezetimibe 10 mg daily was administered alone in 2396 patients, or with a statin in 11,308 patients or with fenofibrate in 185 patients. Adverse reactions were usually mild and transient. The overall incidence of side effects was similar between Ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between Ezetimibe and placebo.

According to available data 1200 patients took Rosuvastatin and Ezetimibe combination in clinical studies. As reported in the published literature, the most frequent common adverse events related to Rosuvastatin-Ezetimibe combination treatment in hypercholesterolemic patients are increased hepatic transaminases, gastrointestinal problems and muscle pain. These are known undesirable effects of the active substances. However, a pharmacodynamic interaction, in terms of adverse effects, between Rosuvastatin and Ezetimibe cannot be ruled out.

Adverse drug reactions previously reported with one of the individual components (Ezetimibe or Rosuvastatin) may be potential undesirable effects with ROSUVASTATIN/EZETIMIBE.

Tabulated list of adverse reactions

The frequencies of adverse events are ranked according to the following: Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

MedDRA system organ class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			thrombo-cytopenia[2]		thrombo-cytopenia[5]
Immune system disorders			hypersensitivity reactions including angioedema[2]		hypersensitivity (including rash, urticaria, anaphylaxis and angioedema)[5]
Endocrine disorders	diabetes mellitus[1,2]				
Metabolism and Nutrition Disorders		decreased appetite[3]			
Psychiatric disorders					depression[2,5]
Nervous system disorders	headache[2,4], dizziness[3]	paraesthesia[4]		polyneuropathy[2], memory loss[2]	peripheral neuropathy[2], sleep disturbances (including insomnia and nightmares)[2] dizziness[5]; paraesthesia[5]
Vascular Disorders		hot flush[3]; hypertension[3]			
Respiratory, thoracic and mediastinal disorders		cough[3]			cough[5], dyspnoea[2,5]
Gastrointestinal disorders	constipation[3], nausea[2], abdominal pain[2,3] diarrhoea[3], flatulence[2]	dyspepsia[3]; gastro-oesophageal reflux disease[3]; nausea[4] dry mouth[4]; gastritis	pancreatitis[2]		diarrhoea[2] pancreatitis[5]; constipation[5]
Hepatobiliary disorders			increased hepatic transaminases[3]	jaundice[2], hepatitis[2]	hepatitis[2], cholelithiasis[5], cholecystitis[5]
Skin and subcutaneous tissue disorders		pruritus[2,4], rash[2,4], urticaria[2,4]			Stevens-Johnson syndrome[2], erythema multiforme[5]
Musculoskeletal and connective tissue disorders	myalgia[2,4]	arthralgia[2]; muscle spasms[3]; neck pain[3]; back pain[4]; muscular weakness[4]; pain in extremity[4]	myopathy (including myositis)[2], rhabdomyolysis[2] lupus-like syndrome, muscle rupture	arthralgia[2]	immune-mediated necrotising myopathy[2], tendon disorders, sometimes complicated by rupture[2], arthralgia[5], myalgia[5], myopathy/ rhabdomyolysis[5]
Renal and urinary disorders				haematuria[2]	
Reproductive system and breast disorders				gynecomastia[2]	
General disorders and administration site conditions	asthenia[2], fatigue[3]	chest pain[3], pain[3], asthenia[4]; oedema peripheral[4]			oedema[2], asthenia[5]
Investigations	ALT and/or AST increased[4]	ALT and/or AST increased[2]; blood CPK increased[3]; gamma-glutamyl-transferase increased[3]; liver function test abnormal[3]			

1. Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m^2, raised triglycerides, history of hypertension) – for Rosuvastatin.
2. Adverse reaction profile for Rosuvastatin based on data from clinical studies and extensive post-marketing experience.
3. Ezetimibe in monotherapy. Adverse reactions were observed in patients treated with Ezetimibe (N=2396) and at a greater incidence than placebo (N=1159)
4. Ezetimibe co-administered with a statin. Adverse reactions were observed in patients with Ezetimibe co-administered with a statin (N=11308) and at a greater incidence than statin administered alone (N=9361).
5. Additional adverse reactions of Ezetimibe, reported in post-marketing experience. Because these adverse experiences have been identified from spontaneous reports, their true frequencies are not known and cannot be estimated.

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

Renal effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with Rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in <1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.
Haematuria has been observed in patients treated with Rosuvastatin and clinical trial data show that the occurrence is low.

Skeletal Muscle Effects: Effects on skeletal muscle e.g. myalgia, myopathy (including myositis), and, rarely, rhabdomyolysis with and without acute renal failure have been reported in Rosuvastatin-treated patients with all doses and in particular with doses >20 mg.

A dose-related increase in CK levels has been observed in patients taking Rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK - levels are elevated (>5xULN), the treatment should be discontinued.

Liver Effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking Rosuvastatin; the majority of cases were mild, asymptomatic and transient.

The following adverse events have been reported with some statins:
- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) are higher at the 40 mg rosuvastatin dose.

Laboratory values
In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ⩾3X ULN, consecutive) was similar between Ezetimibe (0.5%) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with ezetimibe co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

In clinical trials, CPK >10X ULN was reported for 4 of 1,674 (0 .2%) patients administered Ezetimibe alone vs 1 of 786 (0.1%) patients administered placeb o, and for 1 of 917 (0.1%) patients co-administered Ezetimibe and a statin vs 4 of 929 (0.4%) patie nts administered a statin alone.
There was no excess of myopathy or rhabdomyolysis associated with Ezetimibe compared with the relevant control arm (placebo or statin alone).

Paediatric population
The safety and efficacy of ROSUVASTATIN/EZETIMIBE in children below the age of 18 years has not yet been established.

Rosuvastatin:

Creatine kinase elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of children and adolescents compared to adults. In other respects, the safe ty profile of Rosuvastatin was similar in children and adolescents compared to adults.

Ezetimibe :

Paediatric (6 to 17 years of age) patients
In a study involving paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia (n = 138), elevations of ALT and /or AST (⩾ 3X ULN, consecutive) were observed in 1.1% (1 patient) of the Ezetimibe patients compared to 0% in the placebo group. There were no elevations of CPK (⩾10X ULN). No cases of myopathy were reported.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

ADVERSE DRUG REACTIONS
Inform doctors about unexpected reactions after using drugs.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Studies to determine the effect of Rosuvastatin and/or Ezetimibe on the ability to drive and use machines have not been conducted. However, when driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

FERTILITY, PREGNANCY AND LACTATION
ROSUVASTATIN/EZETIMIBE is contraindicated in pregnancy and breast-feeding. Women of childbearing potential should use appropriate contraceptive measures.

Pregnancy
Rosuvastatin:
Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of ROSUVASTATIN/EZETIMIBE, treatment should be discontinued immediately.
Ezetimibe :
No clinical data are available on the use of ezetimibe during pregnancy.
Animal studies on the use of Ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development , birth or postnatal development.

Breast-feeding
Rosuvastatin:
Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion of Rosuvastatin in milk in humans.

Ezetimibe :
Studies on rats have shown that Ezetimibe is secreted into milk . It is not known if Ezetimibe is secreted into human breast milk.

Fertility
No clinical trial data are available on the effects of Ezetimibe on human fertility. Ezetimibe had no effect on the fertility of male or female rats

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents; HMG CoA reductase inhibitors in combination with other lipid modifying agents
ATC code: C10BA06

Rosuvastatin

Mechanism of action
Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of Rosuvastatin is the liver, the target organ for cholesterol lowering.
Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Pharmacodynamic effects
Rosuvastatin reduces elevated LD L-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I.
Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Ezetimibe

Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe is orally active, and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g. statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of Ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

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; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS

Contraindications
Ciclosporin: During concomitant treatment with Rosuvastatin and ciclosporin, Rosuvastatin AUC values were on average 7 times higher than those observed in he althy volunteers.
Concomitant administration did not affect plasma concentrations of ciclosporin.
Co-administration of ROSUVASTATIN/EZETIMIBE with ciclosporin is contraindicated.

In a study of eight post-renal transplant patients with creatinine clearance of > 50 ml/min on a stable dose of ciclosporin, a single 10-mg dose of Ezetimibe resulted in a 3.4-fold (range 2.3 to 7.9-fold) increase in the mean AUC for total Ezetimibe compared to a healthy control population, receiving Ezetimibe alone, from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency who was receiving ciclosporin and multiple other medications, demonstrated a 12-fold greater exposure to total Ezetimibe compared to concurrent controls receiving Ezetimibe alone. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg Ezetimibe for 8 days with a single 100-mg dose of ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin AUC (range 10 % decrease to 51 % increase) compared to a single 100-mg dose of ciclosporin alone. A controlled study on the effect of co-administered Ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted.

Not-recommended combinations
Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase Rosuvastatin exposure. For instance, in a pharmacokinetic study, co-administration of 10 mg Rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in Rosuvastatin AUC and Cmax respectively. The concomitant use of Rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of Rosuvastatin dose adjustments based on the expected increase in Rosuvastatin exposure. The combination is not suitable for initial therapy.
Treatment initiation or dose adjustment if necessary should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Transporter protein inhibitors: Rosuvastatin is a substrate fo r certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of ROSUVASTATIN/EZETIMIBE with medicinal products that are inhibitors of these transporter proteins may result in increased Rosuvastatin plasma concentrations and an increased risk of myopathy.

Gemfibrozil and other lipid-lowering products: Concomitant use of Rosuvastatin and gemfibrozil resulted in a 2-fold increase in Rosuvastatin Cmax and AUC.
Concomitant gemfibrozil administration modestly increased total **Ezetimibe** concentrations (approximately 1.7-fold).
Based on data from specific interaction studies no pharmacokinetic relevant interaction between rosuvastatin and fenofibrate is expected, however a pharmacodynamic interaction may occur. Concomitant fenofibrate administration modestly increased total Ezetimibe concentrations (approximately 1.5- fold).
Fenofibrate and other fibrates increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone.
In patients receiving fenofibrate and Ezetimibe, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease. If cholelithiasis is suspected in a patient receiving Ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued.
Co-administration of Ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, Ezetimibe sometimes increased cholesterol in the gallbladder bile, but no t all species. A lithogenic risk associated with the therapeutic use of Ezetimibe cannot be ruled out.

Fusidic Acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

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

Other interactions
Antacid: The simultaneous dosing of Rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in Rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after Rosuvastatin.The clinical relevance of this interaction has not been studied.
Concomitant antacid administration decreased the rate of absorption of Ezetimibe but had no effect on the bioavailability of Ezetimibe. This decreased rate of absorption is not considered clinically significant.

Erythromycin: Concomitant use of Rosuvastatin and erythromycin resulted in a 20% decrease in AUC0-t and a 30% decrease in Cmax of Rosuvastatin. This interacti on may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes: Results from in vitro and in vivo studies show that Rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, Rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. No clinically relevant interactions have been observed between Rosuvastatin and either fluconazole (an inhibi tor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).
In preclinical studies, it has been shown that Ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between Ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

Vitamin K antagonists: As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of Rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of Rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.
Concomitant administration of Ezetimibe (10 mg once daily) had no effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had Ezetimibe added to warfarin or fluindione. If ROSUVASTATIN/EZETIMIBE is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of Rosuvastatin and oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant Rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.
In clinical interaction studies, Ezetimibe had no effect on the pharmacokinetics of oral contraceptives (ethinyl estradiol and levonorgestrel).

Cholestyramine: Concomitant cholestyramine administration decreased the mean ar ea under the curve (AUC) of total Ezetimibe (Ezetimibe + Ezetimibe glucuronide) approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding Ezetimibe to cholestyramine may be lessened by this interaction.

Statins: No clinically significant pharmacokinetic interactions were seen when Ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin or Rosuvastatin.

Other medicinal products: Based on data from specific interaction studies no clinically relevant interaction between Rosuvastatin and digoxin is expected.
In clinical interaction studies, Ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, glipizide, tolbutamide, or midazolam, during co-administration. Cimetidine, co-administered with Ezetimibe had no effect on the bioavailability of Ezetimibe.

Interactions requiring Rosuvastatin dose adjustments (see also Table below): When it is necessary to co-administer Rosuvastatin with other medicinal products known to increase exposure to Rosuvastatin, doses should be adjusted. Start with a 5 mg once daily dose of Rosuvastatin if the expected increase in exposure (AUC) is approximately 2-fold or higher. The maximum daily dose should be adjusted so that the expected Rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of Rosuvastatin taken without interacting medicinal products, for example a 20 mg dose of Rosuvastatin with gemfibrozil (1.9-fold increase), and a 10 mg dose of Rosuvastatin with combination atazanavir/ritonavir (3.1-fold increase).

Effect of co-administered medicinal products on Rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in Rosuvastatin AUC*
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold↑
Simeprevir 150 mg OD, 7 days	10 mg, single dose	2.8-fold↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold↑
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold↑
Dronedarone 400 mg BID	Not available	1.4-fold↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	1.4-fold↑**
Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 days	10 mg, single dose	↔
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mg TID, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	↔
Rifampin 450 mg OD, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20%↑
Baicalin 50 mg TID, 14 days	20 mg, single dose	47%↑
Regorafenib 160 mg OD, 14 days	5 mg, single dose	3.8
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold↑
Velpatasvir 100 mg once daily	10 mg, single dose	2.69 (2.46-2.94)
Elbasvir 50 mg/grazoprevir 200 mg OD	10 mg, single dose	2.26 (1.89-2.69)

*Data given as x-fold change represent a simple ratio between co-administration and Rosuvastatin alone. Data given as % change represent % difference relative to Rosuvastatin alone. Increase is indicated as " ↑ " no change as "↔" decrease as " ↓ "

**Several interaction studies have been performed at different rosuvastatin dosages, the table shows the most significant ratio OD = once daily; BID = twice daily; TID = three times daily; QI D = four times daily

The combination is not suitable for initial therapy. Treatment initiation or dose adjustment if necessary should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

OVERDOSE AND TREATMENT
There is no published literature data on Rosuvastatin overdose.
There is no specific treatment in the event of overdose with Rosuvastatin.
In clinical studies, administration of Ezetimibe, 50 mg/day, to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. In animals, no toxicity was observed after single oral doses of 5,000 mg/kg of Ezetimibe in rats and mice and 3,000 mg/kg in dogs.
A few cases of overdosage with Ezetimibe have been reported: most have not been associated with adverse experiences. Reported adverse experiences have not been serious.
In the event of an overdose, symptomatic and supportive measures should be employed. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

SHELF-LIFE
36 Months for EZERO tablet 10mg/10mg
36 Months for EZERO tablet 20mg/10mg

STORAGE CONDITION
Store below 30°C.
Store in the original package in order to protect from light and moisture.
Keep all medicines out of reach of children.
Do not use this medicines after the expiration date "EXP" listed on the box and blister.
The expiration date refers to the last day of the month.

Packaging and Registration number
EZERO film-coated tablet 10/10 mg: Box, 3 blisters @ 10 film-coated tablets.
Reg.No.DKIxxxxxxxxxxxx

EZERO film-coated tablet 20/10 mg: Box, 3 blisters @ 10 film-coated tablets.
Reg.No.DKIxxxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

Manufactured by
MEDREICH LIMITED
Bengaluru-India

Licensed by
Althera Pharmaceutical LLC
New Jersey-USA

Imported and marketed by

meiji **PT. MEIJI INDONESIAN PHARMACEUTICAL INDUSTRIES**
Bangil, Pasuruan-Jawa Timur, Indonesia

DISETUJUI BPOM 21 JANUARI 2022

EREG10025312000033; EREG10025312000034

INFORMASI PRODUK UNTUK PASIEN

EZERO

Rosuvastatin 10 mg / Ezetimibe 10 mg
Rosuvastatin 20 mg / Ezetimibe 10 mg

tablet salut selaput

Bacalah informasi dalam leaflet ini dengan seksama sebelum Anda menggunakan obat ini karena mengandung informasi penting untuk Anda.
- Simpanlah leaflet ini. Anda mungkin akan perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada Dokter atau Apoteker Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan kepada orang lain. Hal ini dapat membahayakan mereka, meskipun memiliki gejala yang sama dengan Anda.
- Jika Anda mengalami efek samping, konsultasikan kepada Dokter atau Apoteker Anda. Hal ini mungkin termasuk efek yang tidak tercantum dalam leaflet ini. Lihat bagian 4.

Informasi apa yang ada di dalam leaflet ini

1. Apakah EZERO dan digunakan untuk apa

EZERO mengandung 2 (dua) zat aktif berbeda didalam satu tablet salut selaput. Salah satu zat aktifnya adalah Rosuvastatin, yang termasuk dalam golongan statin, sedangkan zat aktif lainnya adalah Ezetimibe.

EZERO merupakan obat yang digunakan pada pasien dewasa untuk menurunkan tingkat kolesterol total, kolesterol "jahat" (kolesterol LDL) dan zat lemak yang disebut trigliserida dalam darah. Selain itu, obat ini juga meningkatkan kadar kolesterol "baik" (kolesterol HDL). Obat ini berkhasiat untuk mengurangi kadar kolesterol Anda dengan dua cara, yaitu dengan mengurangi jumlah kolesterol yang diserap dalam saluran pencernaan Anda dan mengurangi jumlah kolesterol yang diproduksi oleh tubuh Anda sendiri.

Bagi kebanyakan orang, kolesterol tinggi tidak mempengaruhi apa yang mereka rasakan karena tidak menimbulkan gejala apa pun. Namun, jika tidak diobati, timbunan lemak dapat menumpuk di dinding pembuluh darah Anda sehingga menyebabkan penyempitan pembuluh darah. Kadang-kadang, pembuluh darah yang menyempit ini dapat tersumbat sehingga menghambat suplai darah ke jantung atau otak yang mengarah ke serangan jantung atau stroke. Dengan menurunkan kadar kolesterol Anda, Anda dapat mengurangi resiko terkena serangan jantung, stroke, atau masalah kesehatan lainnya yang terkait.

Obat ini digunakan pada pasien yang mempunyai kadar kolesterol yang tidak dapat terkontrol hanya oleh diet penurun kolesterol saja. Anda harus tetap menjalani diet penurun kolesterol walaupun sedang mengkonsumsi obat ini.

EZERO digunakan sebagai tambahan pada diet untuk pengobatan hiperkolesterolemia primer, yaitu sebagai terapi substitusi pada pasien dewasa dengan hiperkolesterolemia primer yang terkontrol secara cukup dengan obat Rosuvastatin dan Ezetimibe yang diberikan secara terpisah pada dosis yang sama dengan obat kombinasinya.
EZERO tidak boleh digunakan sebagai terapi awal.

DISETUJUI BPOM 21 JANUARI 2022

2. Apa yang perlu Anda ketahui sebelum menggunakan EZERO

Jangan menggunakan EZERO jika Anda
- Alergi terhadap rosuvastatin, ezetimibe atau kandungan lain dari obat ini (tercantum dalam bagian 6).
- Memiliki penyakit hati.
- Memiliki gangguan ginjal yang berat.
- Minum obat yang disebut ciclosporin (misalnya, digunakan setelah transplantasi organ).
- Sedang hamil atau menyusui. Jika Anda hamil saat menggunakan EZERO, segera hentikan minum obat dan beritahukan Dokter Anda. Saat minum obat ini, pasien wanita harus menghindari kehamilan dengan menggunakan kontrasepsi yang sesuai.
- Pernah mengalami berulang-ulang, nyeri otot yang tidak dapat dijelaskan atau nyeri miopati.

Jika salah satu hal diatas terjadi pada Anda (atau jika Anda tidak yakin), silahkan hubungi Dokter Anda.

Peringatan dan perhatian
Konsultasikan dengan Dokter atau Apoteker Anda sebelum menggunakan EZERO jika Anda:
- Memiliki masalah dengan ginjal Anda.
- Memiliki penyakit hati.
- Pernah mengalami nyeri atau nyeri otot berulang atau nyeri yang tidak dapat dijelaskan; memiliki riwayat masalah otot, baik personal atau keluarga; atau riwayat masalah otot ketika menggunakan obat penurun kolesterol. Katakan segera pada Dokter Anda jika Anda memiliki nyeri atau nyeri otot yang tidak dapat dijelaskan, terutama jika Anda merasa tidak sehat atau mengalami demam. Juga katakan pada Dokter atau Apoteker Anda jika Anda mengalami kelemahan otot yang menetap.
- Berasal dari Asia (Jepang, Cina, Filipina, Vietnam, Korea dan India). Dokter Anda perlu memilih dosis yang tepat yang sesuai dengan Anda.
- Menggunakan obat untuk melawan infeksi, termasuk infeksi HIV atau hepatitis C misalnya lopinavir/ritonavir dan/atau atazanavir atau simeprevir, Silakan lihat "Obat-obatan lain dan EZERO".
- Mengalami gagal napas berat.
- Menggunakan obat lain yang disebut fibrat untuk menurunkan kolesterol Anda. Silakan lihat "Obat-obatan lain dan EZERO".
- Secara teratur minum alkohol dalam jumlah besar.
- Menderita hipotiroidisme, dimana kelenjar tiroid Anda kurang aktif.
- Berusia di atas 70 tahun (Dokter Anda perlu memilihkan dosis awal yang sesuai untuk Anda).
- Mengalami operasi, Anda perlu menghentikan obat ini untuk jangka pendek.
- Sedang atau dalam 7 hari terakhir menggunakan obat ini dengan asam fusidat dapat menyebabkan kelemahan otot, lunglai atau nyeri (*rhabdomyolysis*) walaupun jarang terjadi.
  Jika salah satu hal diatas terjadi pada Anda (atau jika Anda tidak yakin), tanyakan kepada Dokter atau Apoteker Anda sebelum Anda menggunakan dosis obat ini.
  Pada sejumlah kecil orang, statin dapat mempengaruhi hati. Hal ini diidentifikasi oleh tes sederhana yang terlihat untuk peningkatan kadar enzim hati dalam darah. Untuk alasan ini, Dokter Anda akan melakukan secara teratur tes darah ini (tes fungsi hati) selama perawatan dengan obat ini. Hal ini penting untuk memeriksakan ke Dokter untuk pemeriksaan laboratorium.
  Saat Anda dalam pengobatan ini, Dokter Anda akan memantau Anda dengan seksama jika Anda penderita diabetes atau berisiko terkena diabetes. Anda mungkin berisiko terkena diabetes jika Anda memiliki tingkat glukosa tinggi dan lemak dalam darah Anda, kelebihan berat badan dan memiliki tekanan darah tinggi.

Anak-anak dan remaja
Penggunaan obat ini tidak dianjurkan pada anak-anak dan remaja di bawah usia 18 tahun.

Obat-obatan lain dan EZERO
Beritahukan Dokter atau Apoteker Anda jika Anda sedang, baru saja atau mungkin menggunakan obat-obatan yang lain.
Konsultasikan kepada Dokter Anda jika Anda menggunakan salah satu obat berikut ini:
- Ciclosporin (misalnya, digunakan setelah transplantasi organ untuk mencegah penolakan transplantasi organ. Efek rosuvastatin meningkat jika digunakan bersamaan dengan ciclosporin).
  Jangan menggunakan EZERO saat menggunakan ciclosporin.
- Pengencer darah; misalnya warfarin, acenocoumarol atau fluindione (efek pengencer darah dan risiko perdarahan dapat meningkat saat digunakan bersamaan dengan obat ini), atau clopidogrel.
- Obat-obatan lain untuk menurunkan kolesterol Anda yang disebut fibrates, yang juga memperbaiki kadar trigliserida darah (misalnya gemfibrozil dan fibrat lainnya). Ketika gemfibrozil digunakan bersama dengan obat ini, efek Rosuvastatin meningkat.
- Cholestyramine (obat untuk menurunkan kolesterol), karena mempengaruhi cara kerja Ezetimibe.
- Obat antivirus seperti ritonavir dengan lopinavir dan/atau atazanavir atau simeprevir (digunakan untuk mengobati infeksi, termasuk infeksi HIV atau hepatitis C). Lihat bagian "Peringatan dan perhatian".
- Obat gangguan pencernaan yang mengandung aluminium dan magnesium (digunakan untuk menetralkan asam dalam lambung Anda); mereka menurunkan tingkat plasma Rosuvastatin). Efek ini dapat dikurangi dengan menggunakan obat jenis ini 2 jam setelah Rosuvastatin.
- Erythromycin (antibiotik). Efek Rosuvastatin menurun ketika digunakan bersamaan dengan antibiotik ini.
- Asam fusidat. Jika Anda perlu menggunakan asam fusidat oral untuk mengobati infeksi bakteri, Anda harus menghentikan sementara penggunaan obat ini. Dokter Anda akan memberitahu Anda kapan mulai kembali menggunakan EZERO dengan aman. Menggunakan obat ini dengan asam fusidat dapat menyebabkan kelemahan otot, lunglai atau nyeri (rhabdomyolysis) walaupun jarang terjadi. Lihat informasi lebih lanjut tentang rhabdomyolysis di bagian 4.
- Kontrasepsi oral (pil). Kadar hormon seksual yang diabsorpsi dari pil dapat meningkat.
- Terapi penggantian hormon (meningkatkan kadar hormon dalam darah).

Jika Anda memeriksakan ke rumah sakit atau menerima perawatan untuk kondisi lain, beritahukan tenaga kesehatan bahwa Anda sedang menggunakan EZERO.

Kehamilan dan menyusui
Jangan menggunakan EZERO jika Anda sedang hamil, sedang program kehamilan atau Anda merasa ada kemungkinan hamil. Jika Anda hamil saat menggunakan obat ini, segera hentikan menggunakan obat ini dan beritahukan Dokter Anda. Pasien wanita harus menggunakan kontrasepsi selama terapi dengan obat ini.
Jangan menggunakan EZERO, jika Anda sedang menyusui, karena belum diketahui keamanannya apakah obat tersebut dapat masuk ke dalam ASI.

Mengemudi dan menggunakan mesin
Obat ini belum diketahui apakah mengganggu kemampuan Anda untuk mengemudi atau menggunakan mesin. Namun demikian harus diperhitungkan bahwa beberapa orang menjadi pusing setelah menggunakan obat ini. Jika Anda pusing, Anda tidak boleh mengemudi atau menggunakan mesin.

3. Bagaimana cara menggunakan EZERO

Gunakan selalu obat ini dengan tepat seperti yang disarankan oleh Dokter atau Apoteker Anda. Konsultasikan dengan Dokter atau Apoteker Anda jika Anda tidak yakin.

Obat ini tidak dapat digunakan untuk terapi awal.

Sebelum mulai menggunakan EZERO, Anda harus melakukan diet untuk menurunkan kolesterol dan diobati dengan statin atau dengan Rosuvastatin dan Ezetimibe.
Anda harus tetap melakukan diet rendah kolesterol dan berolahraga walaupun sedang menggunakan EZERO.

Dosis harian yang disarankan untuk orang dewasa adalah satu tablet salut selaput.

Gunakan EZERO sekali sehari.
Anda dapat menggunakannya kapan saja, dengan atau tanpa makanan. Minumlah obat Anda pada waktu yang sama setiap hari. Telan tablet salut selaput seluruhnya dengan segelas air.

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Periksakan kolesterol secara teratur
Penting untuk kembali ke Dokter untuk pemeriksaan kolesterol secara rutin agar memastikan kolesterol Anda telah mencapai dan tetap pada kadar normal.

Jika Anda berlebihan mengkonsumsi EZERO dari yang seharusnya
Hubungi Dokter Anda atau bagian gawat darurat rumah sakit terdekat karena Anda mungkin perlu bantuan medis.

Jika Anda lupa untuk menggunakan EZERO
Jangan khawatir, lewati dosis yang terlewat dan minum dosis untuk jadwal berikutnya pada waktu yang tepat. Jangan mengkonsumsi dosis ganda untuk mengganti dosis yang terlupakan.

Jika Anda berhenti menggunakan EZERO
Konsultasikan dengan Dokter Anda jika Anda ingin berhenti menggunakan obat ini. Kadar kolesterol Anda mungkin dapat meningkat lagi jika Anda berhenti menggunakan obat ini.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada Dokter atau Apoteker Anda.

4. Kemungkinan efek samping

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, walaupun tidak semua orang mendapatkannya.
Penting bagi Anda untuk mengetahui apa efek samping ini.

Hentikan penggunaan EZERO dan segera cari bantuan medis jika Anda mengalami salah satu efek samping dibawah ini:

Efek samping yang jarang terjadi (dapat terjadi hingga 1 dari 1.000 orang):
Reaksi alergi seperti pembengkakan pada wajah, bibir, lidah dan/atau tenggorokan, yang dapat menyebabkan kesulitan bernafas dan menelan.

Nyeri otot yang tidak biasa yang berlangsung lebih lama dari yang Anda duga. Jarang hal ini dapat berkembang menjadi kerusakan otot yang berpotensi mengancam jiwa yang dikenal sebagai *rhabdomyolysis*, yang mengarah ke malaise, demam dan gangguan ginjal.

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia):
Bisul atau lepuh pada kulit, mulut, mata dan alat kelamin. Hal ini bisa menjadi tanda-tanda sindrom *Stevens-Johnson* (reaksi alergi yang mengancam jiwa yang mempengaruhi kulit dan membran mukosa).

Efek samping lainnya

Efek samping yang umum (dapat terjadi hingga 1 dari 10 orang)
- Sakit kepala
- Sembelit
- Merasa sakit
- Nyeri otot
- Merasa lemah
- Pusing
- Diabetes. Hal ini lebih mungkin jika Anda memiliki kadar gula dan lemak yang tinggi dalam darah Anda, kelebihan berat badan dan memiliki tekanan darah tinggi. Dokter Anda akan memantau Anda saat Anda menggunakan obat ini.
- Sakit perut
- Diare
- Perut kembung (kelebihan gas dalam saluran usus)
- Merasa lelah
- Peningkatan pada beberapa tes darah laboratorium untuk fungsi hati (transaminase)

Efek samping yang tidak umum (dapat terjadi hingga 1 dari 100 orang)
- Ruam, gatal, sangat gatal
- Peningkatan pada beberapa tes darah laboratorium untuk fungsi otot (tes Creatine Kinase)
- Batuk
- Gangguan pencernaan
- Mulas
- Nyeri sendi
- Kejang otot
- Sakit leher
- Kurang nafsu makan
- Nyeri
- Nyeri dada
- Panas
- Tekanan darah tinggi
- Sensasi kesemutan
- Mulut kering
- Radang lambung
- Sakit punggung
- Lemah otot
- Rasa sakit di lengan dan kaki
- Pembengkakan, terutama di tangan dan kaki

Efek samping yang jarang (dapat terjadi hingga 1 dari 1.000 orang)
- Radang pankreas, yang menyebabkan nyeri perut berat yang dapat meluas ke punggung
- Pengurangan trombosit darah

Efek samping yang sangat jarang (dapat terjadi hingga 1 dari 10.000 orang)
- Penyakit kuning (kulit dan mata menguning)
- Peradangan hati (hepatitis)
- Terdapat darah dalam urin
- Kerusakan pada saraf kaki dan lengan Anda (seperti mati rasa)
- Hilang ingatan
- Pembesaran payudara pada pria (ginekomastia)

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia)
- Sesak napas
- Edema (pembengkakan)
- Gangguan tidur, termasuk insomnia dan mimpi buruk
- Kesulitan seksual
- Depresi
- Masalah pernapasan termasuk batuk terus-menerus dan/atau sesak napas atau demam
- Cedera tendon
- Lemah otot yang tetap
- Batu empedu atau radang kantong empedu (yang dapat menyebabkan sakit perut, mual, muntah)

Pelaporan efek samping
Jika Anda mengalami efek samping, konsultasikan dengan Dokter, Apoteker, atau perawat Anda. Hal ini termasuk semua kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Bagaimana cara menyimpan EZERO

Simpan pada suhu dibawah 30°C.

Simpan dalam kemasan asli untuk melindungi dari cahaya dan kelembaban.

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa "EXP" yang tercantum pada dus dan blister. Tanggal kedaluwarsa mengacu pada hari terakhir bulan.

Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan Apoteker Anda bagaimana membuang obat yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Kemasan dan informasi lainnya

Apa yang terkandung dalam EZERO
- Kandungan aktif setiap tablet salut selaput adalah Rosuvastatin kalsium yang setara dengan 10 mg atau 20 mg Rosuvastatin dan 10 mg Ezetimibe.
- Kandungan lainnya adalah:
  - Tablet Inti Rosuvastatin
    Starch, Pregelatinised (maize); Microcrystalline Cellulose (E460); Meglumine; Calcium hydrogen phosphate dihydrate (E341); Crospovidone (E1202); Colloidal anhydrous silica (E551); Sodium stearyl fumarate.
  - Tablet Inti Ezetimibe
    Mannitol (E421); Butylhydroxyanisole (E320); Sodium laurilsulfate (E487); Croscarmellose sodium (E468); Povidone (K-30) (E1201); Iron oxide red (E172); Magnesium stearate (E470 b); Sodium stearyl fumarate.
  - Tablet salut
    Hypromellose (E464); Titanium dioxide (E171); Macrogol 4000; Iron oxide red (E172).

Seperti apa pemerian EZERO dan kandungannya dalam kemasan
EZERO 10 mg/10 mg merupakan tablet salut selaput berwarna merah muda berbentuk bulat dengan diameter 10.0 mm yang diembos dengan tulisan “AL” di satu sisi.
EZERO 20 mg/10 mg tablet salut selaput berwarna merah muda berbentuk bulat dengan diameter 10,6 mm, polos di kedua sisi.

Kemasan:
EZERO tablet salut selaput 10/10 mg: Dus, 3 blister @ 10 tablet salut selaput.
No. Reg. DKIxxxxxxxxxxxx

EZERO tablet salut selaput 20/10 mg: Dus, 3 blister @ 10 tablet salut selaput.
No. Reg. DKIxxxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

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Bengaluru-India

Atas lisensi dari
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