For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ROZUCOR EZ

1. Generic Name

Rosuvastatin Calcium and Ezetimibe Tablets I.P.

2. Qualitative and quantitative composition

Each film coated tablet contains:

Rosuvastatin Calcium I.P.

Eq. to Rosuvastatin……10 mg

Ezetimibe I.P. ……10 mg

Excipients……...q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Lactose mono spray dried, Isopropyl alcohol, Tween 80, Butylated Hydroxytoluene, Butylated Hydroxy Anisole, Sodium Lauryl Sulphate, Croscarmellose sodium, Mannitol, Crospovidone, Sodium Stearyl Fumarate, Dichloromethane, Hydroxy Propyl Methyl Cellulose, Poly Ethylene Glycol, Purified Talc Powder, Titanium dioxide.

3. Dosage form and strength

Dosage form: Film Coated tablet

Strength: Rosuvastatin 10 mg and Ezetimibe 10 mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of patients with primary hypercholesterolemia.

4.2 Posology and method of administration

Dosage: As directed by the physician, the dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines.

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with this medicine.

Method of administration

Rosuvastatin may be given at any time of day, with or without food.

4.3 Contraindications

ROZUCOR EZ is contraindicated in patients:

- With known hypersensitivity to any component of this medication
- Myopathy secondary to other lipid lowering agents

- During pregnancy, in nursing mothers and in women of childbearing potential, unless they are taking adequate contraceptive precautions.
- With active liver disease including unexplained persistent elevations in serum transaminases and any serum transaminase elevation exceeding 3x the upper limit of normal in combination with fenofibrate in patients with gall bladder disease concomitant use of fusidic acid.

ROZUCOR EZ is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- Hypothyroidism
- Personal or family history of hereditary muscular disorders
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- Alcohol abuse
- Situations where an increase in rosuvastatin plasma levels may occur
- Severe renal impairment (CrCl<30mL/min)
- Asian patients
- Concomitant use of fibrates.

4.4 Special warnings and precautions for use

Rosuvastatin

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.

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. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with Rosuvastatin in post-marketing use is higher at the 40 mg dose.

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 result. 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, as with 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 levels are ≤5xULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Rosuvastatin or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. 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 characterised by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In reported 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 macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of Rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40 mg dose is contraindicated with concomitant use of a fibrate.

Rosuvastatin 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. Patients 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 and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Rosuvastatin 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).

Liver Effects

As with other HMG-CoA reductase inhibitors, Rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

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 transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

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

Race

Reported 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 in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating Rosuvastatin doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of Rosuvastatin is adjusted.

Lactose Intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 >30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

In the reported 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.

Paediatric Population

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients 6 to 17 years of age taking rosuvastatin is limited to a two-year period. After two years of study treatment, no effect on growth, weight, BMI or sexual maturation was detected.

In a reported clinical trial of children and adolescents receiving rosuvastatin for 52 weeks, CK elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently compared to observations in clinical trials in adults.

Ezetimibe

In reported 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 medicinal products known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

In reported clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam, during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Antacids

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

Colestyramine

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

Fibrates

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.

Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1.5- and 1.7-fold respectively).

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 not in all species. A lithogenic risk associated with the therapeutic use of Ezetimibe cannot be ruled out.

Statins

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

Ciclosporin

In a reported 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 reported study, a renal transplant patient with severe renal impairment who was receiving ciclosporin and multiple other medicinal products, 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 reported controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating Ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe and ciclosporin.

Anticoagulants

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored.

Paediatric population

Interaction studies have only been performed in adults.

4.5 Drugs interactions

Antacids

Ezetimibe

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.

Rosuvastatin

Simultaneous administration of rosuvastatin and 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.

Cholestyramine

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

Therefore, dosing of ROZUCOR EZ and a bile acid binding sequestrant should take place several hours apart. However, efficacy and safety of such combination have not been studied.

Cyclosporin

Ezetimibe

The effect of cyclosporin on ezetimibe was reported studied in eight post-renal transplant patients with creatinine clearance of > 50 mL/min who were on a stable dose of cyclosporin. 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 group of historical healthy volunteers (n=17) who had taken a single 10-mg dose of ezetimibe alone.

In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2mL/min/1.73m2) who was receiving multiple medications, including cyclosporin, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls.

In a reported two-period crossover study in twelve healthy subjects, daily administration of 20mg ezetimibe for 8 days with a single dose 100mg dose of cyclosporin on day 7 resulted in a mean 15% increase in cyclosporin AUC (range 10% decrease to 51% increase) compared to a single 100 mg dose of cyclosporin alone.

Rosuvastatin

Co-administration of rosuvastatin with cyclosporin resulted in no significant changes in cyclosporin plasma concentration. However, rosuvastatin steady state AUC (0-t) increased up to 7-fold over that seen in healthy volunteers administered the same dose.

These increases are clinically significant and require special consideration in the dosing of ROZUCOR EZ

Fenofibrate

Ezetimibe

In a reported pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold.

Rosuvastatin

Co-administration of fenofibrate with rosuvastatin resulted in no significant changes in plasma concentrations of rosuvastatin or fenofibrate.

Gemfibrozil

Ezetimibe

In a reported pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. This increase is not considered clinically significant. No clinical data are available.

Rosuvastatin

Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC (0-t). This increase is considered to be clinically significant.

Anticoagulants

Ezetimibe

Concurrent administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability and prothrombin time in a reported study of twelve healthy adult males administered a single dose of warfarin. There have been post-marketing reports of increased International Normalised Ratio in patients who had ezetimibe added to warfarin. Most of these patients were also on other medications.

Rosuvastatin

Co-administration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (> 4, baseline 2-3). In patients taking vitamin K antagonists and rosuvastatin concomitantly, INR should be determined before starting ROZUCOR EZ and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR has been documented, INR can be monitored at the intervals usually recommended for patients on vitamin K antagonists.

Cytochrome P450 enzymes

Ezetimibe

In reported 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.

Rosuvastatin

In reported in vitro and in vivo data indicate that rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. This has been confirmed in studies with known cytochrome P450 3A4 inhibitors (ketoconazole, erythromycin, itraconazole).

Ketoconazole:

Co-administration of ketoconazole (200 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in no change in plasma concentrations of rosuvastatin.

Erythromycin:

Co-administration of erythromycin (500 mg four times daily for 7 days) with rosuvastatin (80 mg) decreased AUC and Cmax of rosuvastatin by 20% and 31%, respectively. These reductions are not considered clinically significant.

Itraconazole:

Itraconazole (200 mg twice daily for 5 days) resulted in a 39% and 28% increase in AUC of rosuvastatin after 10 mg and 80 mg dosing, respectively. These increases are not considered clinically significant.

Fluconazole:

Co-administration of fluconazole (200 mg twice daily for 11 days) with rosuvastatin (80 mg) resulted in a 14% increase in AUC of rosuvastatin. This increase is not considered clinically significant.

Oral contraceptives

Co-administration of oral contraceptives (ethinyl estradiol and norgestrel) with rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively. This increase is not considered clinically significant.

Other medications

Ezetimibe

Ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide or midazolam during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Rosuvastatin

In reported clinical studies, rosuvastatin was co-administered with anti-hypertensive agents and anti-diabetic agents. These studies did not produce any evidence of clinically significant adverse interactions.

Digoxin

Co-administration of digoxin with rosuvastatin resulted in no change to digoxin plasma concentrations.

Protease Inhibitors

Increased systemic exposure to rosuvastatin has been reported in subjects receiving rosuvastatin with various protease inhibitors in combination with ritonavir.

Consideration should be given both to the benefit of lipid lowering by the use of ROZUCOR EZ in HIV patients receiving protease inhibitors and the ROZUCOR EZ potential for increased rosuvastatin plasma concentrations when initiating and uptitrating ROZUCOR EZ doses in patients treated with protease inhibitors.

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. Co-administration of this combination may cause increased plasma concentrations of both agents. 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. If treatment with fusidic acid is necessary, ROZUCOR EZ treatment should be discontinued throughout the duration of the fusidic acid treatment.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

ROZUCOR EZ is contraindicated in pregnancy and lactation.

Women of child bearing potential should use appropriate contraceptive measures.

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 this product, treatment should be discontinued immediately.

Rosuvastatin/ ezetimibe is excreted in the milk of rats. ROZUCOR EZ should not be used during lactation. There are no data with respect to excretion in milk in humans.

4.7 Effects on ability to drive and use machines

Reported studies to determine the effect of ROZUCOR EZ on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, it is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

Rosuvastatin

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

Tabulated list of adverse reactions

Based on reported data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for rosuvastatin. Adverse reactions listed below are classified according to frequency and system organ class (SOC).

The frequencies of adverse reactions are ranked according to the following convention: Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Adverse reactions based on data from clinical studies and post-marketing experience

System organ class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			Thrombocytopenia		
Immune system disorders			Hypersensitivity reactions including angioedema		
Endocrine disorders	Diabetes mellitus[1]				

System organ class	Common	Uncommon	Rare	Very rare	Not known
Psychiatric disorders					Depression
Nervous system disorders	Headache Dizziness			Polyneuropathy Memory loss	Peripheral neuropathy Sleep disturbances (including insomnia and nightmares)
Respiratory, thoracic and mediastinal disorders					Cough Dyspnoea
Gastro-intestinal disorders	Constipation Nausea Abdominal pain		Pancreatitis		Diarrhoea
Hepatobiliary disorders			Increased hepatic transaminases	Jaundice Hepatitis	
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria			Stevens-Johnson syndrome
Musculo-skeletal and connective tissue disorders	Myalgia		Myopathy (including myositis) Rhabdomyolysis	Arthralgia	Tendon disorders, sometimes complicated by rupture Immune-mediated necrotising myopathy

System organ class	Common	Uncommon	Rare	Very rare	Not known
Renal and urinary disorders				Haematuria	
Reproductive system and breast disorders				Gynaecomastia	
General disorders and administration site conditions	Asthenia				Oedema
[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI >30 kg/m^2, raised triglycerides, history of hypertension).					

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), 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) is higher at the 40 mg dose.

Paediatric population: 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 safety profile of rosuvastatin was similar in children and adolescents compared to adults.

Ezetimibe

Tabulated list of adverse reactions (clinical studies and post-marketing experience)

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

Ezetimibe administered alone or co-administered with a statin:

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

Frequencies are defined as: very common (≥1/10); 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) and not known (cannot be estimated from the available data)

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

Additional adverse reactions with ezetimibe co-administered with a statin		
System organ class	**Adverse reactions**	**Frequency**
Investigations	ALT and/or AST increased	common
Nervous system disorders	headache	common
	paraesthesia	uncommon
Gastrointestinal disorders	dry mouth; gastritis	uncommon
Skin and subcutaneous tissue disorders	pruritus; rash; urticaria	uncommon
Musculoskeletal and connective tissue disorders	myalgia	common
	back pain; muscular weakness; pain in extremity	uncommon
General disorders and administration site condition	asthenia; oedema peripheral	uncommon
Post-marketing Experience (with or without a statin)		
System organ class	**Adverse reactions**	**Frequency**
Blood and lymphatic system disorders	thrombocytopaenia	Not known
Nervous system disorders	dizziness; paraesthesia	Not known
Respiratory, thoracic and mediastinal disorders	dyspnoea	Not known
Gastrointestinal disorders	pancreatitis; constipation	Not known
Skin and subcutaneous tissue disorders	erythema multiforme	Not known
Musculoskeletal and connective tissue disorder	myalgia; myopathy/rhabdomyolysis (see section 4.4)	Not known
General disorders and administration site conditions	asthenia	Not known
Immune system disorders	hypersensitivity, including rash, urticaria, anaphylaxis and angio-oedema	Not known
Hepatobiliary disorders	hepatitis; cholelithiasis; cholecystitis	Not known
Psychiatric disorders	depression	Not known

Paediatric (6 to 17 years of age) population

In a reported 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 reported 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 reported trials were not suited for comparison of rare adverse reactions.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. Pharmacological properties

5.1 Mechanism of Action

Rosuvastatin

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.

Ezetimibe

Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol. 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). The molecular target of ezetimibe is the sterol transporter, Niemann- Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol.

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. In a reported 2-week clinical study in 18 hypercholesterolaemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.

5.2 Pharmacodynamic properties

Rosuvastatin

Rosuvastatin is a fully synthetic competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B

(ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich.

Cholesterol-rich low density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver. Rosuvastatin produces its lipid-modifying effects in two ways; it 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.

High density lipoprotein (HDL), which contains ApoA-I, is involved, amongst other functions, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

The involvement of LDL-C in atherogenesis has been reported to be well documented.

Epidemiological studies reported have established that high LDL-C and TG, and low HDL C and ApoA-I have been linked to a higher risk of cardiovascular disease. Intervention studies have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent reported data has linked the beneficial effects of HMG-CoA reductase inhibitors to the lowering of nonHDL-C (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio

Ezetimibe

Ezetimibe is in a class of lipid-modifying compounds that inhibit the intestinal absorption of cholesterol and related plant sterols.

Ezetimibe 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 sterols).

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 therefore inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.

Ezetimibe does not increase bile acid excretion (like bile acid sequestrants) and does not inhibit cholesterol synthesis in the liver (like statins).

In a 2-week clinical study in 18 hypercholesterolaemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54 %, compared with placebo. By inhibiting the absorption of intestinal cholesterol, ezetimibe reduces the delivery of cholesterol to the liver. Statins reduce cholesterol synthesis in the liver. Together these distinct mechanisms provide complementary cholesterol reduction. Ezetimibe, administered with a statin, reduces total-C, LDL-C, Apo B, and TG and increases HDL-C in patients with hypercholesterolaemia, beyond either treatment alone.

Clinical studies demonstrate that elevated levels of total-C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis.

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [14C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat soluble vitamins A and D.

5.3 Pharmacokinetic properties

Rosuvastatin

In a reported bioequivalence study comparing 40mg rosuvastatin tablets with the innovator's tablets, following an oral administration of a single-dose of rosuvastatin to healthy subjects under fasting conditions, a mean peak plasma concentration (Cmax) of rosuvastatin of approximately 26.18ng/mL was achieved within approximately 3.62 hours (Tmax).

Absorption

Peak plasma levels occur 5 hours after dosing. Absorption increases linearly over the dose range. Absolute bioavailability is 20%. The half-life is 19 hours and does not increase with increasing dose. There is minimal accumulation on repeated once daily dosing.

Distribution

Volume of distribution of rosuvastatin at steady state is approximately 134 litres. Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin.

Metabolism

Rosuvastatin is not extensively metabolised; approximately 10% of a radiolabelled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P4502C9, and in vitro studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin.

Excretion

Rosuvastatin undergoes limited metabolism (approximately 10%), mainly to the Ndesmethyl form, and 90% is eliminated as unchanged drug in the faeces with the remainder being excreted in the urine.

Ezetimibe

Absorption

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (Cmax) occur within 1 to 2 hours for ezetimibeglucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as 10mg tablets. Ezetimibe can be administered with or without food.

Distribution

Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

Metabolism

Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively.

Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Excretion

It is reported that following oral administration of 14C-ezetimibe (20mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

6. Nonclinical properties

Rosuvastatin

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been evaluated. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels were as follows: In repeated-dose toxicity studies histopathologic liver changes likely due to the pharmacologic action of rosuvastatin were observed in mouse, rat, and to a lesser extent with effects in the gall bladder in dogs, but not in monkeys. In addition, testicular toxicity was observed in monkeys and dogs at higher dosages. Reproductive toxicity was evident in rats, with reduced litter sizes, litter weight and pup survival observed at maternally toxic doses, where systemic exposures were several times above the therapeutic exposure level.

Ezetimibe

In reported animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe ($\geq$ 0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a reported one-year study on dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of Ezetimibe cannot be ruled out.

In reported co-administration studies with ezetimibe and statins the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in co-administration therapy. No such interactions occurred in the clinical studies. Myopathies occurred in rats only after exposure to doses that were several times

higher than the human therapeutic dose (approximately 20 times the AUC level for statins and 500 to 2,000 times the AUC level for the active metabolites).

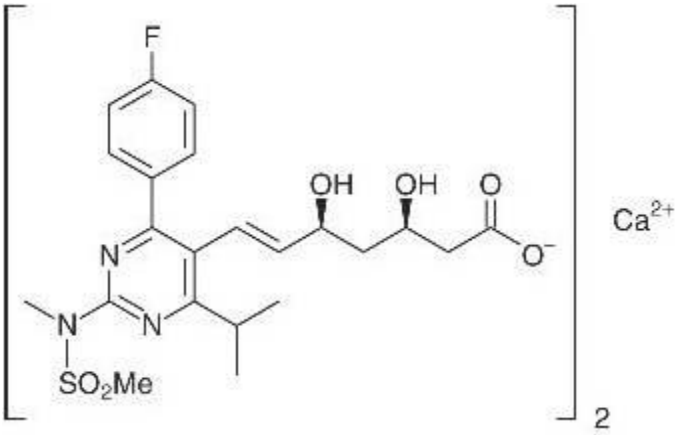
In a reported series of in vivo and in vitro assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential. Long-term carcinogenicity tests on ezetimibe were negative.

Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1,000 mg/kg/day. The co-administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed. The co-administration of ezetimibe with lovastatin resulted in embryolethal effects

7. Description

Rosuvastatin Calcium

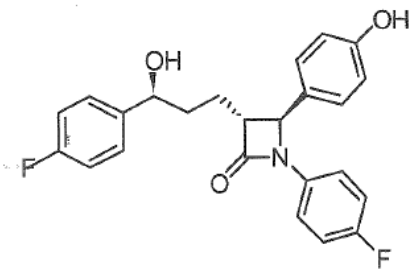
Rosuvastatin calcium is a synthetic lipid-lowering agent for oral administration. The chemical name for rosuvastatin calcium is bis [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl (methyl sulfonyl) amino] pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt with the following structural formula:



The molecular formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2$.Ca and the molecular weight is 1001.1 g/mol. Rosuvastatin calcium is off-white to creamish white powder that is freely soluble in acetonitrile and soluble in acetone.

Ezetimibe

Ezetimibe is (3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2.azetidione. The empirical formula is $(C_{24}H_{21}F_2NO_3$ and its molecular weight is 409.4 g/mol. The chemical structure of Ezetimibe is:



ROZUCOR EZ is White coloured, capsule shaped, biconvex, film coated tablet plain on both sides. The excipients used are Lactose mono spray dried, Isopropyl alcohol, Tween 80, Butylated Hydroxytoluene, Butylated Hydroxy Anisole, Sodium Lauryl Sulphate, Croscarmellose sodium, Mannitol, Crospovidone, Sodium Stearyl Fumarate, Dichloromethane, Hydroxy Propyl Methyl Cellulose, Poly Ethylene Glycol, Purified Talc Powder, Titanium dioxide.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

ROZUCOR EZ is packed in Strip of 10 Tablets

8.4 Storage and handing instructions

Store below 30°C at dry and dark place.

Keep all medicines out of reach of children.

9. Patient counselling information

ROZUCOR EZ

Rosuvastatin Calcium and Ezetimibe Tablets I.P

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- Keep all medicines out of reach of children
- If you have any further questions, ask your doctor or pharmacist.
- **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1.What ROZUCOR EZ is and what it is used for

9.2.What you need to know before you take ROZUCOR EZ

9.3.How to take ROZUCOR EZ

9.4.Possible side effects

9.5.How to store ROZUCOR EZ

9.6.Contents of the pack and other information

9.1 What ROZUCOR EZ is and what it is used for

ROZUCOR EZ is fixed dose combination of Rosuvastatin Calcium and Ezetimibe used for the treatment of patients with primary hypercholesterolemia.

Rosuvastatin: Rosuvastatin belongs to a group of medicines called statins, used to prevent cardiovascular disease in those at high risk and treat abnormal lipids. It is recommended to be used together with dietary changes, exercise, and weight loss.

Ezetimibe: Ezetimibe lowers levels of total cholesterol, "bad" cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood. In addition, ezetimibe raises levels of "good" cholesterol (HDL cholesterol).
Ezetimibe, the active ingredient of ezetimibe, works by reducing the cholesterol absorbed in your digestive tract.

Ezetimibe adds to the cholesterol-lowering effect of statins, a group of medicines that reduce the cholesterol your body makes by itself.

Cholesterol is one of several fatty substances found in the bloodstream. Your total cholesterol is made up mainly of LDL and HDL cholesterol.

LDL cholesterol is often called "bad" cholesterol because it can build up in the walls of your arteries forming plaque. Eventually this plaque build-up can lead to a narrowing of the arteries. This narrowing can slow or block blood flow to vital organs such as the heart and brain. This blocking of blood flow can result in a heart attack or stroke.

HDL cholesterol is often called "good" cholesterol because it helps keep the bad cholesterol from building up in the arteries and protects against heart disease.

Triglycerides are another form of fat in your blood that may increase your risk for heart disease.

It is used for patients who cannot control their cholesterol levels by cholesterol lowering diet alone. You should stay on your cholesterol lowering diet while taking this medicine.

9.2 What you need to know before you take ROZUCOR EZ

Do not take ROZUCOR EZ

If you are allergic to Rosuvastatin or Ezetimibe or any of the other ingredients of this medicine.

- If you are pregnant or breast-feeding. If you become pregnant while taking ROZUCOR EZ stop taking it immediately and tell your doctor. Women should avoid becoming pregnant while taking ROZUCOR EZ by using suitable contraception
- If you have liver disease
- If you have severe kidney problems
- If you have repeated or unexplained muscle aches or pains

- If you take a drug called ciclosporin (used, for example, after organ transplants)
- If any of the above applies to you (or you are in doubt), go back and see your doctor.

Warning and Precautions

Talk to your doctor or pharmacist before taking ROZUCOR EZ

- Tell your doctor about all your medical conditions including allergies.
- If you have problems with your kidneys.
- If you have problems with your liver.
- If you have had repeated or unexplained muscle aches or pains, a personal or family history of muscle problems, or a previous history of muscle problems when taking other cholesterol-lowering medicines. Tell your doctor immediately if you have unexplained muscle aches or pains, especially if you feel unwell or have a fever. Also, tell your doctor or pharmacist if you have a muscle weakness that is constant.
- If you regularly drink large amounts of alcohol
- If your thyroid gland is not working properly
- If you take other medicines called fibrates to lower your cholesterol.
- If you take medicines used to treat the HIV infection e.g. ritonavir with lopinavir and/or atazanavir etc.
- 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 Rosuvastatin can lead to serious muscle problems (rhabdomyolysis).
- If you are over 70 (as your doctor needs to choose the right start dose of ROZUCOR EZ to suit you)
- If you have severe respiratory failure
- If any of the above applies to you (or if you are not sure).
- Your doctor should do a blood test before you start taking ezetimibe with a statin. This is to check how well your liver is working.
- Your doctor may also want you to have blood tests to check how well your liver is working after you start taking ezetimibe with a statin.
- If you have moderate or severe liver problems, ROZUCOR EZ is not recommended.

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Children and adolescents

Do not give ROZUCOR EZ to children and adolescents (6 to 17 years of age) unless prescribed by a specialist because there are limited data on safety and efficacy. Do not give this medicine to children less than 6 years old because there is no information in this age group.

Other medicines and Rosuvastatin

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular, tell your doctor if you are taking medicine(s) with any of the following active ingredients:

- ciclosporin (used for example, after organ transplants)
- warfarin or clopidogrel (or any other medicine used for thinning the blood)

- medicines with an active ingredient to prevent blood clots, such as warfarin, phenprocoumon, acenocoumarol or fluindione (anticoagulants)
- colestyramine (also used to lower cholesterol), because it affects the way ezetimibe works
- fibrates that are also used to lower cholesterol (such as gemfibrozil, fenofibrate) or any other medicine used to lower cholesterol (such as ezetimibe)
- indigestion remedies (used to neutralise acid in your stomach)
- erythromycin (an antibiotic), fusidic acid
- an oral contraceptive (the pill), hormone replacement therapy
- regorafenib (used to treat cancer)
- any of the following drugs used to treat viral infections, including HIV or hepatitis C infection, alone or in combination: ritonavir, lopinavir, atazanavir, simeprevir, ombitasvir, paritaprevir, dasabuvir, velpatasvir, grazoprevir, elbasvir, glecaprevir, pibrentasvir

Pregnancy and breast-feeding

Do not take ROZUCOR EZ if you are pregnant or breast-feeding. If you become pregnant while taking this medicine stop taking it immediately and tell your doctor. Women should avoid becoming pregnant while taking this medicine by using suitable contraception.

Do not take ROZUCOR EZ if you are breast-feeding, because it is not known if the medicines are passed into breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

ROZUCOR EZ is not expected to interfere with your ability to drive or to use machinery. Most people can drive a car and operate machinery while using this medicine– it will not affect their ability. However, some people feel dizzy during treatment with this medicine. If you feel dizzy, consult your doctor before attempting to drive or use machines.

ROZUCOR EZ contains lactose and sodium

If you have been told by your doctor that you have an intolerance to some sugars (lactose or milk sugar), contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

9.3 How to take ROZUCOR EZ

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

ROZUCOR EZ Tablets should be administered orally with food to enhance absorption.

If you take more ROZUCOR EZ than you should

Contact your doctor if you took more tablets than you should. Your doctor will establish the best possible treatment of overdose.

The possible side effects of an overdose of ROZUCOR EZ are nausea, vomiting, pain or discomfort right below your ribs in the area of your upper abdomen (epigastric distress), and diarrhoea.

If you forget to take ROZUCOR EZ

Contact your doctor if you have missed one or more doses.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking ROZUCOR EZ

Should your doctor decide to stop your ROZUCOR EZ treatment, he/she will instruct you about the gradual withdrawal of ROZUCOR EZ.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

It is important that you are aware of what these side effects may be. They are usually mild and disappear after a short time.

Stop taking ROZUCOR RZ and seek medical help immediately if you have any of the following allergic reactions:

- Difficulty in breathing, with or without swelling of the face, lips, tongue and/or throat
- Swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing
- Severe itching of the skin (with raised lumps)

Also, stop taking Rosuvastatin and talk to your doctor immediately

- If you have any unusual aches or pains in your muscles which go on for longer than you might expect. Muscle symptoms are more common in children and adolescents than in adults. As with other statins, a very small number of people have experienced unpleasant muscle effects and rarely these have gone on to become a potentially life threatening muscle damage known as rhabdomyolysis.
- If you experience muscle rupture.
- If you have lupus-like disease syndrome (including rash, joint disorders and effects on blood cells).

Common side effects (may affect up to 1 in 10 people)

- Headache
- Nausea
- Stomach pain/Abdominal pain
- Constipation
- Diarrhoea
- Flatulance
- Feeling sick
- Muscle pain
- Feeling tired/ unusual tiredness or weakness/ tenderness
- Dizziness
- Elevations in some laboratory blood tests of liver (transaminases) or muscle (CK) function

Uncommon side effects (may affect up to 1 in 100 people)

- Cough

- Indigestion
- Heartburn
- Joint pain
- Back pain
- Neck pain
- Decreased appetite
- Pain
- Chest pain
- Hot flush
- High blood pressure
- Rash, itching, hives or other skin reactions
- Tingling sensation
- Dry mouth
- swelling, especially in the hands and feet

Rare side effects (may affect up to 1 in 1,000 people)

- Severe allergic reaction – signs include swelling of the face, lips, tongue and/or throat, difficulty in swallowing and breathing, a severe itching of the skin (with raised lumps). If you think you are having an allergic reaction, then stop taking Rosuvastatin and seek medical help immediately
- Muscle damage in adults – as a precaution, stop taking Rosuvastatin and talk to your doctor immediately if you have any unusual aches or pains in your muscles which go on for longer than expected.
- A severe stomach pain (inflamed pancreas)
- Increase in liver enzymes in the blood
- Bleeding or bruising more easily than normal due to low level of blood platelets
- Lupus-like disease syndrome (including rash, joint disorders and effects on blood cells).

Very rare side effects (may affect up to 1 in 10,000 people)

- Jaundice (yellowing of the skin and eyes)
- Hepatitis (an inflamed liver)
- Traces of blood in your urine
- Damage to the nerves of your legs and arms (such as numbness)
- Memory loss
- Breast enlargement in men (gynaecomastia).

Not known (frequency cannot be estimated from the available data)

- Steven-Johnson syndrome (serious blistering condition of the skin, mouth, eyes and genitals)
- Cough
- Shortness of breath
- Oedema (swelling)
- Sleep disturbances, including insomnia and nightmares
- Sexual difficulties
- Depression
- Breathing problems, including persistent cough and/or shortness of breath or fever

- Tendon injury

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store ROZUCOR EZ

Store below 30°C at dry and dark place.

Keep all medicines out of reach of children

9.6 Contents of the pack and other information

What **ROZUCOR EZ** contains

The active substances are Rosuvastatin Calcium and Ezetimibe.

Rosuvastatin……10 mg and Ezetimibe I.P……...10 mg

The excipients used are Lactose mono spray dried, Isopropyl alcohol, Tween 80, Butylated Hydroxytoluene, Butylated Hydroxy Anisole, Sodium Lauryl Sulphate, Croscarmellose sodium, Mannitol, Crospovidone, Sodium Stearyl Fumarate, Dichloromethane, Hydroxy Propyl Methyl Cellulose, Poly Ethylene Glycol, Purified Talc Powder, Titanium dioxide.

10. Details of manufacturer

Manufactured in India by:

Windlas Biotech Pvt. Limited (Plant-2)

Khasra No. 141 to 143 & 145, Mohabewala Industrial Area, Dehradun-248110, Uttarakhand.

11. Details of permission or licence number with date

Mfg. Lic. No. 34/UA/2013 issued on 06.01.2020

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ROZUCOR EZ/10, 10 mg/AUG-20/01/PI