ROSCA®-EZ

(Rosuvastatin + Ezetimibe)
Tablets

5mg +10mg
10mg +10mg
20mg +10mg

روسکا۔ای ذی ۵ ملی گرام + ۱۰ ملی گرام
(روزواسٹیٹن+ایزیٹیمائب) ۱۰ ملی گرام + ۱۰ ملی گرام
ٹیبلٹس ۲۰ ملی گرام + ۱۰ ملی گرام

QUALITATIVE AND QUANTITATIVE DESCRIPTION

ROSCA®-EZ 5mg+10mg Tablets
Each film-coated tablet contains:
Rosuvastatin Calcium U.S.P. eq. to
Rosuvastatin.....5mg
Ezetimibe U.S.P. 10mg
Innovator's Specifications

ROSCA®-EZ 10mg+10mg Tablets
Each film-coated tablet contains:
Rosuvastatin Calcium U.S.P. eq. to
Rosuvastatin.....10mg
Ezetimibe U.S.P. 10mg
Innovator's Specifications

ROSCA®-EZ 20mg+10mg Tablets
Each film-coated tablet contains:
Rosuvastatin Calcium U.S.P. eq. to
Rosuvastatin.....20mg
Ezetimibe U.S.P. 10mg
Innovator's Specifications

DESCRIPTION

ROSCA®-EZ contains two lipid lowering agents rosuvastatin & ezetimibe. Rosuvastatin is an HMG-CoA reductase inhibitor or statin and ezetimibe is a cholesterol absorption inhibitor.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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 LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol.

Ezetimibe

Mechanism of action:

Ezetimibe is a 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. 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 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.

Pharmacodynamic Effects:

Ezetimibe inhibited the absorption of [14C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat-soluble vitamins A and D. Administration of ezetimibe with a statin is effective in reducing the risk of cardiovascular events in patients with coronary heart disease and ACS event history.

Pharmacokinetics

Rosuvastatin and ezetimibe combination therapy:

Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemia subjects.

Rosuvastatin

Absorption:

Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%.

Distribution:

Rosuvastatin is taken up extensively by the liver, which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Biotransformation:

Rosuvastatin undergoes limited metabolism (approximately 10%). The main metabolites identified are the N-desmethyl- and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Elimination:

Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses.

Renal Insufficiency:

Patients with varying degrees of renal insufficiency, mild to moderate renal disease Rosuvastatin + Ezetimibe had no influence on plasma concentration of rosuvastatin or the N desmethyl metabolite. Patients with severe insufficiency (creatinine clearance <30 mL/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in patients undergoing haemodialysis were approximately 50% greater compated to healthy volunteers.

Hepatic Insufficiency:

In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased. In patients with Child-Pugh A disease, Cmax and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, Cmax and AUC were increased 100% and 21% respectively, compared with patients with normal liver function.

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 ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe. Ezetimibe can be administered with or without food.

Distribution:

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

Biotransformation:

Ezetimibe is metabolised primarily in the small intestine and liver. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours. Elimination:

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

Renal impairment:

After a single 10 mg dose of ezetimibe in patients with severe renal disease (n = 8; mean CLcr ≤ 30 mL/min/1.73 m2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n = 9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients. An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Hepatic impairment:

After a single 10 mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score > 9) hepatic impairment,

INDICATIONS AND USAGE

Primary hypercholesterolemia:

Rosuvastatin + Ezetimibe 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. Prevention of cardiovascular events:
Rosuvastatin + Ezetimibe is indicated as substitution treatment in adult patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), who are adequately controlled with the individual substances administered simultaneously at the same dose level as in the fixed combination medicinal product, but as separate products.

DOSAGE AND 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 tablet of the given strength with or without food. Rosuvastatin + Ezetimibe 5 mg/10 mg, 10 mg/10 mg and 20 mg/10 mg tablets are not suitable for the treatment of patients requiring 40 mg dose of rosuvastatin.

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.

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.

Renal impairment:

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 is 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.

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (Child Pugh score 5 to 6).

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 (see sections 4.4 and 5.2.). Rosuvastatin + Ezetimibe is contraindicated in patients with active liver disease.

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 tablet should be swallowed whole with a drink of water.

CONTRAINDICATIONS:

- In patients with hypersensitivity to the active substances (rosuvastatin, ezetimibe) or to any of the excipients.
- In patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (ULN).
- During pregnancy and breast-feeding and in women of childbearing potential not using appropriate contraceptive measures.
- In patients with severe renal impairment (creatinine clearance < 30 mL/min).
- In patients with myopathy.
- In patients receiving concomitant combination of sofosbuvir/velpatasvir/voxilaprevir
- In patients receiving concomitant ciclosporin

Other Adverse Reactions:

- Increased Hepatic Transaminases
- Gastrointestinal Problems
- Muscle Pain

DRUG INTERACTIONS:

Ciclosporin:

Co-administration of Rosuvastatin + Ezetimibe with ciclosporin is contraindicated.

Protease inhibitors:

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.

Transporter protein inhibitors:

Rosuvastatin is a substrate for 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:

Gemfibrozil significantly increased rosuvastatin exposure. Therefore, combination therapy with Rosuvastatin and gemfibrozil should be avoided. if used, do not exceed Rosuvastatin 10mg once daily. Co-administration of ezetimibe with other fibrates has not been studied.

Fusidic Acid:

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

Erythromycin:

Concomitant use of rosuvastatin and erythromycin resulted in a 20% decrease in AUC0-tand a 30% decrease in Cmax of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Coumarin:

In patients talking coumarin anticoagulants Rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occur. Concomitant administration of ezetimibe (10 mg once daily) had no effect on bioavailability of warfarin and pro-thrombin time. If Rosuvastatin + Ezetimibe are added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored.

Ticagrelor:

Ticagrelor might affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. Although the exact mechanism is not known, in some cases, concomitant use of ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and rhabdomyolysis.

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.

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.

Statins:

No clinically significant pharmacokinetic interactions were seen when ezetimibe was coadministered 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:

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 10mg dose of rosuvastatin with combination atazanavir/ritonavir (3.1-fold increase). If medicinal product is observed to increase rosuvastatin AUC less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the rosuvastatin dose above 20

mg.

USE IN SPECIFIC POPULATIONS

Fertility, pregnancy and lactation

Pregnancy:

Rosuvastatin + Ezetimibe is contraindicated in pregnancy and breast-feeding. Women of childbearing potential should use appropriate contraceptive measures.

Breast-feeding

Animal studies shows that Rosuvastatin + Ezetimibe is secreted in milk. No clinical trial on human is available.

Fertility:

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

OVERDOSAGE:

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 creatinine kinase levels should be monitored. Haemodialysis is unlikely to be of benefit.

Special warnings and precautions for use

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with rosuvastatin. At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of this reaction appears, Rosuvastatin + Ezetimibe should be discontinued immediately and an alternative treatment should be considered.

If the patient has developed a serious reaction such as SJS or DRESS with the use of Rosuvastatin + Ezetimibe, treatment with Rosuvastatin + Ezetimibe must not be re-started in this patient at any time.

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.

Myasthenia gravis, ocular myasthenia

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. Rosuvastatin + Ezetimibe should be discontinued in case of aggravation of symptoms.

Recurrences when the same or a different statin was (re-) administered have been reported.

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 (> 5 × ULN) a confirmatory test should be carried out within 5-7 days. If the repeat test confirms a baseline CK> 5 × ULN, treatment should not be started.

Before treatment

Rosuvastatin + Ezetimibe, as other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with re-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
– 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 (> 5 × ULN) treatment should not be started.

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).

Interstitial lung disease

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.

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.

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.

DOSAGE:

As directed by the physician.

INSTRUCTIONS:

Store below 30°C. Protect from heat, light and moisture.
Keep all medicines out of the reach of children.

PRESENTATION:

Rosca®-EZ 5mg + 10mg tablets are available in Alu/Alu blister pack of 2 x 10's.
Rosca®-EZ 10mg + 10mg tablets are available in Alu/Alu blister pack of 1 x 10's.
Rosca®-EZ 20mg + 10mg tablets are available in Alu/Alu blister pack of 1 x 10's.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، روشنی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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