ROVIROS EZ Tablets

(Rosuvastatin + Ezetimibe)

روّیروز ایز ٹیبلیٹس

(روزواسٹیٹن + ایزیٹیمائب)

COMPOSITION:

Roviros EZ 5mg + 10mg Tablets
Each film coated bi-layered tablet contains:
Rosuvastatin calcium USP eq. to Rosuvastatin 5mg
Ezetimibe USP 10mg
[Innovator's Specs.]

Roviros EZ 10mg + 10mg Tablets
Each film coated bi-layered tablet contains:
Rosuvastatin calcium USP eq. to Rosuvastatin 10mg
Ezetimibe USP 10mg
[Innovator's Specs.]

Roviros EZ 20mg + 10mg Tablets
Each film coated bi-layered tablet contains:
Rosuvastatin calcium USP eq. to Rosuvastatin 20mg
Ezetimibe USP 10mg
[Innovator's Specs.]

DESCRIPTION: ROVIROS EZ contains Rosuvastatin calcium and Ezetimibe. Rosuvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA)-reductase inhibitor. Ezetimibe is a dietary cholesterol absorption inhibitor.

INDICATIONS: ROVIROS EZ is indicated as:
- An adjunct to diet in patients with primary non-familial hyperlipidemia to reduce low-density lipoprotein cholesterol (LDLC).
- Alone or as an adjuct to other LDL-C lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.

DOSAGE AND ADMINISTRATION: The recommended starting dose is 5mg + 10mg or 10mg + 10mg once per day. The combination of Rosuvastatin + Ezetimibe can be administered at any time of the day, with or without food. Each tablet should be taken with water at the same time daily and is not to be chewed or crushed. Therapy should be individualized according to the target lipid levels, the recommended goal of therapy and the patients response. The dose should also take into account the potential risk for adverse reactions. A dose adjustment can be made after 4 weeks of therapy where necessary. The usual maximum dose is 20mg + 10mg once per day. This combination product is not indicated for first-line use.

CLINICAL PHARMACOLOGY: Mechanism of Action: Rosuvastatin: Rosuvastatin is an inhibitor of HMG CoA-reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. In in vivo and in vitro studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

Ezetimibe: The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes 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. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.

Pharmacokinetics: Absorption: Rosuvastatin: In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both C_{max} and AUC increased in approximate proportion to Rosuvastatin dose. The absolute bioavailability of Rosuvastatin is approximately 20%.The AUC of Rosuvastatin does not differ following evening or morning drug administration. Administration of Rosuvastatin with food did not affect the AUC of Rosuvastatin.

Ezetimibe: After oral administration, Ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10mg dose of Ezetimibe to fasted adults, mean Ezetimibe peak plasma concentrations (C_{max}) of 3.4 to 5.5ng/ml were attained within 4 to 12 hours (T_{max}). ezetimibe-glucuronide mean C_{max} values of 45 to 71ng/ml were achieved between 1 and 2 hours (T_{max}). There was no substantial deviation from dose proportionality between 5 and 20mg. 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 extent of absorption of Ezetimibe when administered as Ezetimibe 10mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high-fat meals.

Distribution: Rosuvastatin: Mean volume of distribution at steady state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Ezetimibe: Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Metabolism: Rosuvastatin: Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 / 2C9, and in vitro studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound.

Ezetimibe: Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. In humans, Ezetimibe is rapidly metabolized to ezetimibe-glucuronide. 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.

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Elimination:
Rosuvastatin: Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound. Following oral administration, Rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life ($t_{1/2}$) of Rosuvastatin is approximately 19 hours. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.
Ezetimibe: Both Ezetimibe and ezetimibe-glucuronide are eliminated from plasma with a half-life of approximately 22 hours for both Ezetimibe and ezetimibe-glucuronide. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

CONTRAINDICATIONS: ROVIROS EZ is contraindicated in patients with:
- Acute liver failure or decompensated cirrhosis.
- Hypersensitivity to Rosuvastatin, Ezetimibe, or any excipients used in **ROVIROS EZ**. Hypersensitivity reactions including anaphylaxis, angioedema, and erythema multiforme have been reported.

WARNINGS AND PRECAUTIONS: Myopathy and Rhabdomyolysis: The combination of Rosuvastatin + Ezetimibe may cause myopathy and rhabdomyolysis. Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis with statins, including Rosuvastatin. Discontinue the combination of Rosuvastatin + Ezetimibe if markedly CK levels or myopathy is diagnosed and suspected.
Immune-Mediated Necrotizing Myopathy: There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. Consider risk of IMNM carefully prior to initiation of a different statin. If therapy is initiated with a different statin, monitor for signs and symptoms of IMNM.
Hepatic Dysfunction: Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury. Consider liver enzyme testing before the initiation of combination of Rosuvastatin + Ezetimibe and thereafter, when clinically indicated. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue the combination of Rosuvastatin + Ezetimibe.
Proteinuria and Hematuria: Consider a dose reduction for patients on the combination of Rosuvastatin + Ezetimibe therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.
Increases in HbA1c and Fasting Serum Glucose Levels: Increases in HbA1c and fasting serum glucose levels have been reported with statins, including rosuvastatin. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

Pregnancy and Lactation:
Pregnancy: Discontinue **ROVIROS EZ** when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient. **ROVIROS EZ** decreases synthesis of cholesterol and possibly other biologically active substances derived from cholesterol; therefore, **ROVIROS EZ** may cause fetal harm when administered to pregnant patients based on the mechanism of action.
Lactation: There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production.

SIDE EFFECTS: The following are the side effects as described below:
- Headache - Weakness - Diarrhea - Dizziness - Nausea - Constipation - Joint pain - Stomach pain - Common cold and flu - Tiredness

DRUG INTERACTIONS: Antacids: Simultaneous administration of Rosuvastatin and an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in Rosuvastatin plasma concentration of approximately 50%. Administer the combination of Rosuvastatin + Ezetimibe atleast 2 hours before the antacid.
Darolutamide: Darolutamide increase the Rosuvastatin exposure more than 5-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.
Regorafenib: Regorafenib increased Rosuvastatin exposure and may increase the risk of myopathy.
Colestyramine: Concomitant colestyramine administration decreased the mean AUC of total Ezetimibe (Ezetimibe + ezetimibe glucuronide) approximately 55%.
Bile acid sequestrants: In patients taking a bile acid sequestrants administer the combination of Rosuvastatin + Ezetimibe atleast 2 hours before or atleast 4 hours after the bile acid sequestrants.
Niacin: Concomitant use of niacin with Rosuvastatin may cause myopathy and rhabdomyolysis.
Fenofibrates: Fenofibrate administration increased total Ezetimibe concentrations approximately 1.5-fold. Fenofibrate may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors.

OVERDOSE: In the event of an overdose, symptomatic and supportive measures should be employed. In symptomatic patients, monitor serum creatinine, BUN, creatinine phosphokinase and urine myoglobin for indications of renal impairment secondary to rhabdomyolysis. Liver function tests should be performed in symptomatic patients. Hemodialysis is unlikely to be of benefit.

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

PRESENTATION:
ROVIROS EZ 5mg + 10mg Tablets are available in pack size of 10's.
ROVIROS EZ 10mg + 10mg Tablets are available in pack size of 10's.
ROVIROS EZ 20mg + 10mg Tablets are available in pack size of 10's.

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

Manufactured by:
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PHARMA
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