Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Rovista EZ Tablets 10 mg + 10 mg

2. Qualitative and quantitative composition

Each film-coated tablet contains rosuvastatin calcium equivalent to 10 mg of rosuvastatin and 10 mg of ezetimibe.
Excipient with known effect: each film-coated tablet contains lactose monohydrate.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.
Light pink coloured, round shaped film-coated tablet, engraved "GETZ" on one side and plain on the other side. No score line is present; the tablet cannot be divided into equal doses.

4. Clinical particulars

4.1 Therapeutic indications

Primary hypercholesterolaemia
Rovista EZ is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate, in patients not adequately controlled with rosuvastatin or ezetimibe alone, or already treated with rosuvastatin and ezetimibe.
Homozygous familial hypercholesterolaemia
Rovista EZ is indicated for patients with homozygous familial hypercholesterolaemia. Patients may also receive adjunctive treatments such as LDL apheresis.

4.2 Posology and method of administration

Posology
Rovista EZ may be administered within the dosage range of 5 mg + 10 mg to 20 mg + 10 mg as a single daily dose. The recommended starting dose is 5 mg + 10 mg or 10 mg + 10 mg once daily. Therapy should be individualised according to the target lipid levels, the recommended goal of therapy and the patient's response, and should take into account the potential risk of adverse reactions. A dose adjustment may be made after 4 weeks of therapy where necessary. The usual maximum dose is 20 mg + 10 mg once daily. This combination product is not indicated for first-line use.
Special populations
Use in the elderly
A start dose of 5mg rosuvastatin is recommended in patients >70 years.

Use in pediatric patients
Not recommended for use in children.

Dosage in patients with hepatic impairment
No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with Rovista EZ (Rosuvastatin + Ezetimibe) is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction.

Dosage in patients with renal insufficiency
No dosage adjustment is required for patients with mild to moderate renal impairment. For patients with severe renal impairment (CLcr<30 mL/min/1.73m2) not on dialysis the dose of Rovista EZ (Rosuvastatin + Ezetimibe) should be started at 5mg+10mg once daily and not exceed 10mg+10mg once daily.

Dosage in Asian patients
Initiation of therapy with Rovista EZ (Rosuvastatin + Ezetimibe) 5mg+10mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolemia is not adequately controlled at doses of 5mg+10mg, 10mg+10mg or 20mg+10mg once daily.

Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is rosuvastatin 5mg in patients with predisposing factors to myopathy. The fixed dose combination is not suitable for initial therapy. Treatment initiation should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Dosage in patients taking other drugs
Ciclosporin
Dosage should be limited to Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 5mg+10mg once daily.

Gemfibrozil
Dosage should be limited to Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 10mg+10mg once daily.
Antiviral Medication
Concomitant use of sofosbuvir / velpatasvir / voxilaprevir and ledipasvir / sofosbuvir with Rovista EZ (Rosuvastatin + Ezetimibe) is not recommended. In patients taking simeprevir, dasabuvir / ombitasvir / paritaprevir / ritonavir, elbasvir / grazoprevir, Sofosbuvir / velpatasvir, glecaprevir / pibrentasvir, atazanavir / ritonavir, and lopinavir /ritonavir initiate

Rovista EZ (Rosuvastatin + Ezetimibe) at 5mg+10mg. Do not exceed Rovista EZ (Rosuvastatin + Ezetimibe) 10mg+10mg once daily.
No dose adjustment is needed for concomitant use with fosamprenavir / ritonavir or tipranavir / ritonavir.
Darolutamide
Do not exceed Rovista EZ (Rosuvastatin + Ezetimibe) 5mg+10mg once daily.
Regorafenib
Do not exceed Rovista EZ (Rosuvastatin + Ezetimibe) 10mg+10mg once daily.
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4.3 Contraindications

The combination of rosuvastatin and ezetimibe is contraindicated:
In patients with hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
In patients with acute liver failure or decompensated cirrhosis.
During pregnancy and breast-feeding, and in women of childbearing potential not using appropriate contraceptive measures.
In patients with myopathy.
In patients receiving concomitant ciclosporin.
In combination with fenofibrate.
In patients with gall bladder disease.
In patients receiving fusidic acid therapy.

4.4 Special warnings and precautions for use

Myopathy and rhabdomyolysis
The combination 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. Treatment should be discontinued if creatine kinase levels are markedly elevated or if myopathy is diagnosed or suspected.
Immune-mediated necrotising myopathy
There have been rare reports of immune-mediated necrotising myopathy, an autoimmune myopathy, associated with statin use. The risk should be considered carefully prior to initiation of a different statin; if therapy is initiated with a different statin, patients should be monitored for signs and symptoms.
Hepatic dysfunction
Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk of hepatic injury. Liver enzyme testing should be considered before initiation and thereafter when clinically indicated. If serious hepatic injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs, treatment should be discontinued promptly.
Proteinuria and haematuria
A dose reduction should be considered for patients with unexplained persistent proteinuria and/or haematuria during routine urinalysis testing.
Increases in HbA1c and fasting serum glucose

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including rosuvastatin. Lifestyle measures, including regular exercise, maintaining a healthy body weight and making healthy food choices, should be optimised.

Creatine kinase measurement

Creatine kinase should not be measured following strenuous exercise or in the presence of a plausible alternative cause of elevation, which may confound interpretation. If 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 value above 5 × ULN, treatment should not be started.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with statins, especially with long-term therapy. Presenting features may include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If interstitial lung disease is suspected, treatment should be discontinued.

Paediatric population

The safety and efficacy of the combination in children below the age of 18 years has not been established; its use is therefore not recommended in this age group.

4.5 Interaction with other medicinal products and other forms of interaction

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%. Rovista EZ should be administered at least 2 hours before the antacid.

Darolutamide: increases rosuvastatin exposure more than 5-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.

Regorafenib: increases rosuvastatin exposure and may increase the risk of myopathy.

Colestyramine: concomitant administration decreased the mean AUC of total ezetimibe (ezetimibe plus ezetimibe glucuronide) by approximately 55%.

Bile acid sequestrants: in patients taking a bile acid sequestrant, Rovista EZ should be administered at least 2 hours before or at least 4 hours after the sequestrant.

Niacin: concomitant use with rosuvastatin may cause myopathy and rhabdomyolysis.

Fenofibrate: increases total ezetimibe concentrations approximately 1.5-fold and may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors.

Gemfibrozil: increases total ezetimibe concentrations approximately 1.7-fold. Concomitant use with rosuvastatin resulted in a 2-fold increase in rosuvastatin Cmax and AUC. Gemfibrozil may increase the risk of myopathy.

Other fibric acid derivatives, including nicotinic acid, may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors.

Anticoagulants: 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 concomitantly, INR should be determined before starting Rovista EZ and frequently enough during early therapy to ensure that no significant alteration occurs.
Oral contraceptives: co-administration with rosuvastatin resulted in increases in plasma concentrations of ethinylestradiol and norgestrel of 26% and 34% respectively.
Inhibitors of breast cancer resistance protein (BCRP): concomitant administration of BCRP inhibitors (e.g. elbasvir and grazoprevir) may lead to increased plasma concentrations of rosuvastatin and an increased risk of myopathy.
Fusidic acid: the risk of myopathy including rhabdomyolysis may be increased by concomitant administration of systemic fusidic acid with statins. Co-administration may cause increased plasma concentrations of both agents.
Colchicine: cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, co-administered with colchicine.
Daptomycin: the risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration with HMG-CoA reductase inhibitors.
Erythromycin: concomitant use with rosuvastatin resulted in a 20% decrease in AUC and a 30% decrease in Cmax of rosuvastatin, possibly caused by the increase in gut motility produced by erythromycin.

4.6 Pregnancy and Lactation

Rovista EZ (Rosuvastatin + Ezetimibe) is contraindicated during pregnancy, breast-feeding and in women of childbearing potential not using appropriate contraceptive measures.

4.7 Effects on ability to drive and use machines

Ezetimibe

No studies on the effects on the ability to drive and use machines have been performed. Patients who may experience dizziness as an adverse reaction should avoid driving vehicles or using machines.

Rosuvastatin

Pharmacological testing revealed no evidence of a sedative effect of rosuvastatin. From the safety profile, rosuvastatin is not expected to adversely affect the ability to drive or operate machinery.

4.8 Undesirable effects

Common

Diabetes mellitus, headache, dizziness, diarrhoea, flatulence, myalgia, asthenia, fatigue, constipation, nausea, abdominal pain, increased ALT and/or AST.

Uncommon
Decreased appetite, paraesthesia, hot flush, hypertension, cough, dyspepsia, gastro-oesophageal reflux disease, dry mouth, gastritis, pruritus, rash, urticaria, arthralgia, muscle spasm, neck pain, back pain, muscular weakness, pain in extremity, chest pain, oedema peripheral, increased blood creatine phosphokinase, increased gamma-glutamyl transferase and abnormal liver function test.
Rare
Thrombocytopenia, hypersensitivity reaction including angioedema, pancreatitis, increased hepatic transaminases, myopathy (including myositis), rhabdomyolysis, lupus-like syndrome and muscle rupture.
Allergic dermatitis, eczema, skin exfoliation, polyneuropathy, memory loss, jaundice, hepatitis, arthralgia, haematuria, gynaecomastia, depression, peripheral neuropathy, sleep disturbance (including insomnia and nightmares), paraesthesia, cough, dyspnoea, cholelithiasis, cholecystitis, Stevens-Johnson syndrome, erythema multiforme, immune-mediated necrotising myopathy and tendon disorders.
Reporting of suspected adverse reactions
Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS): https://pv.pharmacyboardkenya.org

4.9 Overdose
In the event of an overdose, symptomatic and supportive measures should be employed. In symptomatic patients, serum creatinine, blood urea nitrogen, creatine phosphokinase and urine myoglobin should be monitored for indications of renal impairment secondary to rhabdomyolysis. Liver function tests should be performed in symptomatic patients. Haemodialysis is unlikely to be of benefit.

5. Pharmacological properties
5.1 Pharmacodynamic properties
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: it increases the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL, and it inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.
Mechanism of action – 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 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. This causes

a reduction of hepatic cholesterol stores and an increase in the clearance of cholesterol from the blood.

5.2 Pharmacokinetic properties

Absorption – rosuvastatin

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

Absorption – ezetimibe

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10 mg dose in fasted adults, mean peak plasma concentrations of ezetimibe of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours; ezetimibe-glucuronide mean Cmax values of 45 to 71 ng/mL were achieved between 1 and 2 hours. There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection. Concomitant food administration had no effect on the extent of absorption; the Cmax was increased by 38% with consumption of high-fat meals.

Distribution

Rosuvastatin: the mean volume of distribution at steady state is approximately 134 litres. 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.

Biotransformation

Rosuvastatin: rosuvastatin is not extensively metabolised; approximately 10% of a radiolabelled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, formed principally by CYP2C9; in vitro studies have demonstrated that it has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound.

Ezetimibe: ezetimibe is primarily metabolised in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. In humans, ezetimibe is rapidly metabolised 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 total drug in plasma respectively.

Elimination

Rosuvastatin: 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 faeces (90%). The elimination half-life 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. Ezetimibe was the major component in faeces, accounting for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine, accounting for 9% of the administered dose.

Special populations

Elderly: in a multiple-dose study with ezetimibe 10 mg once daily for 10 days, plasma concentrations of total ezetimibe were about 2-fold higher in older (≥ 65 years) healthy subjects compared with younger subjects.
Gender: in the same study, plasma concentrations of total ezetimibe were slightly higher (< 20%) in women than in men.
Hepatic impairment – rosuvastatin: in patients with chronic alcoholic liver disease, plasma concentrations were modestly increased. In patients with Child-Pugh A disease, Cmax and AUC were increased by 60% and 5% respectively compared with patients with normal liver function; in Child-Pugh B disease they were increased by 100% and 21% respectively.
Hepatic impairment – ezetimibe: after a single 10 mg dose, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 to 6) compared with healthy subjects. The mean AUC values for total ezetimibe and ezetimibe increased approximately 3- to 4-fold and 5- to 6-fold respectively in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score 10 to 15) hepatic impairment. In a 14-day multiple-dose study in patients with moderate hepatic impairment, the mean AUC for total ezetimibe and ezetimibe increased approximately 4-fold on both day 1 and day 14 compared with healthy subjects.
Renal impairment – rosuvastatin: mild to moderate renal impairment (CLcr ≥ 30 mL/min/1.73 m²) had no influence on plasma concentrations. However, plasma concentrations increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CLcr < 30 mL/min/1.73 m²) not receiving haemodialysis compared with healthy subjects. Steady-state plasma concentrations in patients on chronic haemodialysis were approximately 50% greater than in healthy volunteers with normal renal function.
Renal impairment – ezetimibe: after a single 10 mg dose in patients with severe renal disease (mean CLcr ≤ 30 mL/min/1.73 m²), the mean AUC values for total ezetimibe, ezetimibe-glucuronide and ezetimibe were increased approximately 1.5-fold compared with healthy subjects.

6. Pharmaceutical Particulars

6.1 List of Excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Sodium lauryl sulfate

Povidone K-25
Colloidal anhydrous silica
Magnesium stearate
Talc
Opadry Pink 03F640031
Ferric oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

2 years. The expiry date refers to the product correctly stored under the required conditions.

6.4 Special Precautions for storage

Do not store above 30°C. Protect from sunlight and moisture.

6.5 Nature and Content of container

Alu-Alu blister packs of 3 × 10 tablets in a unit carton together with a package insert.

6.6 Special precautions for disposal and other handling

Keep out of the reach and sight of children.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Getz Pharma (Private) Limited
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8. Marketing Authorization Number

H2024/CTD10798/22784

9. Date of first authorization/renewal of the authorization

2024 March 25

10. Date of revision of the text

2024 March 25