Summary of Product Characteristics for Pharmaceutical Products

1. NAME OF DRUG PRODUCT

Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 10mg + 10mg
Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 20mg + 10mg
Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 5mg + 10mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 10mg + 10mg
Each film-coated tablet contains:
Rosuvastatin calcium equivalent to
Rosuvastatin.....10mg
Ezetimibe.....10mg

Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 20mg + 10mg
Each film-coated tablet contains:
Rosuvastatin calcium equivalent to
Rosuvastatin.....20mg
Ezetimibe.....10mg

Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 5mg + 10mg
Each film-coated tablet contains:
Rosuvastatin calcium equivalent to
Rosuvastatin..... 5mg
Ezetimibe..... 10mg

Excipient(s) with known effect: Each film coated contains lactose monohydrate 141.00mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 10mg + 10mg
Light Pink colored, round shaped, film coated tablet, engraved "GETZ" on one side andplain on other side.

Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 20mg + 10mg
Light Pink colored, round shaped, film coated tablet, plain on both sides.

Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 5mg + 10mg
Yellow colored, round shaped, film coated tablet, engraved "GETZ" on one side and plain on other side

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Primary Hypercholesterolemia

Rovista EZ (Rosuvastatin + Ezetimibe) is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolemia where use of combination product is appropriate in patients:

not appropriately controlled with rosuvastatin or ezetimibe alone; or
already treated with rosuvastatin and ezetimibe

Homozygous Familial Hypercholesterolemia (HoFH)

Rovista EZ (Rosuvastatin + Ezetimibe) is indicated for patients with Homozygous Familial Hypercholesterolemia (HoFH). Patients may also receive adjunctive treatments (e.g., LDL apheresis).

4.2 Posology and Method of Administration

Rovista EZ (Rosuvastatin + Ezetimibe) can be administered within the dosage range of 5mg+10mg to 20mg+10mg as a single daily dose. The recommended starting dose is 5mg+10mg or 10 mg+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 patient's 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.

4.3 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 recommendedin 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 dailyshould 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+10mgonce daily.

Gemfibrozil
Dosage should be limited to Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 10mg+10mgonce daily.

Antiviral Medication
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 ortipranavir / 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.

Contraindications

The combination of Rosuvastatin + Ezetimibe is contraindicated;
In patients with hypersensitivity to the active substances (rosuvastatin, ezetimibe) orto any
of the excipients of the product.
In patients with acute liver failure or decompensated cirrhosis.
During pregnancy, breast-feeding and in women of childbearing potential not usingappropriate contraceptive measures.
In patients with myopathy.
In patients receiving concomitant ciclosporin.
In combination with fenofibrate.

In patients with gall bladder disease.
In patients with fusidic acid therapy.

4.4 Special warnings and special precautions for use

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 diseasemay 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 occurs, promptly discontinue thecombination 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.

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

Interstitial Lungs Disease
Exceptional cases of interstitial lung disease have been reported with some especially with long term therapy. Presenting features can include dyspnea, non-productive cough anddeterioration in general health (fatigue, weight loss and fever). If it is suspected that apatient has developed interstitial lung disease, the combination of Rosuvastatin + Ezetimibe should be discontinued.

Pediatric population

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

4.5 Interaction with other medicaments

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.

Gemfibrozil
Concomitant gemfibrozil administration results in the increase of total ezetimibe concentrations approximately 1.7-fold. Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC. Gemfibrozil may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors.

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

Anticoagulant

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 the combination of Rosuvastatin + Ezetimibe and frequently enough during early therapy to ensure that no significant alteration of INR occurs.

Oral contraceptives
Co-administration of oral contraceptives with rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively.

Inhibitors of Breast Cancer Resistance Protein (BCRP)
Concomitant administration of products that are inhibitors of BCRP (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 the concomitant administration of systemic fusidic acid with statins. Co-administration of this combination 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 colchicines.

Daptomycin
The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors and daptomycin.

Erythromycin
Concomitant use of rosuvastatin and erythromycin resulted in a 20% decrease in AUC_{0-t} and a 30% decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Overdosage
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.

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 machine

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, diarrhea, flatulence, myalgia, asthenia, fatigue, constipation, nausea, abdominal pain, ALT and/or AST increased.

Uncommon*:* Decreased appetite, paraesthesia, hot flush, hypertension, cough, dyspepsia,gastro-oesophageal reflux disease, dry mouth, gastritis, pruritus, rash, utricaria, arthralgia, muscles spasm, neck pain, back pain, muscular weakness, pain in extremity, chest pain, asthenia, oedema peripheral, ALT and/or AST increased, blood CPK increased, gammaglutamyl transferase increased and liver function test abnormal.
Rare: Thrombocytopenia, hypersensitivity reaction, including angioedema, pancreatitis, increased hepatic transaminases, myopathy (including myositis), rhabdomyolysis, lupus like syndrome, muscle rupture.

Others: Allergic dermatitis, eczema, skin exfoliation, polyneuropathy, memory loss, jaundice, hepatitis, arthralgia, hematuria, gynecomastia, depression, peripheral neuropathy, sleep disturbance (including insomnia and nightmares), paraesthesia, cough, dyspnoea, hepatitis, cholelithiasis, cholycystitis, Stevens Johnson syndrome, erythema multiforme, immune mediated necrotising and tendon disorder.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic propertiesMechanism of Action

Rosuvastatin
Rosuvastatin is an inhibitor of HMG CoA-reductase, the rate-limiting enzyme that converts 3-hydroxy3-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.

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 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 10- mg 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 (Tmax). Ezetimibe-*glucuronide* mean
Cmax values of 45 to 71ng/mL were achieved between 1 and 2 hours (Tmax). 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 10-mg 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.

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 (t1/2) 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 glucuronide was the major component in urine and accounted for 9% of the administered dose.

Special Populations
Geriatric Patients
In a multiple-dose study with ezetimibe given 10mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

Gender
In a multiple-dose study with ezetimibe given 10mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Hepatic Impairment
Rosuvastatin
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
After a single 10mg 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 to 6), compared to 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 hepatic impairment (Child-Pugh score 10 to 15). In a 14 day, multiple-dose study (10mg daily) 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 when compared to healthy subjects.

Renal Impairment
Rosuvastatin
Mild to moderate renal impairment (CLcr ≥30 mL/min/1.73m2) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3 fold) in patients with severe renal impairment (CL_{cr} < 30mL/min/1.73m^2) not receiving hemodialysis compared with healthy subjects (CL_{cr} > 80mL/min/1.73m^2). Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Ezetimibe
After a single 10 mg dose of ezetimibe in patients with severe renal disease (mean CL_{cr} ≤ 30mL/min/1.73m2), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5 fold, compared to healthy subjects

6. **PHARMACEUTICAL** PARTICULARS

6.1 List of Excipients

Lactose Monohydrate, Croscarmellose Sodium, Sodium Lauryl Sulfate, Povidone K-25 (PVP K-25), Purified Water, Avicel PH 112 (Microcrystalline Cellulose), Magnesium Stearate, Pharmatose DCL 11 (Lactose Monohydrate), Aerosil 200 (Colloidal Anhydrous Silica),Ferric Oxide Red, Opadry Pink 03F640031, Purified Talc.

6.2 Incompatibilities

None

6.3 Shelf-life

2 Years
The expiration date refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

Do not store above 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

6.5 Nature and contents of container

Alu-Alu blisterpacks of 3 x 10 tablets in a unit carton along with a package insert.

6.6 Instructions for use/handling

Keep out of reach of children.
To be sold on prescription of a registered medical practitioner only.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder
Name**:** Getz Pharma (Private) Limited
Address: 29-30/27, Korangi, Industrial Area Karachi 74900.
Country Pakistan

M**anufacturing site addresses**
Name: Getz Pharma (Private) Limited
Address: 29-30/27, Korangi, Industrial Area Karachi 74900.
Country Pakistan

8. Marketing authorization number

H2024/CTD10798/22784- Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 10mg + 10mg
H2024/CTD10799/22788- Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 20mg + 10mg
H2024/CTD10801/22764 Rovista EZ (Rosuvastatin + Ezetimibe) Tablets 5mg + 10mg

9. Date of first registration

CTD10798-27/02/2024
CTD10799-27/02/2024
CTD10801-27/02/2024

10. Date of revision of the text

November 202