

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rozavel EZ

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rozavel EZ 10/10 mg tablet

Each uncoated bilayer tablet contains:

Rosuvastatin Calcium

Equivalent to Rosuvastatin.....10 mg

Ezetimibe.....10 mg

Rozavel EZ 10/20 mg

Each uncoated bilayer tablet contains:

Rosuvastatin Calcium equivalent to Rosuvastatin.....20 mg

Ezetimibe.....10 mg

Excipients of known effect

Each tablet contains 55.0 mg of Lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Uncoated bilayer Tablet

Circular uncoated bilayer tablets with white color on both layer and plain on both side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia/Homozygous Familial Hypercholesterolaemia (HoFH)

Rozavel EZ is indicated as adjunct to diet for treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or homozygous familial hypercholesterolaemia in adult patients:

- who are not appropriately controlled with statin alone.
- who are adequately controlled with rosuvastatin and ezetimibe given concurrently at the same dose level as in the fixed combination, but as separate products.

Prevention of Cardiovascular Events

Rozavel EZ is indicated as substitution therapy in adult patients who are adequately controlled with rosuvastatin and ezetimibe given concurrently,

at the same dose level as in the fixed dose combination, but as separate products to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS).

4.2 Posology and method of administration

Rozavel EZ is available as fixed dose combination of ezetimibe/rosuvastatin 10/10 mg, 10/20 mg, and 10/40 mg tablets only and may not be suitable for all dosing recommendations mentioned below. In such cases, other suitable approved strengths of ezetimibe and rosuvastatin should be used.

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

Rozavel EZ is not suitable for initial therapy.

When **Rozavel EZ** is indicated for patients not controlled by statin alone, the dose of **Rozavel EZ** should be individualized according to the target lipid levels and the patient's response.

When **Rozavel EZ** is indicated for patients who are adequately controlled with rosuvastatin and ezetimibe given concurrently at the same dose level as in the fixed combination, but as separate product, 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.

Patient should use the strength corresponding to their previous treatment. The recommended dose is one

Rozavel EZ tablet daily.

Co-administration with bile acid sequestrants

Dosing of ezetimibe/rosuvastatin should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant (see **section 4.5**).

Paediatric population

The safety and efficacy of ezetimibe/rosuvastatin in children below the age of 18 years have not yet been established. The reported data are described in **section 4.8, and 5.2** but no recommendations on posology can be made.

Elderly

A starting dose of 5 mg rosuvastatin is recommended in patients >70 years (see **section 4.4**). 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.

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment (Child Pugh score 5 to 6). Treatment with ezetimibe/rosuvastatin 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**). Ezetimibe/rosuvastatin is contraindicated in patients with active liver disease (see **section 4.3**).

Renal impairment

No dose adjustment is necessary in patients with mild renal impairment.

The recommended start dose is rosuvastatin 5 mg in patients with moderate renal impairment (creatinine clearance <60 ml/minute).

Ezetimibe/rosuvastatin 10 mg/40 mg dose is contraindicated in patients with moderate renal impairment. The use of ezetimibe/rosuvastatin in patients with severe renal impairment is contraindicated for all doses (see **sections 4.3 and 5.2**).

Race

Increased systemic exposure of rosuvastatin has been reported in Asian subjects (see **sections 4.4 and 5.2**). The recommended start dose is rosuvastatin 5 mg for patients of Asian ancestry. The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose. Ezetimibe/rosuvastatin 10 mg/40 mg tablets are contraindicated in these patients (see **sections 4.3 and 5.2**).

Genetic polymorphisms

Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure (see **section 5.2**). For patients who are known to have such specific types of polymorphisms, a lower daily dose of ezetimibe/rosuvastatin is recommended.

Dosage in patients with pre-disposing factors to myopathy

The recommended start dose is rosuvastatin 5 mg in patients with pre-disposing factors to myopathy (see **section 4.4**). The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.

Ezetimibe/rosuvastatin 10 mg/40 mg film-coated tablets are contraindicated in some of these patients (see **section 4.3**).

Concomitant therapy

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when ezetimibe/rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir; see **sections 4.4 and 4.5**).

Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing ezetimibe/rosuvastatin therapy. In situations where co-administration of these medicinal products with ezetimibe/rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered (see **section 4.5**).

Method of administration

Route of administration is oral.

Rozavel EZ can be administered at any time of the day, with or without food. The tablet should be swallowed whole with a drink of water.

4.3 Contraindications

- Hypersensitivity to ezetimibe, rosuvastatin or to any of the excipients listed in **section 6.1**.

- Pregnancy, breast-feeding and in women of childbearing potential not using appropriate contraceptive measures (see **section 4.6**).
- Active liver disease or unexplained persistent elevations in serum transaminases and any serum transaminase elevation exceeding 3x the upper limit of normal (ULN) (see **section 4.4**).
- In patients with severe renal impairment (creatinine clearance < 30 ml/min) (see **section 4.4**).
- In patients with myopathy (see **section 4.4**).
- In patients receiving concomitant ciclosporin (see **section 4.5**).

Ezetimibe/rosuvastatin 10 mg/40 mg dose is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- Moderate renal impairment (creatinine clearance <60 ml/min).
- 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 plasma levels of rosuvastatin may occur.
- Asian patients.
- Concomitant use of fibrates.

(see **sections 4.4, 4.5 and 5.2**)

4.4 Special warnings and precautions for use

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. As with other HMGCoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with rosuvastatin in postmarketing use is higher at the 40 mg dose.

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis.

If myopathy is suspected based on muscle symptoms or is confirmed by a creatine phosphokinase (CPK) level, ezetimibe/rosuvastatin and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with ezetimibe/rosuvastatin should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness (see **section 4.8**).

In few cases, statins have been reported to induce *de novo* or aggravate pre-existing myasthenia gravis or ocular myasthenia (see **section 4.8**). Ezetimibe/rosuvastatin 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 result. If CK levels are significantly elevated at baseline ($>5\times\text{ULN}$) a confirmatory test should be carried out within 5-7 days. If the repeat test confirms a baseline CK $>5\times\text{ULN}$, treatment should not be started.

Before treatment

Caution should be exercised 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 (see **sections 4.2, 4.5 and 5.2**),
- 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 ($>5\times\text{ULN}$) 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 ($>5\times\text{ULN}$) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are $\leq 5\times\text{ULN}$). 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 of the patient. 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.

There was no reported 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 reported in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, cyclosporin, 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 of rosuvastatin is contraindicated with concomitant use of a fibrate (see **sections**

4.5 and 4.8).

Ezetimibe/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

In reported co-administration trials in patients receiving ezetimibe with statin, consecutive transaminase elevations ($\geq 3 \times$ the upper limit of normal [ULN]) have been observed. 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.

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, ezetimibe/rosuvastatin is not recommended (see **section 5.2**).

Liver disease and alcohol

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.

Renal effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been reported 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 reported to be predictive of acute or progressive renal disease (see **section 4.8**). 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.

Diabetes mellitus

Some reported 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/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

In a reported study, the 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.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see **section 4.8**). 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.

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 ezetimibe/rosuvastatin must 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 ezetimibe/rosuvastatin, treatment with ezetimibe/rosuvastatin must not be restarted in this patient at any time.

Protease inhibitors

Increased systemic exposure to rosuvastatin has been reported 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 ezetimibe/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 (see **sections 4.2 and 4.5**).

Fibrates

The safety and efficacy of ezetimibe administered with fibrates have not been reported (see above and **sections 4.3 and 4.5**).

If cholelithiasis is suspected in a patient receiving ezetimibe/rosuvastatin and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see **sections 4.5 and 4.8**).

Anticoagulants

If ezetimibe/rosuvastatin is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see **section 4.5**).

Fusidic acid

Ezetimibe/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 (see **section 4.5**). The patient 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 ezetimibe/rosuvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Race

Increase in exposure of rosuvastatin has been reported in Asian subjects compared with Caucasians (see **sections 4.2, 4.3 and 5.2**).

Paediatric population

Ezetimibe/rosuvastatin is not recommended for use in children and adolescents of less than 18 years of age, due to insufficient data on safety and efficacy.

Excipients

Rozavel EZ contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations:

Ciclosporin:

Concomitant administration of ezetimibe/rosuvastatin with ciclosporin is contraindicated because of the rosuvastatin (see **section 4.3**). During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values have been reported to be on average 7 times higher than those reported in healthy volunteers (see **Table 1**). Concomitant administration did not reportedly affect plasma concentrations of ciclosporin.

In a reported study in 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 7.9fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone. In another reported study, a renal transplant patient with severe renal impairment who was receiving

ciclosporin and multiple other medications, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a reported study in 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. The effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been reported.

Not-recommended combinations:

Fibrates and other lipid-lowering products:

In patients receiving fenofibrate and ezetimibe, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease (see **sections 4.4 and 4.8**). If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see **section 4.8**). Concomitant fenofibrate or gemfibrozil administration has been reported to modestly increase total ezetimibe concentrations (approximately 1.5- and 1.7-fold respectively). Co-administration of ezetimibe with other fibrates has not been reported. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. Ezetimibe sometimes increased cholesterol in the gallbladder bile in animals, but not in all species (see **section 5.3**). A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

Concomitant use of rosuvastatin and gemfibrozil has been reported to result in a 2-fold increase in rosuvastatin C_{max} and AUC (see **section 4.4**). No pharmacokinetic relevant interaction with fenofibrate is expected, however, a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. Ezetimibe/rosuvastatin 10 mg/40 mg dose is contraindicated with concomitant use of a fibrate (see **sections 4.3 and 4.4**).

Protease inhibitors:

Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see **Table 1**). Co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir/100 mg ritonavir) in healthy volunteers has been reported to be associated with an approximately three-fold and sevenfold increase in rosuvastatin AUC and C_{max} respectively. 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 (see **sections 4.2, 4.4 and 4.5, Table 1**).

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 with medicinal products that are inhibitors of these transporter proteins may result in increased

rosuvastatin plasma concentrations and an increased risk of myopathy (**see sections 4.2, 4.4 and 4.5, Table 1**).

Fusidic acid:

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with systemic fusidic acid is necessary, rosuvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see **section 4.4**.

Other interactions:

Cytochrome P450 enzymes:

Rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. No clinically relevant interactions have been reported between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

Ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been reported between ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

Antacids:

Concomitant antacid administration has been reported to decrease 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. The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide has been reported to result in a decrease in rosuvastatin plasma concentration of approximately 50%. This effect was reportedly mitigated when the antacid was dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been reported.

Colestyramine:

Concomitant colestyramine administration has been reported to decrease the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) to approximately 55%. The incremental low density lipoprotein cholesterol (LDL C) reduction due to adding ezetimibe to colestyramine may be lessened by this interaction (see **section 4.2**).

Anticoagulants, Vitamin K antagonists:

Concomitant administration of ezetimibe (10 mg once daily) reportedly had no significant effect on bioavailability of warfarin and prothrombin time in 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/rosuvastatin is

added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see **section 4.4**).

As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Clopidogrel:

Clopidogrel has been reported to increase rosuvastatin exposure in patients by 2-fold (AUC) and 1.3-fold ($C_{\max}$) after administration of 300 mg clopidogrel dose, and by 1.4-fold (AUC) without effect on $C_{\max}$ after repeated administration of 75 mg clopidogrel dose.

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.

Erythromycin:

Concomitant use of rosuvastatin and erythromycin has been reported to result 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.

Oral contraceptive/hormone replacement therapy (HRT):

Concomitant use of rosuvastatin and an oral contraceptive has been reported to result 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. There are no pharmacokinetic data reported in women taking concomitant rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in reported clinical studies and has been well tolerated.

Ezetimibe reportedly had no effect on the pharmacokinetics of oral contraceptives (ethinyl estradiol and levonorgestrel).

Other medicinal products:

No clinically relevant interaction of rosuvastatin with digoxin is expected. Ezetimibe reportedly had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, glipizide, tolbutamide, or midazolam, during co-administration. Cimetidine, co-administered with ezetimibe, reportedly had no effect on the bioavailability of ezetimibe.

Interactions requiring rosuvastatin dose adjustments (see also **Table 1**):

When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses should be adjusted. 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 10 mg dose of rosuvastatin with combination ritonavir/atazanavir (3.1-fold increase).

Table 1 Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from reported clinical studies

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Regorafenib 160 mg, OD, 14 days	5 mg single dose	3.8-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Velpatasvir 100 mg OD	10 mg single dose	2.7-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg OD/dasabuvir 400 mg BID, 14 days	5 mg, single dose	2.6-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD, 11 days	10 mg, single dose	2.3-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD, 7 days	5 mg OD, 7 days	2.2-fold ↑
Clopidogrel 300 mg loading dose, followed by 75 mg OD at 24 hours	20 mg, single dose	2-fold ↑
Clopidogrel 300 mg loading dose, followed by 75 mg OD, 7 days	40 mg, OD	2-fold ↑, 1.4-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑

Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedaron 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	**1.4-fold ↑
Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 days	10 mg, single dose	↔
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mg TID, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	↔
Rifampin 450 mg OD, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓

*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as % change represent % difference relative to rosuvastatin alone. Increase is indicated as "↑", no change as "↔", decrease as "↓". **Several interaction studies have been performed at different rosuvastatin dosages, the table shows the most significant ratio OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily.

4.6 Fertility, Pregnancy and lactation

Ezetimibe/rosuvastatin is contraindicated during pregnancy and breast-feeding (see **section 4.3**). Women of childbearing potential should use appropriate contraceptive measures.

Pregnancy

There are no reported data on the use of ezetimibe during pregnancy. There is no reported evidence of direct or indirect harmful effects of ezetimibe in monotherapy on pregnancy, embryofetal development, birth or postnatal development if animals (see **section 5.3**).

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. There is limited evidence of reproductive toxicity in animals (see **section 5.3**). If a patient becomes pregnant during use of ezetimibe/rosuvastatin, treatment should be discontinued immediately.

Breast-feeding

Ezetimibe is secreted into breast milk of rats. It is not known if ezetimibe is secreted into human breast milk. Rosuvastatin is excreted in the milk of rats. There are no reported data with respect to excretion in milk in humans (see **section 4.3**).

Fertility

There are no reported data on the effects of ezetimibe or rosuvastatin on human fertility. Ezetimibe reportedly had no effects on the fertility of male or female rats, rosuvastatin at higher doses showed testicular toxicity in monkeys and dogs (see **section 5.3**).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been reported. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported.

4.8 Undesirable effects

Summary of safety profile

Adverse drug reactions previously reported with one of the individual components (ezetimibe or rosuvastatin) may be potential undesirable effects with ezetimibe/rosuvastatin.

In a reported study, ezetimibe 10 mg daily was administered alone, with a statin or with fenofibrate. Adverse reactions have been reported to be usually mild and transient. The overall incidence of side effects has been reported to be similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences has been reported to be comparable between ezetimibe and placebo.

The adverse events reported with rosuvastatin are generally mild and transient. In reported studies, less than 4% of rosuvastatin-treated patients were withdrawn due to adverse events.

Tabulated list of adverse reactions

The frequencies of adverse reactions are ranked according to the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the reported data).

MedDRA system organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	rare	thrombocytopenia ²
	not known	thrombocytopenia ⁵
Immune system disorders	rare	hypersensitivity reactions including angioedema ²
	not known	hypersensitivity (including rash, urticaria, anaphylaxis and angioedema) ⁵
Endocrine disorders	common	diabetes mellitus ^{1, 2}
Metabolism and nutrition disorders	uncommon	decreased appetite ³
Psychiatric disorders	not known	depression ^{2, 5}

Nervous system disorders	common	headache ^{2, 4} , dizziness ²
	uncommon	paraesthesia ⁴
	very rare	polyneuropathy ² , memory loss ²
	not known	peripheral neuropathy ² , sleep disturbances (including insomnia and nightmares) ² , dizziness ⁵ ; paraesthesia ⁵ , myasthenia gravis ²
Eye disorders	not known	ocular myasthenia ²
Vascular disorders	uncommon	hot flush ³ , hypertension ³
Respiratory, and thoracic mediastinal disorders	uncommon	cough ³
	not known	cough ² , dyspnoea ^{2,5}
Gastrointestinal disorders	common	constipation ² , nausea ² , abdominal pain ^{2,3} , diarrhoea ³ , flatulence ³
	uncommon	dyspepsia ³ ; gastrooesophageal reflux disease ³ , nausea ³ , dry mouth ⁴ ; gastritis ⁴
	rare	pancreatitis ²
	not known	diarrhoea ² , pancreatitis ⁵ ; constipation ⁵
Hepatobiliary disorders	rare	increased hepatic transaminases ²
	very rare	jaundice ² , hepatitis ²
	not known	hepatitis ⁵ , cholelithiasis ⁵ , cholecystitis ⁵
Skin and subcutaneous tissue disorders	uncommon	pruritus ^{2, 4} , rash ^{2, 4} , urticaria ^{2,4}

not known Stevens Johnson syndrome², erythema

multiforme⁵, drug reaction with eosinophilia and systemic symptoms (DRESS)²

Musculoskeletal and connective tissue disorders common myalgia^{2, 4}
uncommon arthralgia³, muscle spasms³, neck pain³,

rare back pain⁴, muscular weakness⁴, pain in extremity⁴
myopathy (including myositis)², rhabdomyolysis² , lupus like syndrome,

muscle rupture
very rare

arthralgia²

CPK			
		not known	immune-mediated necrotising myopathy ² , tendon disorders, sometimes complicated by rupture ² , myalgia ⁵ , myopathy/rhabdomyolysis ⁵ (see section
	4.4)		
	Renal and urinary disorders	very rare	haematuria ²
	Reproductive system and breast gynaecomastia ² disorders		very rare
Investigations		common	ALT and/or AST increased ⁴
		uncommon	ALT and/or AST increased ³ , blood
			increased ³ , gamma-glutamyltransferase increased ³ , liver function test abnormal ³

General disorders and common asthenia², fatigue³
administration site conditions uncommon chest pain³, pain³, asthenia⁴, oedema peripheral⁴

not known oedema², asthenia⁵

1 Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/l, BMI > 30 kg/m², raised triglycerides, history of hypertension) – for rosuvastatin.

2 Adverse reaction profile for rosuvastatin based on data from reported clinical studies and/or extensive post-marketing experience.

3 Ezetimibe in monotherapy. Adverse reactions have been reported in patients treated with ezetimibe and at a greater incidence than placebo.

4 Ezetimibe co administered with a statin. Adverse reactions have been reported in patients with ezetimibe co-administered with a statin and at a greater incidence than statin administered alone. 5 Additional adverse reactions of ezetimibe, reported in post-marketing experience (with or without statin).

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 reported in patients treated with rosuvastatin. Shifts in urine protein from none or trace to ++ or more have been reported 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 +) has been reported with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from reported clinical studies and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been reported in patients treated with rosuvastatin and reported 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 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 reported in patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5xULN), treatment should be discontinued (see **section 4.4**).

Liver effects

As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been reported in a small number of patients taking rosuvastatin; the majority of cases have been reported to be mild, asymptomatic and transient.

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.

The following adverse events have been reported with some statins:

- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy (see **section 4.4**)

Laboratory values

The incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) has been reported to be similar between ezetimibe (0.5%) and placebo (0.3%). The incidence has been reported to be 1.3% for patients treated with ezetimibe co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations have been reported to be generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see **section 4.4**).

CPK > 10 X ULN has been reported for 0.2% patients administered ezetimibe alone vs 0.1% patients administered placebo, and for 0.1% patients co-administered ezetimibe and a statin vs 0.4% patients administered a statin alone. No excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone) has been reported (see **section 4.4**).

Paediatric population

The safety and efficacy of ezetimibe/rosuvastatin in children below the age of 18 years have not yet been reported.

- Rosuvastatin:

Creatine kinase elevations >10xULN and muscle symptoms following exercise or increased physical activity have been reported more frequently in children and adolescents compared to adults. In other respects, the safety profile of rosuvastatin has been reported to be similar in children and adolescents compared to adults.

- Ezetimibe:

Elevations of ALT and/or AST (≥ 3 X ULN, consecutive) have been reported in 1.1% of the ezetimibe treated pediatric patients (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia.

No elevations of CPK ($\geq 10X$ ULN) have been reported. No cases of myopathy have been reported.

Elevations of ALT and/or AST ($\geq 3X$ ULN, consecutive) have been reported in 3% of the ezetimibe/simvastatin adolescent patients (10 to 17 years of age) with heterozygous familial hypercholesterolaemia compared to 2% (2 patients) in the simvastatin monotherapy group; these figures have been reported to be 2% and 0% for elevation of CPK ($\geq 10X$ ULN). No cases of myopathy have been reported.

These reported studies were not suited for comparison of rare adverse drug reactions.

Reporting of Adverse Effects

“Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board PvERS portal:<https://pv.pharmacyboardkenya.org>”

4.9 Overdose

In the event of an overdose, symptomatic and supportive measures should be employed.

Ezetimibe

In reported studies, administration of ezetimibe, 50 mg/day, to healthy subjects for up to 14 days, or 40 mg/day to patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. No toxicity has been reported after single oral doses of 5,000 mg/kg of ezetimibe in rats and mice and 3,000 mg/kg in dogs. A few cases of overdosage with ezetimibe have been reported: most have not been associated with adverse experiences.

Reported adverse experiences have not been serious.

Rosuvastatin

Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors in combination with other lipid modifying agents, rosuvastatin and ezetimibe
ATC code: C10BA06

Mechanism of action

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. **Rozavel EZ** contains rosuvastatin and ezetimibe, two lipid-lowering compounds with complementary mechanisms of action. Ezetimibe/rosuvastatin reduces elevated total cholesterol (total-C), LDL-C, apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increases high-density lipoprotein cholesterol (HDL-C) through dual inhibition of cholesterol synthesis and absorption.

Ezetimibe

Mechanism of action

Ezetimibe inhibits 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 (e.g. statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). 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 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 study in hypercholesterolaemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.

Pharmacodynamic effects

Ezetimibe has been reported to inhibit 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.

Cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

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.

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. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see **Table 2**). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 2: Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)

Dose	LDL-C	Total-C	HDL-C	TG	nonHDL-C	ApoB	ApoA-I
Placebo	-7	-5	3	-3	-7	-3	0
5	-45	-33	13	-35	-44	-38	4

10	-52	-36	14	-10	-48	-42	4
20	-55	-40	8	-23	-51	-46	5
40	-63	-46	10	-28	-60	-54	0

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

5.2 Pharmacokinetics properties

There is no substantial pharmacokinetic interaction between the two components of this fixed-dose preparation.

Mean AUC and C_{max} values for total rosuvastatin and ezetimibe were not reportedly different between the monotherapy and coadministration groups of rosuvastatin 10 mg and ezetimibe 10 mg. **Absorption**

Ezetimibe

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically-active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) have been reported to 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 when administered as ezetimibe 10-mg tablets. Ezetimibe can be administered with or without food.

Rosuvastatin

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

Distribution

Ezetimibe

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

Rosuvastatin

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 reported to be approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Biotransformation

Ezetimibe

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 reported 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 reported to be approximately 22 hours.

Rosuvastatin

Rosuvastatin undergoes limited metabolism (approximately 10%). Rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites reported 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

Ezetimibe

Following oral administration of ¹⁴C-ezetimibe (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 has been reported to be recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, no detectable levels of radioactivity have been reported in the plasma.

Rosuvastatin

Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is reported to be approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is reported to be approximately 50 litres/hour (coefficient of variation 21.7%). As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

Linearity

Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Special populations

Hepatic impairment

- Ezetimibe

After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe has been reported to increase approximately 1.7-fold in patients with mild hepatic impairment (Child Pugh score 5 or 6), compared to healthy subjects. In a reported 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, ezetimibe is not recommended in these patients (see **section 4.4**).

- Rosuvastatin

In a reported study with subjects with varying degrees of hepatic impairment, there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2fold compared to subjects with lower Child-Pugh scores. There is no reported experience in subjects with Child-Pugh scores above 9.

Renal impairment

- Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (mean CrCl 30 ml/min/1.73m²), the mean AUC for total ezetimibe has been reported to increase approximately 1.5-fold, compared to healthy subjects. This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

An additional patient in this reported study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

- Rosuvastatin

In a reported study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (CrCl < 30 ml/min) reportedly 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 subjects undergoing haemodialysis have been reported to be approximately 50% greater compared to healthy volunteers.

Age and gender

- Ezetimibe

Plasma concentrations for total ezetimibe are reported to be about 2 - fold higher in the elderly (65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are reported to be comparable between elderly and young subjects treated with ezetimibe. Therefore, no dosage adjustment is necessary in the elderly.

Plasma concentrations for total ezetimibe are slightly higher (approximately 20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

- Rosuvastatin

No clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin has been reported in adults.

Paediatric population

- Ezetimibe

The pharmacokinetics of ezetimibe are reported to be similar between children ≥6 years and adults. There are no reported data in paediatric population < 6 years of age. Clinical experience in paediatric and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

- Rosuvastatin

Exposure in paediatric patients with heterozygous familial hypercholesterolaemia 10-17 or 6-17 years of age has been reported to be

comparable to or lower than that in adult patients. Rosuvastatin exposure has been reported to be predictable with respect to dose and time over a 2-year period.

Race

- Rosuvastatin

Approximately 2-fold elevation in median AUC and $C_{\max}$ has been reported in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians. Asian-Indians show an approximate 1.3-fold elevation in median AUC and $C_{\max}$. No clinically relevant differences in pharmacokinetics have been reported between Caucasian and Black groups.

Genetic polymorphisms

- Rosuvastatin

Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with a higher rosuvastatin exposure (AUC) compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes. This specific genotyping is not established in clinical practice, but for patients who are known to have these types of polymorphisms, a lower daily dose of rosuvastatin is recommended.

5.3 Preclinical safety data

In reported co-administration studies with statins and ezetimibe, the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects have been reported to be more pronounced than those reported during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in co-administration therapy. No such interactions have been reported in the clinical studies. Myopathies have been reported 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).

The co-administration of statins and ezetimibe has been reported to be non-teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) have been reported.

In a series of reported *in vivo* and *in vitro* assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential.

Ezetimibe

The reported animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (0.03 mg/kg/day) the cholesterol concentration in the cystic bile has been reported to increase by a factor of 2.5 to 3.5. No increased incidence of cholelithiasis or other hepatobiliary effects have been reported in dogs given up to 300 mg/kg/day of ezetimibe for 1 year. The significance of these reported data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

Long-term carcinogenicity tests on ezetimibe have been reported to be negative.

Ezetimibe reportedly had no effect on the fertility of male or female rats, nor was it reported 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.

Rosuvastatin

Preclinical data reveal no special hazard for humans based on reported conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been reported.

Adverse reactions not reported in clinical studies, but reported in animals at exposure levels similar to clinical exposure levels were as follows: In reported 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 has been reported in monkeys and dogs at higher dosages. Reproductive toxicity has been reported 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Povidone
Pregelatinised starch
Sodium lauryl sulphate
Sodium starch glycolate

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C, Protected from moisture. Keep all medicine out of the reach of children.

6.5 Nature and contents of container

Each blister contains 10's tablets

6.6 Special precautions for disposal and other handling

Not Applicable

7. MARKETING AUTHORISATION HOLDER

Manufactured by:

Sun Pharmaceutical Industries Limited,
Industrial Area no.3, A.B. Road,
Dewas-455001, Madhya Pradesh,
India.

Marketing Authorisation Holder

Sun Pharmaceutical Industries Limited,
Sun House, Plot 201 B/1, Western Express
High way, Goregaon (E), Mumbai- 400 063,
India

8. MARKETING AUTHORISATION NUMBER(S)

Rozavel EZ 10/10 mg tablet: H2026/CTD12780/27307

Rozavel EZ 10/10 mg tablet: H2026/CTD12825/27311

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/02/2026

10. DATE OF REVISION OF THE TEXT

2030