Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Roseday EZ
Rosuvastatin 20 mg and Ezetimibe 10 mg Tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains:
Rosuvastatin Calcium BP eq. to Rosuvastatin 20 mg
Ezetimibe USP 10 mg
Excipients: q.s.

Excipients of known effect: Lactose.
For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablets (oral tablets).

4. Clinical particulars

4.1 Therapeutic indications

• As an adjunct to diet in patients with primary non-familial hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).
• Alone or as an adjunct to other LDL-C-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.

4.2 Posology and method of administration

Posology

Rosuvastatin and Ezetimibe Tablets are indicated in adult patients adequately controlled with separately administered monocomponent preparations of the same doses as the recommended combination. The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with Rosuvastatin and Ezetimibe Tablets.
The recommended daily dose is one tablet of the given strength with or without food.
Rosuvastatin and Ezetimibe Tablets are 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.
Co-administration with bile acid sequestrants
Rosuvastatin and Ezetimibe Tablets should be taken either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.
Paediatric population
The safety and efficacy of Rosuvastatin and Ezetimibe Tablets in children below the age of 18 years have not yet been established.
Elderly
A start dose of 5 mg rosuvastatin is recommended in patients ≥ 70 years. The combination is not suitable for initial therapy. Treatment initiation

or dose adjustment, if necessary, should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Renal impairment

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

The recommended start dose is rosuvastatin 5 mg in patients with moderate renal impairment (creatinine clearance < 60 mL/min). The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.

The use of rosuvastatin in patients with severe renal impairment is contraindicated for all doses.

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (Child Pugh score 5 to 6). Treatment with Rosuvastatin and Ezetimibe Tablets is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction.

Rosuvastatin and Ezetimibe Tablets is contraindicated in patients with active liver disease.

Race

Increased systemic exposure of rosuvastatin has been seen in Asian subjects.

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.

Genetic polymorphisms

Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure. For patients who are known to have such specific types of polymorphisms, a lower daily dose of Rosuvastatin and Ezetimibe Tablets is recommended.

Dosage in patients with pre-disposing factors to myopathy

The recommended start dose is rosuvastatin 5 mg in patients with predisposing factors to myopathy. The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.

Concomitant therapy

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when Rosuvastatin and Ezetimibe Tablets are 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).

Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing Rosuvastatin and Ezetimibe Tablets therapy. In situations where co-administration of these medicinal products with Rosuvastatin and Ezetimibe Tablets is

unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered.

Method of administration
For oral use.
Rosuvastatin and Ezetimibe Tablets should be taken each day once at the same time of the day with or without food.
The tablet should be swallowed whole with a drink of water.

4.3 Contraindications
Rosuvastatin and Ezetimibe Tablets is contraindicated in patients with:
• Acute liver failure or decompensated cirrhosis.
• Hypersensitivity to rosuvastatin, ezetimibe, or any excipients in Rosuvastatin and Ezetimibe Tablets. Hypersensitivity reactions including anaphylaxis, angioedema, and erythema multiforme have been reported.

4.4 Special warnings and precautions for use
Myopathy and Rhabdomyolysis
Rosuvastatin and Ezetimibe Tablets may cause myopathy (muscle pain, tenderness, or weakness with creatine kinase [CK] above ten times the upper limit of normal) and rhabdomyolysis. Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis with statins, including rosuvastatin.
Risk Factors for Myopathy
Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs including other lipid-lowering therapies, and higher Rosuvastatin and Ezetimibe Tablets dosage; Asian patients on Rosuvastatin and Ezetimibe Tablets may be at higher risk for myopathy. The myopathy risk is greater in patients taking Rosuvastatin and Ezetimibe Tablets daily compared with lower Rosuvastatin and Ezetimibe Tablets dosages.
Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis
The concomitant use of Rosuvastatin and Ezetimibe Tablets with cyclosporine or gemfibrozil is not recommended. Rosuvastatin and Ezetimibe Tablets dosage modifications are recommended for patients taking certain antiviral medications, darolutamide, and regorafenib. Niacin, fibrates, and colchicine may also increase the risk of myopathy and rhabdomyolysis.
Discontinue Rosuvastatin and Ezetimibe Tablets if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Muscle symptoms and CK increases may resolve if Rosuvastatin and Ezetimibe Tablets is discontinued. Temporarily discontinue Rosuvastatin and Ezetimibe Tablets in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis, e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.
Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the Rosuvastatin and Ezetimibe Tablets dosage.

Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary.

Treatment with immunosuppressive agents may be required. 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

Increases in serum transaminases have occurred with rosuvastatin. In most cases, the elevations appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or improved on continued therapy or after a brief interruption in therapy. In a pooled analysis of placebo-controlled trials, increases in serum transaminases to more than three times the ULN occurred in 1.1% of patients taking rosuvastatin versus 0.5% of patients treated with placebo. Marked persistent increases of hepatic transaminases have also occurred with rosuvastatin. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including rosuvastatin.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury.

Consider liver enzyme testing before Rosuvastatin and Ezetimibe Tablets initiation and thereafter, when clinically indicated.

Rosuvastatin and Ezetimibe Tablets is contraindicated in patients with acute liver failure or decompensated cirrhosis. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue Rosuvastatin and Ezetimibe Tablets.

Proteinuria and Hematuria

In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin treated patients. These findings were more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, consider a dose reduction for patients on Rosuvastatin and Ezetimibe Tablets 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. Based on clinical trial data with rosuvastatin, in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus. Optimize lifestyle measures,

including regular exercise, maintaining a healthy body weight, and making healthy food choices.

4.5 Interaction with other medicinal products and other forms of interaction

Ciclosporin:

During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers. Concomitant administration did not affect plasma concentrations of ciclosporin.

Co-administration of Rosuvastatin and Ezetimibe Tablets with ciclosporin is contraindicated.

In a study of eight 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 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n = 17). In a different 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 two-period crossover study in twelve 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. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted.

Not-recommended combinations

Protease inhibitors:

Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure. For instance, in a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir/100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin AUC and Cmax 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. 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.

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 and Ezetimibe Tablets with medicinal products that are inhibitors of these transporter proteins may

result in increased rosuvastatin plasma concentrations and an increased risk of myopathy.

Gemfibrozil and other lipid-lowering medicines:

Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC. Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur.

Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (≥ 1 g/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. These patients should also start with the 5 mg rosuvastatin dose.

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

Fusidic Acid:

Interaction studies with rosuvastatin and fusidic acid have not been conducted. 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.

Other interactions

Antacid:

The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%.

This effect was mitigated when the antacid was dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied.

Concomitant antacid administration decreased 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.

Erythromycin:

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy

Rosuvastatin:

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. Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of Rosuvastatin and Ezetimibe Tablets, treatment should be discontinued immediately.

Ezetimibe:

No clinical data are available on the use of ezetimibe during pregnancy.

Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development.

Breast-feeding

Rosuvastatin:

Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion of rosuvastatin in milk in humans.

Ezetimibe:

Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.

Fertility

No clinical trial data are available on the effects of ezetimibe on human fertility. Ezetimibe had no effect on the fertility of male or female rats.

4.7 Effects on ability to drive and use machines

Rosuvastatin and Ezetimibe Tablets has no or negligible influence on the ability to drive and use machines. Studies to determine the effect of rosuvastatin and/or ezetimibe on the ability to drive and use machines have not been conducted. However, when driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions seen with rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4% of rosuvastatin-treated patients were withdrawn due to adverse reactions.

In clinical studies of up to 112 weeks duration, ezetimibe 10 mg daily was administered alone in 2396 patients, or with a statin in 11308 patients

or with fenofibrate in 185 patients. Adverse reactions were usually mild and transient. The overall incidence of side effects was similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between ezetimibe and placebo.
According to available data 1200 patients took rosuvastatin and ezetimibe combination in clinical studies. As reported in the published literature, the most frequent common adverse events related to rosuvastatin-ezetimibe combination treatment in hypercholesterolemic patients are increased hepatic transaminases, gastrointestinal problems and muscle pain. These are known undesirable effects of the active substances. However, a pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

Tabulated list of adverse reactions

The frequencies of adverse events are ranked according to the following: Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); Not known (frequency cannot be estimated from the available data).

Superscript key: [1] frequency depends on presence/absence of risk factors (for rosuvastatin); [2] rosuvastatin; [3] ezetimibe (as monotherapy or co-administered with a statin).

MedDRA System Organ Class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Musculoskeletal and connective tissue disorders	myalgia[2], [3]	arthralgia[3], muscle spasms[3], neck pain[3], back pain[3], muscular weakness[3], pain in extremity[3]	myopathy (including myositis)[2], rhabdomyolysis[2], lupus-like syndrome[2], muscle rupture[2]	arthralgia[2]	immune-mediated necrotising myopathy[2], tendon disorders, sometimes complicated by rupture[2], myopathy/rhabdomyolysis[3] (see section 4.4)
Renal and urinary disorders				haematuria[2]	
Reproductive system and breast disorders				gynaecomastia[2]	
General disorders and administration site conditions	asthenia[2], fatigue[3]	chest pain[3], pain[3], asthenia[2], oedema peripheral[3]			oedema[2]
Investigations	ALT and/or AST increased[1]	blood CPK increased[3], gamma-glutamyltransferase increased[3], liver function			

		test abnormal[3]			
Blood and lymphatic system disorders			thrombocytopenia[2]		thrombocytopenia[3]
Immune system disorders			hypersensitivity reactions including angioedema[2]		hypersensitivity, including rash, urticaria, anaphylaxis and angioedema[3]
Endocrine disorders	diabetes mellitus[1],[2]				
Metabolism and nutrition disorders		decreased appetite[3]			
Psychiatric disorders					depression[2],[3]
Nervous system disorders	headache[2],[3], dizziness[2]	paraesthesia[3]		polyneuropathy[2], memory loss[2]	peripheral neuropathy[2], sleep disturbances (including insomnia and nightmares)[2], dizziness[3], myasthenia gravis
Eye disorders					ocular myasthenia
Vascular disorders		hot flush[3], hypertension[3]			
Respiratory, thoracic and mediastinal disorders		cough[3]			cough[2], dyspnoea[2],[3]
Gastrointestinal disorders	constipation[2], nausea[2], abdominal pain[2],[3], diarrhoea[3], flatulence[3]	dyspepsia[3], gastrooesophageal reflux disease[3], nausea[3], dry mouth[3], gastritis[3]	pancreatitis[2]		diarrhoea[3], pancreatitis[3], constipation[3]
Hepatobiliary disorders			increased hepatic transaminases[2]	jaundice[2], hepatitis[2]	hepatitis[3], cholelithiasis[3], cholecystitis[3]
Skin and subcutaneous tissue disorders	pruritus[2],[3], rash[2],[3], urticaria[2],[3]				Stevens-Johnson syndrome[2], drug reaction with eosinophilia and systemic symptoms (DRESS)[2],

					erythema multiforme[3]

Description of selected adverse reactions

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

Adverse reactions observed in clinical studies of ezetimibe (as a monotherapy or co-administered with a statin) or ezetimibe reported from post-marketing use either administered alone or with a statin. Adverse reactions were observed in patients treated with ezetimibe (n = 2396) and at a greater incidence than placebo (n = 1159) or in patients treated with ezetimibe co-administered with a statin (n = 11308) and at a greater incidence than statin administered alone (n = 9361). Post-marketing adverse reactions were derived from reports containing ezetimibe either administered alone or with a statin.

Renal effects:

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in ≤ 1% of patients at some time during treatment with 10 mg and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy.

Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been observed in patients treated with rosuvastatin and clinical trial 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 in rosuvastatin-treated patients with all doses and in particular with doses > 20 mg.

A dose-related increase in CK levels has been observed in patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK-levels are elevated (> 5 × ULN), the treatment should be discontinued.

Liver Effects:

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

The following adverse events have been reported with some statins:

• Sexual dysfunction

• Exceptional cases of interstitial lung disease, especially with long term therapy

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) are higher at the 40 mg rosuvastatin dose.

Paediatric population

The safety and efficacy of Rosuvastatin and Ezetimibe Tablets in children below the age of 18 years have not yet been established.

Rosuvastatin:

Creatine kinase elevations > 10 × ULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of children and adolescents compared to adults. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

Ezetimibe:

Paediatric (6 to 17 years of age) patients

In a study involving paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia (n = 138), elevations of ALT and/or AST (≥ 3 × ULN, consecutive) were observed in 1.1% (1 patient) of the ezetimibe patients compared to 0% in the placebo group. There were no elevations of CPK (≥ 10 × ULN). No cases of myopathy were reported.

In a separate study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n = 248), elevations of ALT and/or AST (≥ 3 × ULN, consecutive) were observed in 3% (4 patients) of the ezetimibe/simvastatin patients compared to 2% (2 patients) in the simvastatin monotherapy group; these figures were respectively 2% (2 patients) and 0% for elevation of CPK (≥ 10 × ULN). No cases of myopathy were reported.

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

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

4.9 Overdose

There is no published literature data on rosuvastatin overdose.

There is no specific treatment in the event of overdose with rosuvastatin. In clinical studies, administration of ezetimibe, 50 mg/day, to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. In animals, no toxicity was observed after single oral doses of 5000 mg/kg of ezetimibe in rats and mice and 3000 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.

In the event of an overdose, symptomatic and supportive measures should be employed. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents; HMG CoA reductase inhibitors in combination with other lipid modifying agents.
ATC code: C10BA06

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 below). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

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

Dose	**N**	**LDL-C**	**Total-C**	**HDL-C**	**TG**	**Non HDL-C**	**ApoB**	**ApoA-I**
Placebo	13	-7	-5	3	-3	-7	-3	0
5 mg	17	-45	-33	13	-35	-44	-38	4
10 mg	17	-52	-36	14	-10	-48	-42	4
20 mg	17	-55	-40	8	-23	-51	-46	5
40 mg	17	-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.

Ezetimibe

Mechanism of action

Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe is orally active and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (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 2-week clinical study in 18 hypercholesterolaemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.

Pharmacodynamic effects

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [14C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat-soluble vitamins A and D.

Epidemiologic studies have established that 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-ezetimibe co-administration

Clinical efficacy and safety

A 6-week, randomized, double-blind, parallel-group, clinical trial evaluated the safety and efficacy of ezetimibe (10 mg) added to stable rosuvastatin therapy versus up-titration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg (n = 440). Pooled data demonstrated that ezetimibe added to stable rosuvastatin 5 mg or 10 mg reduced LDL cholesterol by 21%. In contrast, doubling rosuvastatin to 10 mg or 20 mg reduced LDL cholesterol by 5.7% (between-group difference of 15.2%, $p < 0.001$). Individually, ezetimibe plus rosuvastatin 5 mg reduced LDL cholesterol more than did rosuvastatin 10 mg (12.3% difference, $p < 0.001$), and ezetimibe plus rosuvastatin 10 mg reduced LDL cholesterol more than did rosuvastatin 20 mg (17.5% difference, $p < 0.001$).

A 6-week, randomized study was designed to investigate the efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg in patients at high risk of coronary heart disease (n = 469).

Significantly more patients receiving rosuvastatin/ezetimibe than rosuvastatin alone achieved their ATP III LDL cholesterol goal (< 100 mg/dL, 94.0% vs 79.1%, $p < 0.001$). Rosuvastatin 40 mg was effective at improving the atherogenic lipid profile in this high-risk population.

A randomized, open-label, 12-week study investigated the level of LDL reduction in each treatment arm (rosuvastatin 10 mg plus ezetimibe 10 mg, rosuvastatin 20 mg/ezetimibe 10 mg, simvastatin 40 mg/ezetimibe 10 mg, simvastatin 80 mg/ezetimibe 10 mg). The reduction from baseline with the low dose rosuvastatin combinations was 59.7%, significantly superior to the low dose simvastatin combinations, 55.2% ($p < 0.05$). Treatment with the high-dose rosuvastatin combination reduced LDL cholesterol 63.5% compared with a reduction of 57.4% with the high-dose simvastatin combination ($p < 0.001$).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Rosuvastatin and Ezetimibe Tablets in all subsets of the paediatric population in the treatment of elevated cholesterol.

5.2 Pharmacokinetic properties

Rosuvastatin and ezetimibe combination therapy

Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

Rosuvastatin

Absorption:

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

Distribution:

Rosuvastatin is taken up extensively by the liver, which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L.

Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Biotransformation:

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

Elimination:

Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (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 approximately 19 hours. The elimination half-life does not increase at higher doses.

The geometric mean plasma clearance is 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

Age and sex:

There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The exposure in children and adolescents with heterozygous familial hypercholesterolaemia appears to

be similar to or lower than that in adult patients with dyslipidaemia (see "Paediatric population" below).

Race:

Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and Cmax 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 Cmax.

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal impairment:

In a 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 (CLcr < 30 mL/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

Hepatic impairment:

In a 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, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

Genetic polymorphisms:

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 and Ezetimibe Tablets is recommended.

Paediatric population:

Two pharmacokinetic studies with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolaemia 10-17 or 6-17 years of age (total of 214 patients) demonstrated that exposure in paediatric patients appears comparable to or lower than that in adult patients. Rosuvastatin exposure was predictable with respect to dose and time over a 2-year period.

Ezetimibe

Absorption:

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically-active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (Cmax)

occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe.
The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.
Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe. Ezetimibe can be administered with or without food.
Distribution:
Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.
Biotransformation:
Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed 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 approximately 22 hours.
Elimination:
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 were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Special populations

Age and sex:
Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are 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.
Renal impairment:
After a single 10 mg dose of ezetimibe in patients with severe renal disease (n = 8; mean CLcr = 30 mL/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n = 9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.
An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.
Hepatic impairment:

After a single 10 mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score > 9) hepatic impairment, Rosuvastatin and Ezetimibe Tablets are not recommended in these patients.

Paediatric population:

The pharmacokinetics of ezetimibe are similar between children ≥ 6 years and adults. Pharmacokinetic data in the paediatric population < 6 years of age are not available. Clinical experience in paediatric and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

5.3 Preclinical safety data

In co-administration studies with ezetimibe and statins the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in co-administration therapy. No such interactions occurred in the clinical studies. Myopathies occurred 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 2000 times the AUC level for the active metabolites).

In a series of in vivo and in vitro assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential. Long-term carcinogenicity tests on ezetimibe were negative. The co-administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed.

Rosuvastatin:

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been evaluated. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels were as follows: in 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 was observed in monkeys and dogs at higher dosages. Reproductive toxicity was evident 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.

Ezetimibe:

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 was increased by a factor of 2.5 to 3.5. However, in a one-year study on dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed.
The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.
Ezetimibe had no effect on the fertility of male or female rats, nor was it found 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 1000 mg/kg/day. The co-administration of ezetimibe with lovastatin resulted in embryolethal effects.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose
Croscarmellose Sodium
Sodium Lauryl Sulphate
Microcrystalline Cellulose
Povidone (PVPK-30)
Polysorbate 80
Magnesium Stearate
Opadry 21K580031 White

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container

3 x 10 Alu-Alu Blister with Pack Insert in Unit Carton.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

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8. Marketing authorisation number
H2026/CTD11286/24784

9. Date of first authorisation/renewal of the authorisation
5th February, 2026

10. Date of revision of the text
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