For the use only of Registered Medical Practitioner

Rosuvastatin Calcium & Ezetimibe Tablets I.P.
FORTIUS® EZ 10

1. Generic Name and Brand Name
Rosuvastatin Calcium & Ezetimibe Tablets I.P.
Fortius® EZ 10

Rosuvastatin Calcium & Ezetimibe Tablets I.P.
Fortius® EZ 20

Rosuvastatin Calcium & Ezetimibe Tablets I.P.
Fortius® EZ 40

2. Qualitative and Quantitative Composition:
Fortius EZ® 10
Each film coated tablet contains:
Rosuvastatin Calcium I.P.
Eq. to Rosuvastatin……10 mg
Ezetimibe I.P……..10 mg
Excipients……q.s.
Colour: Titanium Dioxide I.P.

Fortius EZ® 20
Each film coated tablet contains:
Rosuvastatin Calcium I.P.
Eq. to Rosuvastatin……20 mg
Ezetimibe I.P……10 mg
Excipients……...q.s.
Colours: Sunset Yellow FCF Lake &Titanium Dioxide I.P.

Fortius EZ® 40
Each film coated tablet contains:
Rosuvastatin Calcium I.P.
Eq. to Rosuvastatin……...40 mg
Ezetimibe I.P……10 mg
Excipients……..q.s.
Colours: Ferric Oxide USP-NF Yellow &Titanium Dioxide I.P.

3. Dosage Form & strength
Refer section 1 & 2

4. Clinical particulars

4.1 Therapeutic indication
For the treatment of patients with primary hypercholesterolemia.

4.2 Posology and method of administration
Posology
The recommended dosage range is one tablet (containing 5 mg to 40 mg of rosuvastatin and 10 mg of ezetimibe) orally once daily.

Method of Administration:
- Swallow Rosuvastatin Calcium & Ezetimibe Tablets whole at any time of day, with or without food. Do not crush, dissolve, or chew tablets.
- The recommended dose of Rosuvastatin Calcium & Ezetimibe Tablets depends on a patient's indication for usage, LDL- C, and individual risk for cardiovascular events.
- The starting dosage for patients switching to Rosuvastatin Calcium & Ezetimibe Tablets from co-administration of a statin and Ezetimibe is based on an equivalent dose of Rosuvastatin and 10 mg of Ezetimibe.
- Assess LDL-C when clinically appropriate, as early as 2 weeks after initiating Rosuvastatin Calcium & Ezetimibe Tablets and adjust the dosage if necessary.
- If a dose is missed, advise patients not to take an extra dose. Resume treatment with the next dose.

Recommended Dosage in Asian Patients
Initiate Rosuvastatin Calcium & Ezetimibe Tablets at 5 mg/10 mg daily due to increased Rosuvastatin plasma concentrations. Consider the risk/benefit when treating Asian patients not adequately controlled at doses up to 20 mg/10 mg once daily.

Recommended Dosage in Patients with Renal Impairment
In patients with severe renal impairment (CL_{cr} less than 30 mL/min/1.73 m^2) not on haemodialysis, the recommended starting dosage is 5 mg/10 mg once daily and should not exceed 10 mg/10 mg once daily.
There are no dosage adjustment recommendations for patients with mild and moderate renal impairment.

Dosage and Administration Modifications Due to Drug Interactions
- In patients taking a bile acid sequestrant, administer Rosuvastatin Calcium & Ezetimibe Tablets at least 2 hours before or 4 hours after the bile acid sequestrant.
- When taking Rosuvastatin Calcium & Ezetimibe Tablets with an aluminium and magnesium hydroxide combination antacid, administer Rosuvastatin Calcium & Ezetimibe Tablets at least 2 hours before the antacid.

- Concomitant use of Rosuvastatin Calcium & Ezetimibe Tablets with the following drugs requires dosage modifications of Rosuvastatin Calcium & Ezetimibe Tablets.

  Darolutamide

  Do not exceed Rosuvastatin Calcium & Ezetimibe Tablets 5 mg/10 mg once daily.

  Regorafenib

  Do not exceed Rosuvastatin Calcium & Ezetimibe Tablets 10 mg/10 mg once daily.

  Antiviral Medications

  Concomitant use of Sofosbuvir/Velpatasvir/Voxilaprevir and ledipasvir/sofosbuvir with Rosuvastatin Calcium & Ezetimibe Tablets is not recommended.

  In patients taking Simeprevir, Dasabuvir/Ombitasvir/Paritaprevir/ritonavir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, Glecaprevir/Pibrentasvir, atazanavir/ritonavir, and lopinavir/ritonavir initiate Rosuvastatin Calcium & Ezetimibe Tablets at 5 mg/10 mg once daily.

  Do not exceed Rosuvastatin Calcium & Ezetimibe Tablets 10 mg/10 mg once daily.

  No dose adjustment is needed for concomitant use with Fosamprenavir/ritonavir or tipranavir/ritonavir.

4.3 Contraindications

Rosuvastatin Calcium & Ezetimibe Tablets are contraindicated in patients with:

- Acute liver failure or decompensated cirrhosis.
- Hypersensitivity to Rosuvastatin, Ezetimibe, or any excipients in Rosuvastatin Calcium & 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 Calcium & 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 Calcium & Ezetimibe Tablets dosage; Asian patients on Rosuvastatin Calcium & Ezetimibe Tablets may be at higher risk for myopathy. The myopathy risk is greater in patients taking Rosuvastatin Calcium & Ezetimibe Tablets 40 mg/10 mg daily compared with lower Rosuvastatin Calcium & Ezetimibe Tablet dosages.

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

The concomitant use of Rosuvastatin Calcium & Ezetimibe Tablets with cyclosporine or gemfibrozil is not recommended. Rosuvastatin Calcium & Ezetimibe 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 Calcium & Ezetimibe Tablets if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Muscle symptoms and CK increases may resolve if Rosuvastatin Calcium & Ezetimibe Tablets is discontinued. Temporarily discontinue Rosuvastatin Calcium & 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 Calcium & 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 Calcium & Ezetimibe Tablets initiation and thereafter, when clinically indicated. Rosuvastatin Calcium & 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 Calcium & Ezetimibe Tablets.

Proteinuria and Haematuria

In the Rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic haematuria 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 Calcium & Ezetimibe Tablets therapy with unexplained persistent proteinuria and/or haematuria 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 Drug Interactions

Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with Rosuvastatin Calcium & Ezetimibe Tablets

Rosuvastatin is a substrate of CYP2C9 and transporters (such as OATP1B1, BCRP). Rosuvastatin plasma levels can be significantly increased with concomitant administration of inhibitors of CYP2C9 and transporters. Table 1 includes a list of drugs that increase the risk of myopathy and rhabdomyolysis when used concomitantly with Rosuvastatin Calcium & Ezetimibe Tablets and instructions for preventing or managing them.

Table 1: Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with Rosuvastatin Calcium & Ezetimibe Tablets

Cyclosporine or Gemfibrozil	
Clinical Impact:	Cyclosporine increased Rosuvastatin exposure 7-fold. In addition, Ezetimibe and cyclosporine used concomitantly can increase exposure to both Ezetimibe and cyclosporine. Gemfibrozil significantly increased Rosuvastatin exposure and gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with Rosuvastatin Calcium & Ezetimibe Tablets.
Intervention:	Avoid concomitant use of cyclosporine or gemfibrozil with Rosuvastatin Calcium & Ezetimibe Tablets.
Anti-Viral Medications	

Clinical Impact:	Rosuvastatin plasma levels were significantly increased with concomitant administration of many anti-viral drugs, which increases the risk of myopathy and rhabdomyolysis.
Intervention:	Avoid concomitant use of sofosbuvir/velpatasvir/voxilaprevir and ledipasvir/sofosbuvir with Rosuvastatin Calcium & Ezetimibe Tablets. In patients taking simeprevir, dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, atazanavir/ritonavir, and lopinavir/ritonavir initiate with a dose of Rosuvastatin Calcium & Ezetimibe Tablets 5 mg/10mg once daily, and do not exceed a dose of Rosuvastatin Calcium & Ezetimibe Tablets 10 mg/10 mg once daily. No dose adjustment is needed for concomitant use with fosamprenavir/ritonavir or tipranavir/ritonavir. Monitor all patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward titration of either drug.
Darolutamide	
Clinical Impact:	Darolutamide increased Rosuvastatin exposure more than 5-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.
Intervention:	In patients taking darolutamide, do not exceed a dose of Rosuvastatin Calcium & Ezetimibe Tablets 5 mg/10 mg once daily.
Regorafenib	
Clinical Impact:	Regorafenib increased Rosuvastatin exposure and may increase the risk of myopathy.
Intervention:	In patients taking regorafenib, do not exceed a dose of Rosuvastatin Calcium & Ezetimibe Tablets 10 mg/10 mg once daily.
Fenofibrates (e.g., fenofibrate and fenofibric acid)	
Clinical Impact:	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with Rosuvastatin Calcium & Ezetimibe Tablets.
Intervention:	Consider if the benefit of using fibrates concomitantly with Rosuvastatin Calcium & Ezetimibe Tablets outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.
Niacin	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have occurred with concomitant use of niacin with Rosuvastatin.
Intervention:	Consider if the benefit of using niacin concomitantly with Rosuvastatin Calcium & Ezetimibe Tablets outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.
Colchicine	

Clinical Impact:	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with Rosuvastatin Calcium & Ezetimibe Tablets
Intervention:	Consider if the benefit of using colchicine concomitantly with Rosuvastatin Calcium & Ezetimibe Tablets outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.

Drug Interactions that Decrease the Efficacy of Rosuvastatin Calcium & Ezetimibe Tablets

Table 2 presents drug interactions that may decrease the efficacy of Rosuvastatin Calcium & Ezetimibe Tablets and instructions for preventing or managing them.

Table 2: Drug Interactions that Decrease the Efficacy of Rosuvastatin Calcium & Ezetimibe Tablets

Bile Acid Sequestrants	
Clinical Impact:	Concomitant cholestyramine administration decreased the mean exposure of total Ezetimibe by approximately 55%. The incremental LDL-C reduction due to adding Ezetimibe may be attenuated by coadministration with cholestyramine.
Intervention:	In patients taking a bile acid sequestrant, administer Rosuvastatin Calcium & Ezetimibe Tablets at least 2 hours before or at least 4 hours after the bile acid sequestrant.
Antacid	
Clinical Impact:	Concomitant aluminum and magnesium hydroxide combination antacid administration decreased the mean exposure of Rosuvastatin 50% and total Ezetimibe 4%. The incremental LDL-C reduction due to adding Rosuvastatin Calcium & Ezetimibe Tablets may be attenuated by coadministration with antacid.
Intervention:	In patients taking antacid, administer Rosuvastatin Calcium & Ezetimibe Tablets 2 hours after the antacid.

Rosuvastatin Calcium & Ezetimibe Tablets Effects on Other Drugs

Table 3 presents Rosuvastatin Calcium & Ezetimibe Tablets effect on other drugs and instructions for preventing or managing them.

Table 3: Rosuvastatin Calcium & Ezetimibe Tablets Effects on Other Drugs

Warfarin	
Clinical Impact:	Rosuvastatin significantly increased the INR in patients receiving coumarin anticoagulants.
Intervention:	In patients taking warfarin, obtain an INR before starting Rosuvastatin Calcium & Ezetimibe Tablets and frequently enough after initiation, dose titration or discontinuation to ensure that no significant alteration in INR occurs. Once the INR is stable, monitor INR at regularly recommended intervals.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

Pregnancy

Risk Summary

Discontinue Rosuvastatin Calcium & Ezetimibe Tablets when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient. Rosuvastatin Calcium & Ezetimibe Tablets decrease synthesis of cholesterol and possibly other biologically active substances derived from cholesterol; therefore, Rosuvastatin Calcium & Ezetimibe Tablets may cause fetal harm when administered to pregnant patients based on the mechanism of action. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.

Available data from case series and prospective and retrospective observational cohort studies over decades of use with statins in pregnant women have not identified a drug-associated risk of major congenital malformations. Published data from prospective and retrospective observational cohort studies with Rosuvastatin use in pregnant women are insufficient to determine if there is a drug-associated risk of miscarriage. In animal reproduction studies, oral administration of Rosuvastatin to pregnant rats and rabbits during organogenesis at doses equivalent to the maximum recommended human dose (MRHD) of 40 mg/day resulted in no adverse developmental effects
There are insufficient data on Ezetimibe use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of Ezetimibe to pregnant rats and rabbits during organogenesis at doses 10 and 150 times, respectively, the MRHD resulted in no adverse developmental effects.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

A Medicaid cohort linkage study of 1152 statin-exposed pregnant women compared to 886,996 controls did not find a significant teratogenic effect from maternal use of statins in the first trimester of pregnancy, after adjusting for potential confounders – including maternal age, diabetes mellitus, hypertension, obesity, and alcohol and tobacco use – using propensity score-based methods. The relative risk of congenital malformations between the group with statin use and the

group with no statin use in the first trimester was 1.07 (95% confidence interval 0.85 to 1.37) after controlling for confounders, particularly pre-existing diabetes mellitus. There were also no statistically significant increases in any of the organ-specific malformations assessed after accounting for confounders. In the majority of pregnancies, statin treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. Study limitations include reliance on physician coding to define the presence of a malformation, lack of control for certain confounders such as body mass index, use of prescription dispensing as verification for the use of a statin, and lack of information on non-live births.

Animal Data

Rosuvastatin

Rosuvastatin administration did not indicate a teratogenic effect in rats at ≤25 mg/kg/day or in rabbits ≤3 mg/kg/day (doses equivalent to the MRHD of 40 mg/day based on AUC and body surface area, respectively).

In female rats given 5, 15 and 50 mg/kg/day before mating and continuing through to gestation day 7 resulted in decreased fetal body weight (female pups) and delayed ossification at 50 mg/kg/day (10 times the human exposure at the MRHD dose of 40 mg/day based on AUC).
In pregnant rats given 2, 10 and 50 mg/kg/day of Rosuvastatin from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred at 50 mg/kg/day (dose equivalent to 12 times the MRHD of 40 mg/day-based body surface area).

In pregnant rabbits given 0.3, 1, and 3 mg/kg/day of Rosuvastatin from gestation day 6 to day 18, decreased fetal viability and maternal mortality was observed at 3 mg/kg/day (dose equivalent to the MRHD of 40 mg/day based on body surface area).

Rosuvastatin crosses the placenta in rats and rabbits and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18.

Ezetimibe

In oral (gavage) embryo-fetal development studies of Ezetimibe conducted in rats (gestation days 6-15) and rabbits (gestation days 7-19), there was no evidence of maternal toxicity or embryo lethality at any dose tested (250, 500, 1000 mg/kg/day) at exposures equivalent to 10 and 150 times the clinical exposure, based on AUC, in rats and rabbits. In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 times the human exposure at 10 mg daily based on

$AUC_{0\text{-}24hr}$ for total Ezetimibe). In rabbits treated with Ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total Ezetimibe). The animal-to-human exposure multiple for total Ezetimibe at the no observed effect level was 6 times for rat and 134 times for rabbit. Fetal exposure to Ezetimibe (conjugated and unconjugated) was confirmed in subsequent placental transfer studies conducted using a maternal dose of 1000 mg/kg/day. The fetal maternal plasma exposure ratio (total Ezetimibe) was 1.5 for rats on gestation day 20 and 0.03 for rabbits on gestation day 22.
The effect of Ezetimibe on prenatal and postnatal development and maternal function was evaluated in pregnant rats at doses of 100, 300 or 1000 mg/kg/day (gestation day 6 through lactation day 21). No maternal toxicity or adverse developmental outcomes were observed up to and including the highest dose tested (17 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total Ezetimibe).

Multiple dose studies of Ezetimibe given in combination with statins in rats and rabbits during organogenesis resulted in higher Ezetimibe and statin exposures. Reproductive findings occurred at lower doses in combination therapy compared to monotherapy.

Lactation

Risk Summary

Limited data from case reports in published literature indicate that Rosuvastatin is present in human milk. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Statins, including Rosuvastatin Calcium & Ezetimibe, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol and may cause harm to the breastfed infant.

There is no information about the presence of Ezetimibe in human milk. Ezetimibe is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. There is no information about the effects of Ezetimibe on the breastfed infant or the effects of Ezetimibe on milk production.

Because of the potential for serious adverse reactions in a breastfed infant, based on the mechanism of action, advise patients that breastfeeding is not recommended during treatment with Rosuvastatin Calcium & Ezetimibe Tablets.

Data

Ezetimibe was present in the milk of lactating rats. The pup to maternal plasma ratio for total Ezetimibe was 0.5 on lactation day 12.

Pediatric Use
The safety and effectiveness of Rosuvastatin Calcium & Ezetimibe Tablets have not been established in pediatric patients.

Geriatric Use
Advanced age (≥65 years) is a risk factor for Rosuvastatin Calcium & Ezetimibe- associated myopathy and rhabdomyolysis. Dose selection for an elderly patient should be cautious, recognizing the greater frequency of decreased hepatic, renal, or cardiac function; of concomitant disease or other drug therapy; and the higher risk of myopathy. Monitor geriatric patients receiving Rosuvastatin Calcium & Ezetimibe Tablets for the increased risk of myopathy.

Rosuvastatin
Of the 10,275 patients in clinical studies with Rosuvastatin, 3159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older.

Ezetimibe
Of the 2396 patients who received Ezetimibe monotherapy in clinical studies, 669 (28%) were 65 and older, and 111 (5%) were 75 and older. Of the 11,308 patients who received Ezetimibe + statin in clinical studies, 3587 (32%) were 65 and older, and 924 (8%) were 75 and older. No overall differences in safety and effectiveness were observed between these patients and younger patients. In a multiple-dose study with Ezetimibe, plasma concentrations for Ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

Renal Impairment
Renal impairment is a risk factor for myopathy and rhabdomyolysis. Monitor patients with renal impairment for development of myopathy. In patients with severe renal impairment not on hemodialysis, the recommended starting dosage is 5 mg/10 mg daily and should not exceed 10 mg/10 mg daily.

Rosuvastatin
Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CL_{cr}≥30 mL/min/1.73 m^2). Exposure to Rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment (CL_{cr}<30 mL/min/1.73 m^2) who are not receiving hemodialysis.

Ezetimibe
In a trial of 9270 patients with moderate to severe renal impairment (6247 non-dialysis patients with median serum creatinine 2.5 mg/dL and median estimated glomerular filtration rate 25.6

mL/min/1.73 m^2, and 3023 dialysis patients), the incidence of serious adverse events, adverse events leading to discontinuation of study treatment, or adverse events of special interest (musculoskeletal adverse events, liver enzyme abnormalities, incident cancer) was similar between patients ever assigned to Ezetimibe 10 mg plus simvastatin 20 mg (n=4650) or placebo (n=4620) during a median follow-up of 4.9 years.

Hepatic Impairment
Rosuvastatin Calcium & Ezetimibe Tablets are contraindicated in patients with acute liver failure or decompensated cirrhosis.

Asian Population
Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to Rosuvastatin in Asian subjects when compared with Caucasian controls. Adjust the Rosuvastatin Calcium & Ezetimibe dosage in Asian patients.

4.7 Effects on ability to drive and use machines
Rosuvastatin
Pharmacological testing revealed no evidence of a sedative effect of Rosuvastatin. From the safety profile, Rosuvastatin is not expected to adversely affect the ability to drive or operate machinery.

Ezetimibe
No studies of the effects on the ability to drive and use of machines have been performed. However, certain side effects that have been reported with Rosuvastatin Calcium & Ezetimibe may affect some patients' ability to drive or operate machinery. Individual responses to Rosuvastatin Calcium & Ezetimibe Tablets may vary.

4.8 Undesirable effects
The following serious adverse reactions are discussed below:
- Myopathy and Rhabdomyolysis
- Hepatic Dysfunction

Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Rosuvastatin
In double-blind, controlled (placebo-or active-controlled) clinical trials of Rosuvastatin, 5394 patients with primary hyperlipidemia were treated for a duration of up to 12 weeks. Adverse

reactions reported in ≥2% of patients in placebo-controlled clinical studies and at a rate greater than placebo are shown in Table 4.

Table 4. Adverse Reactions Reported in ≥2% of Patients Treated with Rosuvastatin and Greater than Placebo in Placebo-Controlled Trials

Adverse Reactions	Placebo (N=382) %	Total Rosuvastatin 5 mg-40 mg (N=744) %
Headache	5.0	5.5
Nausea	3.1	3.4
Myalgia	1.3	2.8
Asthenia	2.6	2.7
Constipation	2.4	2.4

Other adverse reactions reported in clinical studies were abdominal pain, dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema), and pancreatitis.

In a double-blind, placebo-controlled trial with mean treatment duration of 1.7 years, 981 participants were treated with Rosuvastatin 40 mg (n=700) or placebo (n=281). The most common adverse reactions reported in ≥2% of patients and at a rate greater than placebo are shown in Table 5.

Table 5. Adverse Reactions Occurring in ≥2% of Patients Treated with Rosuvastatin and Greater than Placebo

Adverse Reactions	Placebo (N=281)%	Rosuvastatin 40 mg (N=700)%
Myalgia	12.1	12.7
Arthralgia	7.1	10.1
Headache	5.3	6.4
Dizziness	2.8	4.0
Increased CPK	0.7	2.6
Abdominal pain	1.8	2.4
ALT >3x ULN1	0.7	2.2

1 Frequency recorded as abnormal laboratory value.

In a double-blind, placebo-controlled trial with mean treatment duration of 2 years, 17,802 participants were treated with Rosuvastatin 20 mg (n=8901) or placebo (n=8901). There was a significantly higher frequency of diabetes mellitus reported in patients taking Rosuvastatin (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in Rosuvastatin-treated patients compared to placebo-treated patients. The number of patients with a HbA1c >6.5% at the end of the trial was significantly higher in Rosuvastatin-treated versus placebo-treated patients.

Laboratory Tests

The following laboratory abnormalities have been reported in clinical studies of Rosuvastatin: dipstick-positive proteinuria and microscopic hematuria; elevated creatine phosphokinase, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities.

Ezetimibe Monotherapy

In 10 double-blind, placebo-controlled clinical trials, 2396 patients with primary hyperlipidemia (50% women, 90% Caucasians, 5% Blacks, 3% Hispanics, 2% Asians) and elevated LDL-C were treated with Ezetimibe for a median treatment duration of 12 weeks. Adverse reactions reported in ≥2% of patients treated with Ezetimibe and at an incidence greater than placebo are shown in Table 6.

Table 6: Adverse Reactions Occurring in ≥2% of Patients Treated with Ezetimibe and Greater than Placebo in Placebo-Controlled Trials

Adverse Reactions	Placebo (N=1159) %	Ezetimibe (N=2396) %
Upper respiratory tract infection	2.5	4.3
Diarrhea	3.7	4.1
Arthralgia	2.2	3.0
Sinusitis	2.2	2.8
Pain in extremity	2.5	2.7
Fatigue	1.5	2.4
Influenza	1.5	2.0

The incidence of consecutive elevations (≥3x ULN) in hepatic transaminase levels was similar between Ezetimibe (0.5%) and placebo (0.3%).

Ezetimibe Combination with Statins

In 28 double-blind, controlled (placebo-or active-controlled) clinical trials, 11,308 patients with primary hyperlipidemia (48% women, 85% Caucasians, 7% Blacks, 4% Hispanics, 3% Asians) and elevated LDL-C were treated with Ezetimibe concurrently with or added to ongoing statin therapy for a median treatment duration of 8 weeks. Clinical adverse reactions reported in ≥2% of patients treated with Ezetimibe + statin and at an incidence greater than statin are shown in Table 7.

Table 7: Adverse Reactions Occurring in ≥2% of Patients Treated with Ezetimibe Coadministered with a Statin and at an Incidence Greater than Statin

Adverse Reactions	All Statins[1] (N=9361) %	Ezetimibe + All Statins[1] (N=2396) %
Nasopharyngitis	3.3	3.7
Myalgia	2.7	3.2
Upper respiratory tract infection	2.8	2.9
Arthralgia	2.4	2.6
Diarrhea	2.2	2.5
Back pain	2.3	2.4
Influenza	2.1	2.2
Pain in extremity	1.9	2.1
Fatigue	1.6	2.0

[1] All Statins = all doses of statins

The incidence of consecutive increased transaminases (≥3x ULN) was higher in patients receiving Ezetimibe administered with statins (1.3%) than in patients treated with statins alone (0.4%). These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

Post marketing Experience

The following adverse reactions have been identified during post-approval use of Rosuvastatin and Ezetimibe. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Tabulated list of adverse reactions

The frequencies of adverse reactions are ranked according to the following convention: very common (≥1/10); 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) and not known (cannot be estimated from the available 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	uncommon	decreased appetite[3]

disorders		
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, thoracic and 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]; gastroesophageal 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 syndrome[2], erythema multiforme[5], drug reaction with eosinophilia and systemic symptoms (DRESS)[2]
Musculoskeletal and connective tissue disorders	common	myalgia[2, 4]
	uncommon	arthralgia[3]; muscle spasms[3]; neck pain[3], back pain[4]; muscular weakness[4]; pain in extremity[4]
	rare	myopathy (including myositis)[2], rhabdomyolysis[2], lupus-like syndrome, muscle rupture
	very rare	arthralgia[2]

	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 disorders	very rare	gynaecomastia[2]
Investigations	common	ALT and/or AST increased[4]
	uncommon	ALT and/or AST increased[3]; blood CPK increased[3]; gamma-glutamyl transferase increased[3]; liver function test abnormal[3]
General disorders and administration site conditions	common	asthenia[2], fatigue[3]
	uncommon	chest pain[3], pain[3], asthenia[4]; oedema peripheral[4]
	not known	oedema[2], asthenia[5]

[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/l, BMI > 30 kg/m^2, raised triglycerides, history of hypertension) – for rosuvastatin.

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

[3] Ezetimibe in monotherapy. Adverse reactions were observed in patients treated with ezetimibe (N=2396) and at a greater incidence than placebo (N=1159).

[4] Ezetimibe co administered with a statin. Adverse reactions were observed in patients with ezetimibe co-administered with a statin (N=11308) and at a greater incidence than statin administered alone (N=9361).

[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 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 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 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 (>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 observed in a small number of patients taking rosuvastatin; the majority of cases were 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
In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was similar between ezetimibe (0.5%) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with ezetimibe co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see section 4.4).

In clinical trials, CPK>10 X ULN was reported for 4 of 1,674 (0.2%) patients administered ezetimibe alone vs 1 of 786 (0.1%) patients administered placebo, and for 1 of 917 (0.1%) patients co-administered ezetimibe and a statin vs 4 of 929 (0.4%) patients administered a statin alone. There was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone) (see section 4.4).

Paediatric population
The safety and efficacy of Suvezen in children below the age of 18 years have not yet been established (see section 5.1).

Rosuvastatin: Creatine kinase elevations >10xULN 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: 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 (≥ 3X 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 (≥ 10X 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 (≥3X 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 (≥ 10X ULN). No cases of myopathy were reported.
These trials were not suited for comparison of rare adverse drug reactions.

4.9 Overdose
No specific treatments of over dosage with Rosuvastatin Calcium & Ezetimibe Tablets are known. Hemodialysis does not significantly enhance clearance of Rosuvastatin.

5. Pharmacological properties
5.1 Mechanism of action
Rosuvastatin
Rosuvastatin is an inhibitor of HMG CoA-reductase, the rate-limiting enzyme that converts 3-hydroxy3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. In *in vivo* and *in vitro* studies, Rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, Rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

Ezetimibe
Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine.
The molecular target of Ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.

5.2 Pharmacodynamic Properties
The maximum therapeutic response of Rosuvastatin is usually achieved by 4 weeks and is maintained after that. The maximum therapeutic response of Ezetimibe is generally achieved within 2 weeks and is maintained during chronic therapy.

5.3 Pharmacokinetic properties
Absorption
Rosuvastatin
In clinical pharmacology studies in man, peak plasma concentrations of Rosuvastatin were reached 3 to 5 hours following oral dosing. Both C_{max} and AUC increased in approximate proportion to

Rosuvastatin dose. The absolute bioavailability of Rosuvastatin is approximately 20%. The AUC of Rosuvastatin does not differ following evening or morning drug administration.
Administration of Rosuvastatin with food did not affect the AUC of Rosuvastatin.

Ezetimibe

After oral administration, Ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (Ezetimibe-glucuronide). After a single 10-mg dose of Ezetimibe to fasted adults, mean Ezetimibe peak plasma concentrations (C_{max}) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (T_{max}). Ezetimibe-glucuronide mean C_{max} values of 45 to 71 ng/mL were achieved between 1 and 2 hours (T_{max}). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of Ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of Ezetimibe when administered as Ezetimibe 10-mg tablets. The C_{max} value of Ezetimibe was increased by 38% with consumption of high-fat meals.

Distribution

Rosuvastatin

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

Ezetimibe

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

Metabolism

Rosuvastatin

Rosuvastatin is not extensively metabolized; approximately 10% of a radio labeled dose is recovered as metabolite. The major metabolite is N-desmethyl Rosuvastatin, which is formed principally by cytochrome P450 \ 2C9, and in vitro studies have demonstrated that N-desmethyl Rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of Rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by Rosuvastatin.

Ezetimibe

Ezetimibe is primarily metabolized 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 a evidence of significant enterohepatic recycling. The half-life for Ezetimibe and Ezetimibe-glucuronide is approximately 22 hours.

Excretion

Rosuvastatin

Rosuvastatin undergoes limited metabolism (approximately 10%), mainly to the N-desmethyl form. Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life (t1/2) of rosuvastatin is approximately 19 hours. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

Ezetimibe

Following oral administration of ^{14}C-Ezetimibe (20 mg) to human subjects, total Ezetimibe accounted for approximately 93% of the total radioactivity in plasma.
After 48 hours, there were no detectable levels of radioactivity in the plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period.
Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Specific Populations

Geriatric Patients

Rosuvastatin

There were no differences in plasma concentrations of Rosuvastatin between the nonelderly and elderly populations (age ≥65 years).

Ezetimibe

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

Gender

Rosuvastatin

There were no differences in plasma concentrations of Rosuvastatin between men and women.

Ezetimibe

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

Race

Rosuvastatin

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group.

Ezetimibe

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Black and Caucasian subjects. Studies in Asian subjects indicated that the pharmacokinetics of Ezetimibe were similar to those seen in Caucasian subjects.

Hepatic Impairment

Rosuvastatin

In patients with chronic alcohol liver disease, plasma concentrations of Rosuvastatin were modestly increased. In patients with Child-Pugh A disease, C_{max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function.

Ezetimibe

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 to 6), compared to healthy subjects. The mean AUC values for total Ezetimibe and Ezetimibe increased approximately 3-to 4-fold and 5-to 6-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment, the mean AUC for total Ezetimibe and Ezetimibe increased approximately 4-fold on both Day 1 and Day 14 when compared to healthy subjects.

Renal Impairment

Rosuvastatin

Mild to moderate renal impairment (CL_{cr} ≥30 mL/min/1.73 m^2) had no influence on plasma concentrations of Rosuvastatin. However, plasma concentrations of Rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CL_{cr} <30

mL/min/1.73 m^2) not receiving hemodialysis compared with healthy subjects (CL_{cr}>80 mL/min/1.73 m^2). Steady-state plasma concentrations of Rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Ezetimibe

After a single 10-mg dose of Ezetimibe in patients with severe renal disease (n=8; mean CL_{cr}≤30 mL/min/1.73 m^2), the mean AUC values for total Ezetimibe, Ezetimibe-glucuronide, and Ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

Drug Interactions

No clinically significant pharmacokinetic interaction was seen when Ezetimibe was coadministered with Rosuvastatin. Specific pharmacokinetic drug interaction studies with Rosuvastatin Calcium & Ezetimibe Tablets have not been performed.

Cytochrome P450

Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter organic anion-transporting polyprotein 1B1 (OATP1B1) and efflux transporter breast cancer resistance protein (BCRP).

Ezetimibe had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" study of twelve healthy adult males. This indicates that Ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes.

Rosuvastatin

Table 8: Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure

Coadministered drug and dosing regimen	**Rosuvastatin**		
		Mean Ratio (ratio with/without coadministered drug) No Effect=1.0	
	Dose (mg)[1]	**Change in AUC**	**Change in C_{max}**
Sofosbuvir/velpatasvir/voxilaprevir (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) QD for 15 days	10 mg single dose	7.39[2] (6.68-8.18)[3]	18.88[2] (16.23-21.96)[3]
Cyclosporine – stable dose required (75 mg – 200 mg BID)	10 mg QD for 10 days	7.1[2]	11[2]

Darolutamide 600 mg BID, 5 days	5 mg, single dose	5.2[2]	~5[2]
Regorafenib 160 mg OD, 14 days	5 mg single dose	3.8[2]	4.6[2]
Atazanavir/ritonavir combination 300 mg/100 mg QD for 8 days	10 mg	3.1[2]	7[2]
Simeprevir 150 mg QD, 7 days	10 mg, single dose	2.8[2] (2.3-3.4)[3]	3.2[2] (2.6-3.9)[3]
Velpatasvir 100 mg once daily	10 mg single dose	2.69[2] (2.46-2.94)[3]	2.61[2] (2.32-2.92)[3]
Ombitasvir 25 mg/paritaprevir 150 mg/ ritonavir 100 mg + dasabuvir 400 mg BID	5 mg single dose	2.59[2] (2.09-3.21)[3]	7.13[2] (5.11-9.96)[3]
Elbasvir 50 mg/grazoprevir 200 mg QD	10 mg single dose	2.26[2] (1.89-2.69)[3]	5.49[2] (4.29-7.04)[3]
Glecaprevir 400 mg/pibrentasvir 120 mg QD	5 mg once daily	2.15[2] (1.88-2.46)[3]	5.62[2] (4.80-6.59)[3]
Lopinavir/ritonavir combination 400 mg/100 mg BID for 17 days	20 mg QD for 7 days	2.1[2] (1.7-2.6)[3]	5[2] (3.4-6.4)[3]
Gemfibrozil 600 mg BID for 7 days	80 mg	1.9[2] (1.6-2.2)[3]	2.2[2] (1.8-2.7)[3]
Eltrombopag 75 mg QD, 5 days	10 mg	1.6 (1.4-1.7)[3]	2 (1.8-2.3)[3]
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg QD for 7 days	1.5 (1.0-2.1)[3]	2.4 (1.6-3.6)[3]
Tipranavir/ritonavir combination 500 mg/200 mg BID for 11 days	10 mg	1.4 (1.2-1.6)[3]	2.2 (1.8-2.7)[3]
Dronedarone 400 mg BID	10 mg	1.4	
Itraconazole 200 mg QD, 5 days	10 mg or 80 mg	1.4 (1.2-1.6)[3] 1.3 (1.1-1.4)[3]	1.4 (1.2-1.5)[3] 1.2 (0.9-1.4)[3]
Ezetimibe 10 mg QD, 14 days	10 mg QD for 14 days	1.2 (0.9-1.6)[3]	1.2 (0.8-1.6)[3]
Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 days	10 mg	1.1	1.5
Fenofibrate 67 mg TID for 7 days	10 mg	↔	1.2 (1.1-1.3)[3]
Rifampicin 450 mg QD, 7 days	20 mg	↔	

Aluminum & magnesium hydroxide combination antacid Administered simultaneously Administered 2 hours apart	40 mg 40 mg	0.5[2] (0.4-0.5)[3] 0.8 (0.7-0.9)[3]	0.5[2] (0.4-0.6)[3] 0.8 (0.7-1.0)[3]
Ketoconazole 200 mg BID for 7 days	80 mg	1.0 (0.8-1.2)[3]	1.0 (0.7-1.3)[3]
Fluconazole 200 mg QD for 11 days	80 mg	1.1 (1.0-1.3)[3]	1.1 (0.9-1.4)[3]
Erythromycin 500 mg QID for 7 days	80 mg	0.8 (0.7-0.9)[3]	0.7 (0.5-0.9)[3]

QD= Once daily, BID= Twice daily, TID= Three times daily, QID= Four times daily

[1] Single dose unless otherwise noted.

[2] Clinically significant

[3] Mean ratio with 90% CI (with/without coadministered drug, e.g., 1= no change, 0.7 = 30% decrease,11=11-fold increase in exposure)

Table 9: Effect of Rosuvastatin Coadministration on Systemic Exposure to Other Drugs

Rosuvastatin Dosage Regimen	**Coadministered Drug**		
		Mean Ratio (ratio with/without coadministered drug) No Effect=1.0	
	Name and Dose	**Change in AUC**	**Change in C_{max}**
40 mg QD for 10 days	Warfarin[1] 25 mg single dose	R-Warfarin 1.0 (1.0-1.1)[2] S-Warfarin 1.1 (1.0-1.1)[2]	R-Warfarin 1.0 (0.9-1.0)[2] S-Warfarin 1.0 (0.9-1.1)[2]
40 mg QD for 12 days	Digoxin 0.5 mg single dose	1.0 (0.9-1.2)[2]	1.0 (0.9-1.2)[2]
40 mg QD for 28 days	Oral Contraceptive (Ethinyl estradiol 0.035 mg & norgestrel 0.180, 0.215 and 0.250 mg) QD for 21 Days	EE 1.3 (1.2-1.3)[2] NG 1.3 (1.3-1.4)[2]	EE 1.3 (1.2-1.3)[2] NG 1.2 (1.1-1.3)[2]

EE = ethinyl estradiol, NG = norgestrel, QD= Once daily

[1] Clinically significant pharmacodynamic effects

[2] Mean ratio with 90% CI (with/without coadministered drug, e.g., 1= no change, 0.7=30% decrease, 11=11•fold increase in exposure)

Ezetimibe

Table 10: Effect of Co-Administered Drugs on Total Ezetimibe

Coadministered Drug and Dosing Regimen	Total Ezetimibe*	
	Change in AUC	Change in C_{max}
Cyclosporine-stable dose required (75-150 mg BID)[1,2]	↑240%	↑290%
Fenofibrate, 200 mg QD, 14 days[2]	↑48%	↑64%
Gemfibrozil, 600 mg BID, 7 days[2]	↑64%	↑91%
Cholestyramine, 4 g BID, 14 days[2]	↓55%	↓4%
Aluminum & magnesium hydroxide combination antacid, single dose[3]	↓4%	↓30%
Cimetidine, 400 mg BID, 7 days	↑6%	↑22%
Glipizide, 10 mg, single dose	↑4%	↓8%
Statins		
Lovastatin 20 mg QD, 7 days	↑9%	↑3%
Pravastatin 20 mg QD, 14 days	↑7%	↑23%
Atorvastatin 10 mg QD, 14 days	↓2%	↑12%
Rosuvastatin 10 mg QD, 14 days	↑13%	↑18%
Fluvastatin 20 mg QD, 14 days	↓19%	↑7%

* Based on 10-mg dose of Ezetimibe

[1] post-renal transplant patients with mild impaired or normal renal function. In a different study, a renal transplant patient with severe renal impairment (creatinine clearance of 13.2 mL/min/1.73m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total Ezetimibe compared to healthy subjects.

[2] Drug Interactions

[3] Magnesium Hydroxide suspension, 20 mL

Table 11: Effect of Ezetimibe Coadministration on Systemic Exposure to Other Drugs

Coadministered Drug and its Dosage Regimen	Ezetimibe Dosage Regimen	Change in AUC of Coadministered Drug	Change in C_{max} of Coadministered Drug
Warfarin, 25 mg single dose on Day 7	10 mg QD, 11 days	↓2% (R-warfarin) ↓4% (S-warfarin)	↓3% (R-warfarin) ↓1% (S-warfarin)
Digoxin, 0.5 mg single dose	10 mg QD, 8 days	↑2%	↓7%
Gemfibrozil, 600 mg BID, 7 days*	10 mg QD, 7 days	↓1%	↓11%

Ethinyl estradiol and levonorgestrel, QD, 21 days	10 mg QD, Days 8-14 of 21-day oral contraceptive cycle	Ethinyl estradiol 0% Levonorgestrel 0%	Ethinyl estradiol ↓9% Levonorgestrel ↓5%
Glipizide, 10 mg on Days 1 and 9	10 mg QD, Days 2-9	↓3%	↓5%
Fenofibrate, 200 mg QD, 14 days*	10 mg QD, 14 days	↑11%	↑7%
Cyclosporine, 100 mg single dose Day 7*	20 mg QD, 8 days	↑15%	↑10%
Statins			
Lovastatin 20 mg QD, 7 days	10 mg QD, 7 days	↑19%	↑3%
Pravastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓20%	↓24%
Atorvastatin 10 mg QD, 14 days	10 mg QD, 14 days	↓4%	↑7%
Rosuvastatin 10 mg QD,14 days	10 mg QD, 14 days	↑19%	↑17%
Fluvastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓39%	↓27%

* See Drug Interactions

Pharmacogenomics

Disposition of rosuvastatin, involves OATP1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1 (SLCO1B1 521T > C). The frequency of this genotype (i.e., SLCO1B1 521T>C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on rosuvastatin is unknown.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal carcinogenicity or fertility studies have been conducted with the combination of Rosuvastatin and Ezetimibe.

Rosuvastatin

In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses.

In a 107-week carcinogenicity study in mice given 10, 60, or 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times the human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test.

In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times the human exposure at 40 mg/day based on AUC). In testicles of dogs treated with Rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times the human exposure at 40 mg/day based on body surface area. Similar findings have been seen with other drugs in this class.

Ezetimibe

A 104-week dietary carcinogenicity study with Ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total Ezetimibe). A 104-week dietary carcinogenicity study with Ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total Ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of Ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total Ezetimibe).

7. Description

Fortius EZ® 10: White coloured, elongated, biconvex, film coated tablets, plain on both sides.

Fortius EZ® 20: Orange coloured, elongated, biconvex, film coated tablet, plain on both sides.

Fortius EZ® 40: Yellow coloured, elongated, biconvex, film coated tablet, plain on both sides.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

10 tablets in a blister pack.

8.4 Storage condition & handling instructions

Store protected from moisture at a temperature not exceeding 30°C.
Medicine: Keep out of reach of children.

9. Patient Counseling Information

What is Rosuvastatin Calcium & Ezetimibe Tablet?

Rosuvastatin Calcium & Ezetimibe Tablet contains two medicines, Rosuvastatin and Ezetimibe, to lower cholesterol. Rosuvastatin Calcium & Ezetimibe Tablet is used:

- Along with diet in adults with high blood cholesterol levels to reduce low density lipoprotein cholesterol (LDL-C) or bad cholesterol.
- Alone or together with other LDL-lowering medicines in adults with a type of high cholesterol called homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.

It is not known if Rosuvastatin Calcium & Ezetimibe Tablet is safe and effective in children.

Do not take Rosuvastatin Calcium & Ezetimibe Tablet if you:

- Have liver problems or repeated blood tests showing possible liver problems.
- Are allergic to Ezetimibe or Rosuvastatin or any of the ingredients in Rosuvastatin Calcium & Ezetimibe Tablet.

Before you take Rosuvastatin Calcium & Ezetimibe Tablet, tell your healthcare provider about all of your medical conditions, including if you:

- Have unexplained muscle aches or weakness.
- Have thyroid problems.
- Have kidney problems.
- Drink more than 2 glasses of alcohol daily or have had liver problems.
- Have diabetes.
- Are pregnant or plan to become pregnant. Rosuvastatin Calcium & Ezetimibe Tablet may harm your unborn baby. If you become pregnant, stop taking Rosuvastatin Calcium & Ezetimibe Tablet and call your healthcare provider right away.

- Are breast feeding. Rosuvastatin Calcium & Ezetimibe can pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take Rosuvastatin Calcium & Ezetimibe Tablet. Do not breastfeed while taking Rosuvastatin Calcium & Ezetimibe Tablet.
- are 65 years of age or older.
- are of Asian descent.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Talk to your healthcare provider before you start taking any new medicines. Taking Rosuvastatin Calcium & Ezetimibe Tablet with certain other medicines can increase the risk of muscle problems or other side effects. Especially tell your healthcare provider if you take medicines for:

- Heartburn (such as antacids that contain aluminium and magnesium hydroxide)
- Your immune system (such as Cyclosporine)
- Cholesterol (such as Niacin or Nicotinic Acid, Gemfibrozil, Fibrates)
- Infections or anti-fungal (such as Itraconazole, Ketoconazole, and Fluconazole)
- Heart failure including coumarin anticoagulants (such as Warfarin)
- Gout (such as Colchicine)
- Darolutamide (a medicine for the treatment of Prostate Cancer)
- Regorafenib (a medicine used to treat cancer of the colon and rectum)
- Anti-Viral medicines including certain HIV or hepatitis C virus drugs such as:
    - Lopinavir, Ritonavir, Fosamprenavir, Tipranavir, Atazanavir, Simeprevir
    - combination of:
        - Sofosbuvir/Yelpatasvir/Oxilaprevir
        - Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir
        - Elbasvir/Grazoprevir
        - Sofosbuvir/Yelpatasvir
        - Glecaprevir/Pibrentasvir and
        - all other combinations with ledipasvir including Ledipasvir/Sofosbuvir

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure. Know all of the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get new medicine.

What are the possible side effects of Rosuvastatin Calcium & Ezetimibe Tablet?

Rosuvastatin Calcium & Ezetimibe Tablet may cause serious side effects, including:

- Allergic reactions, including a severe reaction known as anaphylaxis. Tell your healthcare provider right away if you have any of the following symptoms:
    - swelling of the face, lips, tongue, and/or throat which makes it difficult to swallow or breathe

- breathing problems or wheezing
- feeling dizzy or fainting
- rash or hives
- itching

- Muscle pain, tenderness and weakness (myopathy). Muscle problems, including muscle breakdown, can be serious in some people and rarely causes kidney damage that can lead to death. You have a higher chance for muscle problems if you are taking certain other medicines with Rosuvastatin Calcium & Ezetimibe Tablet. Tell your healthcare provider right away if:
  - you have unexplained muscle pain, tenderness, or weakness, especially if you have a fever or feel more tired than usual, while you take Rosuvastatin Calcium & Ezetimibe Tablet.
  - you have muscle problems that do not go away even after your healthcare provider has advised you to stop taking Rosuvastatin Calcium & Ezetimibe Tablet. Your healthcare provider may do further tests to diagnose the cause of your muscle problems.

Your chances of getting muscle problems are higher if you:
- are taking certain other medicines while you take Rosuvastatin Calcium & Ezetimibe Tablet
- are 65 years of age or older
- are of Asian descent
- have thyroid problems (hypothyroidism) that are not controlled
- have kidney problems
- are taking higher doses of Rosuvastatin Calcium & Ezetimibe Tablet

- **Liver problems.**
  Your healthcare provider may do blood tests to check your liver before you start taking Rosuvastatin Calcium & Ezetimibe Tablet and if you have symptoms of liver problems while you take Rosuvastatin Calcium & Ezetimibe Tablet. Call your healthcare provider right away if you have the following symptoms of liver problems:
    - feel tired or weak
    - loss of appetite
    - upper belly pain
    - dark urine
    - yellowing of your skin or the whites of your eyes

The most common side effects of Rosuvastatin Calcium & Ezetimibe Tablet include:
- headache
- nausea
- muscle aches and pains
- weakness
- constipation

- common cold and flu
- diarrhea
- dizziness
- joint pain
- stomach pain
- runny nose and sore throat
- tiredness
- pain (back, hands, legs)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Rosuvastatin Calcium & Ezetimibe Tablet.

General information about the safe and effective use of Rosuvastatin Calcium & Ezetimibe Tablet.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use Rosuvastatin Calcium & Ezetimibe Tablet for a condition for which it was not prescribed. Do not give Rosuvastatin Calcium & Ezetimibe Tablet to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about Rosuvastatin Calcium & Ezetimibe Tablet that is written for health professionals.

10. Details of manufacturer

Manufactured in India by:
Windlas Biotech Ltd.
(Plant-2) Khasra No. 141 to 143 &
145, Mohabewala Industrial Area,
Dehradun-248110, Uttarakhand.

Marketed by:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 & 11 to 13 Ground Floor,
101 to 106 & 111 to 116 First Floor, 201 to 206 & 211 to 216 2nd
Floor, Pimplas, Dist. Thane, Bhiwandi-421 302, Maharashtra, India.
® - Regd. Trade Mark of Abbott Healthcare Pvt. Ltd.

11. Details of permission or licence number with date

Fortius EZ 10: Mfg. Lic No. 34/UA/2013, dated 14-May-26
Fortius EZ 20 & 40: Mfg. Lic No. 34/UA/2013, dated 11-Jun-26

12. Date of revision

Version 1.0, dated 23-Jun-26

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com