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ROSUVASTATIN (AS CALCIUM) + EZETIMIBE

IMD

ZEVAS

10mg /10mg Film-coated Tablet
Lipid Modifying Agents

[DESCRIPTION] White to off-white, round film-coated tablet
[COMPOSITON] Each tablet contains
Rosuvastatin Calcium ····· 10.4 mg (10 mg as Rosuvastatin)
Ezetimibe ····· 10.0 mg

[INDICATIONS]
Primary hypercholesterolaemia
It is indicated as adjunctive therapy to diet to reduce elevated total cholesterol (total-C), LDL cholesterol (LDL-C), Apolipoprotein B (Apo B), non-HDL-cholesterol, and triglycerides (TG) and to increase HDL cholesterol (HDL-C) in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidemia.
Many risk factors should be considered when administering lipid-altering agents to patients with an increased risk of atherosclerotic vascular disease due to hypercholesterolemia.
Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate.
Prior to administration of this drug, other secondary causes of dyslipidemia (e.g., diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, drugs that increase LDL-cholesterol, and drugs that decrease HDL-cholesterol [progestin, anabolic steroid, and corticosteroid]should be checked and treated if necessary.
Lipid tests should include total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. If the triglyceride level is more than 400 mg/dL (>4.5 mmol/L), the concentration of LDL-cholesterol should be measured by ultracentrifugation.
If hospitalized due to an acute coronary artery, lipid tests should be measured at admission or within 24 hours of admission. These measurements may be helpful in starting LDL-lowering treatment at discharge from the hospital or before.

[DOSAGE AND ADMINISTRATION]
This drug can be administered as a single dose at any time of day, with or without food.
Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualized according to the baseline of the patient's LDL-C, the goal of therapy and patient response.
Primary hypercholesterolaemia
The dose range for this drug is 10/5 mg to 10/20 mg once daily. The recommended start dose is 10/5mg once daily. For patients requiring more LDL-cholesterol reduction, the dose can be adjusted. After initiation or upon titration of this drug, lipid levels should be analyzed at intervals of 4 weeks or more and the dosage adjusted accordingly. The recommended maximum dose is 10/20 mg once daily.
When administered concomitantly with rosuvastatin and ezetimibe, it can be converted to this drug (the same as the content of each active ingredient) for the convenience of taking

[WARNINGS]
Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including rosuvastatin.
This drug should also be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).

[CONTRAINDICATIONS]
It is contraindicated in the following conditions
1) Patients with a known hypersensitivity to any component of this product. 2) Patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels
3) Patients with myopathy 4) Patients receiving concomitant cyclosporine. 5) Patients with severe renal impairment (creatinine clearance <30 ml/min).
6) During pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures
7) The 40 mg dose is contraindicated in patients with pre-disposing factors for myopathy / rhabdomyolysis. Such factors include:
· Moderate renal impairment (creatinine clearance < 60 ml/min) · Hypothyroidism · Personal or family history of hereditary muscular disorders
· Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate · Alcohol abuse · Situations where an increase in plasma levels may occur · Asian patients · Concomitant use of fibrates
8) Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption

[PRECAUTIONS]
The following patients should be carefully administrated.
1) Alcoholics and Patients who have a history of chronic liver disease
2) Patients with moderate or severe hepatic dysfunction: Administration of this drug in patients with moderate or severe hepatic dysfunction is not recommended because the increased systemic exposure to rosuvastatin and ezetimibe may result in unexpected effects.
3) Patients with pre-disposing factors for myopathy / rhabdomyolysis
· renal impairment or history of renal disorders · hypothyroidism · personal or family history of hereditary muscular disorders · previous history of muscular toxicity with statins or fibrate
· in case of consuming substantial quantities of alcohol or having history of liver disease · elderly over 70 years of age with factors of rhabdomyolysis · situations where an increase in plasma levels may occur
4) Patients who are co-administered with fibrates.
5) Patients with an acute, serious condition suggestive of myopathy or renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).

[ADVERSE REACTIONS]
The safety of this drug was evaluated in the rosuvatatin controlled clinical studies of 369 patients with primary hypercholesterolaemia. The study consist of a treatment duration of 8 weeks and a extension duration of 12 weeks, the extension duration administration of 12 weeks was conducted in 258 patients whose LDL-C level reached the treatment goal according to the risk of cardiovascular disease after completion of the treatment duration of 8 weeks.

1) Adverse reactions reported in the treatment duration of 8 weeks
The most common adverse reactions in the duration were nasopharyngitis (2.4%), arthralgia (1.4%), headache (1.4%). Adverse reactions related to this drug were 2 cases of ALT elevation, 2 cases of AST elevation, 2 case of myalgia, 1 case of edema, 1 case of serum bilirubin elevation, 1 case of acne dermatitis and 1 case of pruritus, all were mild or moderate.
Table1. Adverse reactions reported in ≥ 1% patients for the treatment duration of 8 weeks

	Rosuvastatin (N=183)			Cretrol Tab. (N=186)			Total
Body System/Organ Class Adverse	5mg (N=61) N	10mg (N=62) N	20mg (N=60) N	10/5mg (N=61) N	10/10mg (N=63) N	10/20mg (N=62) N	(N=369) N(%)
Infections and infestations Nasopharyngitis	4	0	1	2	1	1	9(2.4%)
Musculo-skeletal and connective tissue disorders Arthralgia	0	2	1	1	1	0	5(1.4%)
Nervous system disorders Headache	1	1	1	0	2	0	5(1.4%)

2) Adverse reactions reported in the treatment duration of 12 weeks
The most common adverse reactions in the duration were nasopharyngitis (5.04%), ALT elevation (2.71%), dizziness (1.94%), upper respiratory tract infection (1.55%), myalgia (1.16%), in other all case, the incidence of adverse reactions was less than 1%. As with rosuvastatin controlled clinical studies for 8 weeks, no specific adverse events were observed in this drug alone. The information provided below is based on clinical studies of the individual components of Rosuvastatin and Ezetimibe and those collected from post-marketing experience.

▪ Information collected from Rosuvastatin
1) The reported adverse reactions are generally mild and transient. In controlled clinical studies, less than 4% of rosuvastatin-treated patients were withdrawn due to adverse reactions.
Adverse reactions listed below are classified according to frequency and system organ class.The frequencies of adverse reactions are ranked according to the following convention: Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).
Table 2. Adverse reactions occurring in rosuvastatin administration

System organ class	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity reactions including angioedema
Endocrine disorders	Diabetes mellitus[1]		
Nervous system disorders	Headache, Dizziness		
Gastro-intestinal disorders	Constipation, Nausea, Abdominal pain		Pancreatitis
Skin and subcutaneous tissue disorders		Pruritus, Rash, Urticaria	
Musculo-skeletal and connective tissue disorders	Myalgia		Myopathy (including myositis), Rhabdomyolysis
General disorders and administration site conditions	Asthenia		

[1] In JUPITER clinical trials, the most frequently reported adverse events in patients with fasting blood glucose of 5.6 to 6.9 mmol/L (2.8% in rosuvastatin and 2.3% in placebo)

As with other statins, the adverse events increased with increasing dose
2) 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. Hematuria was observed in patients treated with rosuvastatin and data from clinical trials, but the incidence was low.

3) 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 (>5xULN), treatment should be discontinued.

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.

5) Overseas Post-marketing experience

In addition to the above adverse reactions, the following adverse events have been reported during post-marketing experience.

· Nervous system disorders—Very rare: polyneuropathy, memory loss, Not known: peripheral neuropathy
· Respiratory, thoracic and mediastinal disorders—Not known: cough, dyspnoea · Gastro-intestinal disorders—Not known: diarrhoea · Blood and lymphatic system disorders—Not known: thrombocytopenia
· Hepatobiliary disorders—Rare: increased hepatic transaminases, Very rare: jaundice, hepatitis · Skin and subcutaneous tissue disorders—Not known: Stevens-Johnson syndrome
· Musculo-skeletal and connective tissue disorders—Very rare: arthralgia, Not known: immune-mediated necrotising myopathy
· Renal and urinary disorders—Very rare: haematuria · Other—Not known: oedema

The following adverse events have been reported with some statins:

· Nervous system disorders—Not known: depression sleep disturbances (including insomnia and nightmares) · Respiratory disorders—Exceptional cases of interstitial lung disease, especially with long term therapy
· Reproductive system and breast disorders—Not known: sexual dysfunction, gynecomastia · Hepatobiliary disorders—Fatal and non-fatal liver failure

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

6) Domestic Post-marketing experience

In Korea, 3,081 people were surveyed for 6 years, and the incidence rate of adverse reaction was 10.06% (310 people, 415 cases), 0.78% (24 people, 24 cases) of headache, 0.75% (23 people, 23 cases) of dizziness, 0.58% (18 people, 18 cases) of ALT elevation, 0.49% (15 people, 15 cases) of chest pain, cough, and myalgia were reported and the adverse drug reactions that cannot establish a causal relationship to Rosuvastatin were 2.92% (90 people, 106 cases).

Among the adverse reactions reported, 0.55% (17 people, 17 cases) of ALT elevation, 0.42% (13 people, 13 cases) of myalgia, 0.39% (12 people, 12 cases) of headache, 0.29% (9 people, 9 cases) of CK elevation, 0.26% (8 people, 8 cases) of dizziness, 0.16% (5 people, 5 cases) each of constipation and AST elevation, 0.13% (4 people, 4 cases) of asthenia and arthralgia, 0.10% (3 people, 3 cases) each of fatigue and paresthesia, 0.06% (2 cases, 2 cases) each of sensory abnormality, chest discomfort, nausea, abdominal pain, diarrhea, anorexia, abdominal distension, itching and liver function test abnormality, 0.03% (1 case, 1 case) each of Syncope, systemic pain, muscle spasms, gout, and erectile dysfunction were reported.

Myalgia and arthralgia in one of these patients was a significant adverse reaction, the unexpected adverse reactions that did not appear in pre-marketing were 0.13% (4 people, 4 cases) of arthralgia, 0.10% (3 people, 3 cases) each of fatigue and paresthesia, were (2 cases, 2 cases) each of sensory abnormality, chest discomfort, anorexia, abdominal distension and liver function test abnormality, 0.03% (1 people, 1 case) each of syncope, systemic pain, muscle spasm, gout, and erectile dysfunction, 1 case of arthralgia as serious and unexpected adverse reactions was reported.

During the review period, 98 cases of the adverse reactions were reported voluntarily,

2 cases of acute renal failure, 1 case each of oliguria, thrombocytopenia, and increased serum creatinine, were reported as serious and unexpected adverse reactions

7) Paediatric patients (10 to 17 years of age)

Creatine kinase elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of paediatric patients (10 to 17 years of age), compared to adults. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

▪ Information collected from Ezetimibe

The safety of this drug was evaluated in the ezetimibe controlled clinical studies of ≥4700 patients. From the result of clinical studies (Ezetimibe administered alone or co-administered with HMG-CoA reductase inhibitors), adverse reactions were usually mild and transient. The overall incidence of adverse reactions was similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between ezetimibe and placebo.

1) Monotherapy

Adverse reactions reported in ≥2% of patients treated with ezetimibe and at an incidence greater than placebo in placebo-controlled studies of ezetimibe, regardless of causality assessment, are shown in Table 3.

Table 3*. Clinical adverse reactions occurring in ≥2% of patients treated with ezetimibe and at an incidence greater than placebo, regardless of causality

Body System/Organ Class Adverse Reaction	Placebo (%) n = 795	Ezetimibe 10 mg (%) n = 1691
General disorders and administration site conditions		
Fatigue	1.8	2.2
Gastrointestinal disorders		
Abdominal pain	2.8	3
Diarrhea	3	3.7
Infections and infestations		
Viral infection	1.8	2.2
Pharyngitis	2.1	2.3
Sinusitis	2.8	3.6
Musculoskeletal and connective tissue disorders		
Arthralgia	3.4	3.8
Low back pain	3.9	4.1
Upper respiratory tract infection		
Cough	2.1	2.3

* This study included patients who received placebo or ezetimibe alone as shown in Table 4.

The incidence of other adverse events with lower frequency than the above adverse events was similar between the ezetimibe and placebo groups (see Table 4).

2) Co-administration with HMG-CoA reductase inhibitors

The safety of ezetimibe was evaluated in the co-administration clinical studies of ≥2000 patients. When co-administered with HMG-CoA reductase inhibitors, adverse reactions were similar compared to HMG-CoA reductase inhibitors administrated alone. But, the incidence of increased transaminases was higher in patients receiving ezetimibe co-administered with HMG-CoA reductase inhibitors than in patients treated with HMG-CoA reductase inhibitors alone. Clinical adverse reactions reported in ≥2% of patients treated with ezetimibe alone or ezetimibe + HMG-CoA reductase inhibitors and at an incidence greater than placebo, regardless of causality assessment, were shown in Table 4.

Table 4*. Clinical adverse reactions occurring in ≥2% of patients treated with ezetimibe co-administered with a statin and at an incidence greater than placebo, regardless of causality

Body System/Organ Class Adverse Reaction	Placebo (%) n=259	Ezetimibe 10mg (%) n = 262	Statin** (%) n = 936	Ezetimibe + Statin** (%) n = 925
General disorders and administration site conditions				
Chest pain	1.2	3.4	2	1.8
Dizziness	1.2	2.7	1.4	1.8
Fatigue	1.9	1.9	1.4	2.8
Headache	5.4	8	7.4	6.3
Gastrointestinal disorders				
Abdominal pain	2.3	2.7	3.1	3.5
Diarrhea	1.5	3.4	2.9	2.8
Infections and infestations				
Pharyngitis	1.9	3.1	2.5	2.3
Nasopharyngitis	1.9	4.6	3.6	3.5
Upper respiratory tract infection	10.8	13	13.6	11.8
Musculoskeletal and connective tissue disorders				
Arthralgia	2.3	3.8	4.3	3.4
Low back pain	3.5	3.4	3.7	4.3
Myalgia	4.6	5	4.1	4.5

* This clinical study includes 4 placebo-controlled clinical studies of HMG-CoA reductase inhibitor and ezetimibe starting the treatment concurrently.
** All statins = all doses of all HMG-CoA reductase inhibitors

3) Co-administration with fenofibrate

In a multicentre, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidaemia, 625 patients were treated for up to 12 weeks and 576 patients for up to 1 year. This study was not designed to compare treatment groups for infrequent events.

Incidence rates (95 % CI) for clinically important elevations (> 3 X ULN, consecutive) in serum transaminases were 4.5 % (1.9, 8.8) and 2.7 % (1.2, 5.4) for fenofibrate monotherapy and ezetimibe co-administered with fenofibrate, respectively, adjusted for treatment exposure.

Corresponding incidence rates for cholecystectomy were 0.6 % (0.0, 3.1) and 1.7 % (0.6, 4.0) for fenofibrate monotherapy and ezetimibe co-administered with fenofibrate, respectively.

There was no elevation of creatine phosphokinase (> 10 X ULN) in the study.

4) The following common adverse reactions were reported in patients treated with ezetimibe alone (N=1691), in patients treated with ezetimibe co-administered with a statin (N=1675) and in patients treated with ezetimibe co-administered with a fenofibrate (N=185).

· Patients treated with ezetimibe alone: headache, abdominal pain, diarrhea
· Patients treated with ezetimibe co-administered with a statin: headache, fatigue, abdominal pain, constipation, diarrhea, flatulence, nausea, ALT and/or AST increased, myalgia
· Patients treated with ezetimibe co-administered with a fenofibrate: abdominal pain

5) Post-marketing adverse reactions

The following adverse reactions were reported regardless of causality.

Hypersensitivity including rash and urticaria, anaphylaxis and angio-oedema, erythema multiforme, arthralgia, myalgia, CPK increased, myopathy/rhabdomyolysis (see section general precautions), hepatic transaminases increased, hepatitis, abdominal pain, thrombocytopaenia, nausea, pancreatitis, dizziness, senseless, depression, headache, cholelithiasis, cholecystitis

6) Domestic Post-marketing experience
In Korea, 3,536 people were surveyed for 6 years, and the incidence rate of adverse reaction was 7.27% (257 people, 322 cases), a commonly occurring (1.0% or more) adverse event is fatigue (37 people, 37 cases) and the adverse drug reactions that can not establish a causal relationship to ezetimibe were 1.95% (69 people, 108 cases). Among the adverse reactions reported, 0.28% (10 people, 10 cases) of ALT elevation and AST elevation, 0.17% (6 people, 6 cases) of diarrhea, 0.14% (5 people, 5 cases) each of dyspepsia and dizziness, 0.11% (4 people, 4 cases) of nausea were reported and others adverse reactions reported below 0.1% are as follows:
· General disorders and administration site condition: fatigue, chest pain, chest discomfort, edema, asthenia, systemic edema · Nervous system disorders: headache, paresthesia, diabetic neuropathy, tremor
· Gastrointestinal disorders: upper abdominal pain, vomiting, abdominal pain, gastritis, constipation, dry mouth, anticardium discomfort, trim, gastrointestinal disorders, gastroesophageal reflux disease, tongue disease
· Cardiovascular disorders: throbbing, congestive heart failure, myocardial ischemia, flushing · Respiratory disorders: cough, sputum, runny nose · Musculoskeletal and connective tissue disorders: melagia, arthralgia
· Metabolism and nutrition disorder: diabetes, hypoglycemia · Blood and lymphatic system disorders: anemia, spleen enlargement · Skin and subcutaneous tissue disorders: urticaria, hyperhidrosis, rash, itching
· Infections and infestations: upper respiratory infection · Eyes disorder: conjunctival hyperemia · Urinary disorder: renal failure (kidney disease) · Hepatobiliary disorders : abnormal liver function
· Clinical examination: increase in serum creatinine, increase in blood pressure, increase in blood factor, increase in CPK, liver function abnormality

[GENERAL CAUTION]
1) Myopathy / rhabdomyolysis
CPK levels should be measured in patients with pre-disposing factors for myopathy / rhabdomyolysis before initiation of administration. In these patients, the risk of treatment should be considered with benefit and clinical monitoring is recommended. CPK should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CPK increase which may confound interpretation of the result. If CPK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5-7 days. If the repeat test confirms a baseline CK >5xULN, treatment should not be started.
When initiation of administration, the patient should be informed of the risk of myopathy and should be instructed to report to the physician immediately if fatigue or fever accompanied by myalgia, muscle spasms, or muscle weakness occurs during the administration of this drug. In addition, when these symptoms occur, the CPK level should be measured and if the CPK level is significantly increased ((>5xULN), the drug should be discontinued. If the CPK level is less than 5xULN, the drug should be discontinued if the muscle symptoms are severe and cause discomfort in daily life. If symptoms improve and CPK levels return to normal and this drug is re-administered or another statin is administered, the patient should be carefully monitored and administered at the lowest dose.
▪ Rosuvastatin
Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in rosuvastatin-treated patients.
Very rare cases of immune-mediated necrotising myopathy(IMNM) have been reported during or after treatment with statins, including rosuvastatin. IMNM is clinically characterised by proximal muscle weakness and increased serum creatine kinase, which persist despite discontinuation of statins treatment.
In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients treated with rosuvastatin and other drug concomitantly.
However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other statins together with fibric acid derivatives (including gemfibrozil), cyclosporine, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with statins. Therefore, the combination of rosuvatatin and gemfibrozil is not recommended. The benefit of the combination use of rosuvastatin with fibrates or niacin should be carefully evaluated with the risk. Dose of rosuvastatin 40mg is contraindicated with concomitant use of fibrates.
▪ Ezetimibe
The risk of musculoskeletal toxicity increases patients with factors such as concomitant use of a high-dose statin, elderly (≥65 years), hypothyroidism, renal impairment, type of statins administered, and concomitant use of other drugs. In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. However, rhabdomyolysis has been reported with ezetimibe monotherapy and with co-administration of ezetimibe with other drugs such as fibric acid derivatives known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a CPK level >10 times the ULN, co-administration of eztimibe with fenofibrate should be immediately discontinued.
2) Liver enzymes
Liver enzymes test should be conducted before initiation of administration, liver function test should be repeated in patients with clinical signs or symptoms of liver disease. For patients with increased transaminases, monitoring should be continued until the adverse symptoms improve. This drug should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the ULN. From post-marketing experience, fatal and non-fatal liver failure has reported rarely in patients taking statins, including rosuvastatin. If severe hepatic impairment and / or hyperbilirubinemia or jaundice occurs during the treatment with clinical signs, this drug should be discontinued immediately. If no other pathogen is identified, this drug should not be re-administered.
This drug should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease. Patients with active liver disease or a persistent elevation of serum transaminase which cause is unknown are not treated with this drug
▪ Ezetimibe
In a controlled clinical study, the incidence of consecutive elevations of transaminases (≥3 X ULN) was 0.5% for ezetimibe and 0.3% for placebo.
In controlled co-administration studies in patients receiving ezitimibe with a statin, the incidence of consecutive elevations of transaminase (≥3 X ULN) was 0.6% for ezetimibe combined with statins. The transaminase elevation was usually not symptomatic, and was not associated with bile, and was returned to baseline after discontinuation or continued administration.
3) Endocrine system
Increased HbA1c and fasting blood glucose levels have been reported in patients receiving statins, including rosuvastatin. However, the benefit of reduced vascular risk due to statin administration outweighs the risk of hyperglycemia.
4) Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long-term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.
5) Diabetes
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/l, BMI >30 kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.
6) Co-administration with other drug
· Anticoagulants: If this drug is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored.
If a patient treated with coumarin anticoagulant receives concomitantly with this drug, prothrombin time should be measured prior to administration and should be measured sufficiently frequently at the beginning of treatment to confirm that prothrombin time is not significantly altered.
· Fibrates: Fibrates may increase cholesterol release into the bile and cause cholelithiasis. If cholelithiasis is suspected in a patient receiving this drug and fibrates, gallbladder investigations are carried out and alternative therapy of lipid lowering should be considered.
· Bile acid binding resin: The drug should be administered 2 hours before or 4 hours after administration of the bile acid-binding resin.
· Fusidic acid: Muscle-related adverse events, including rhabdomyolysis have been seen in patients receiving rosuvastatin together with fusidic acid in post-marketing experience. Therefore, the combination of rosuvastatin and fusidic acid is not recommended.
· Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. When the drug is administered concomitantly with inhibitors of transporter proteins, care should be taken because the plasma concentration of the drug increases and may increase the risk of myopathy.
7) Genetic polymorphism
The genotypes of SLCO1B1(OATP1B1) c. 521CC or ABCG2(BCRP) c.421AA compared to SLCO1B1 cS211T1 and ABCG2 c.421CC are known that can lead to increased rosuvastatin exposure (AUC). Although the safety and efficacy of the drug according to genetic polymorphisms has not been established, it is necessary to control the dose according to the patient's response and tolerance.
8) Women of childbearing age
Women of child bearing potential should use appropriate contraceptive measures.
9) Effects on ability to drive and use machines
Studies to determine the effect of the drug on the ability to drive and use machines have not been conducted. However it should be taken into account that dizziness may occur during treatment.

[DRUG INTERACTIONS]
No clinically pharmacokinetic interactions were observed with co-administration of rosuvastatin and ezetimibe, the active ingredients of the drug.
Studies on drug interactions with rosuvastatin / ezetimibe combination with other drugs have not been performed, but studies on rosuvastatin and ezetimibe individual drugs were performed as follows
▪ Rosuvastatin
1) Effect of co-administered medicinal products on rosuvastatin
Results from in vitro and in vivo studies, show that rosuvastatin does not interact clinically with cytochrome P450 (does not act as a substrate, inhibitor or inducing agent).
Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of Crestor with inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy.

Table 5 Effect of co-administered medicinal products on rosuvastatin exposure (AUC) from published clinical trials

Co-administered drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC
Cyclosporine 75 mg - 200 mg BID, 6 months	10 mg QD, 10 days	7.1-fold increase
Atazanavir 300 mg/ritonavir 100 mg QD, 8 days	10 mg, single dose	3.1-fold increase
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg QD, 7 days	2.1-fold increase
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold increase
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold increase
Eltrombopag 75 mg QD, 5 days	10 mg, single dose	1.6-fold increase
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg QD, 7 days	1.5-fold increase
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold increase
Dronedarone 400 mg BID	Not available	1.4-fold increase
Itraconazole 200 mg QD, 5 days	10 mg, single dose	1.4-fold increase
	80 mg, single dose	1.3-fold increase
Ezetimibe 10 mg QD, 14 days	10 mg, QD, 14 days	1.2-fold increase
Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 days	10 mg, single dose	no change
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	no change
Silymarin 140 mg TID, 5 days	10 mg, single dose	no change
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	no change
Rifampin 450 mg QD, 7 days	20 mg, single dose	no change
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	no change
Fluconazole 200 mg QD, 11 days	80 mg, single dose	no change
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% decrease
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% decrease

QD = once daily; BID = twice daily; TID = three times daily; QID = four times daily.

Effect of other medicinal products
- 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.
- Fusidic acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted.
  From post-marketing experience, myopathy including rhabdomyolysis has been reported in the concomitant administration of fusidic acid with rosuvastatin as with other statins. Therefore the combination of rosuvastatin and fosdic acid is not recommended. If possible, temporary discontinuation of rosuvastatin is recommended throughout the duration of the fusidic acid treatment, should be closely monitored if the treatment is unavoidable.

2) Effect of rosuvastatin on co-administered medicinal products
- Warfarin: When used in combination with rosuvastatin, Warfarin is not significantly affected by pharmacokinetics. As with other statins, the combination use with rosuvastatin and warfarin may increase INR. In the initiation of treatment, discontinuation or dosage-titration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin), monitoring of INR is recommended.
- Cyclosporine: Co-administration of rosuvastatin and cyclosporine did not affect plasma concentrations of cyclosporine.
- Fenofibrate / Fibric acid derivatives: Pharmacokinetic relevant interaction with fenofibrate and rosuvastatin was not observed, however a pharmacodynamic interaction may occur.
  Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (≥1g/day) of nicotinic acid increase the risk of myopathy when given concomitantly with a statin, probably because they can produce myopathy when given alone. The 40 mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5 mg dose.
- Oral contraceptives: Concomitant use of rosuvastatin and an oral contraceptive resulted in an increase in ethinyl oestradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.
- Others: No clinically relevant interaction with digoxin or ezetimibe has been shown.

▪ Ezetimibe

1) Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55 %. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding ezetimibe to cholestyramine may be lessened by this interaction.
2) Fibrates: safety and have been evaluated in clinical trials evaluated the safety and efficacy of concomitant fenofibrate administration. Co-administration of ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In pre-clinical studies in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the preclinical results and their relevance to humans are not known, concomitant fibrates administration (except fenofibrate) is not recommended until results of the study in patients come out.
   - Gemfibrozil: Concomitant gemfibrozil administration increased the total ezetimibe concentration approximately 1.7-fold, but was not clinically significant. No clinical data are available yet.
   - Fenofibrate: If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated and other lipid-lowering treatments should be considered. Concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold in a pharmacokinetic study.
3) Statins: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.
4) Cyclosporine: Caution should be exercised when using ezetimibe and cyclosporine concomitantly and cyclosporine concentrations should be monitored in patients receiving ezetimbe and cyclosporine. In the study of eight post-renal transplant patients with mild renal impairment or normal renal function (creatinine clearance of > 50 mL/min) on a stable dose of cyclosporine, the concomitant use with ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC and a 3.9-fold (range 3.0- to 4.4-fold) increase in the mean Cmax respectively for total ezetimibe compared to a healthy control group (n=17). In a different study, a renal transplant patient with severe renal impairment (creatinine clearance of 13.2 mL/min/1.73 m^2) who was receiving cyclosporine 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 cyclosporine on Day 7 resulted in a mean 15 % increase in cyclosporine AUC (range 10 % decrease to 51 % increase) compared to a single 100-mg dose of cyclosporine alone.
5) Anticoagulants: If ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, Prothrombin time (INR) should be appropriately monitored. Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adults. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimbe added to warfarin or fluindione. Most of these patients were taking other drug together.

[PREGNACY AND LACTATION]

1) Atherosclerosis is a chronic disease and does not affect long-term treatment results of primary hypercholesterolemia even if the administration of lipid-lowering drugs is stopped during pregnancy. In addition, cholesterol and other producing substance of cholesterol biosynthesis pathways are essential for fetal development, such as steroids and cell membrane synthesis.
   HMG-CoA reductase inhibitors, including rosuvastatin, may reduce cholesterol synthesis and other producing substance of the cholesterol biosynthetic pathway and should not be administered to pregnant or lactating women. Because the safety of this drug for pregnant women is not established, the administration should be discontinued immediately when the pregnancy is confirmed and the patient should be informed of the potential risks to the fetus.
2) It is not known whether the component of this drug is excreted into human breast milk, the drug should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

▪ Rosuvastatin

Rosuvastatin is contraindicated in pregnancy and lactation since the safety of this drug for pregnant women is not established.
Women of childbearing potential should use appropriate contraceptive measures. 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 this product, treatment should be discontinued immediately. Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans

▪ Ezetimibe

1) No clinical data are available on the use of ezetimibe during pregnancy and lactation. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.
2) In oral embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). 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 x the human exposure at 10 mg daily based on AUC0-24hr for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 x the human exposure at 10 mg daily based on AUC0-24hr for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.
3) All HMG-CoA reductase inhibitors and fenofibrate are contraindicated in pregnant and lactating women. When ezetimibe is administered with a statin or fenofibrate in a woman of childbearing potential, refer to the pregnancy category and product labeling for the HMG-CoA reductase inhibitor and fenofibrate.
4) Multiple-dose studies of ezetimibe given in combination with statins in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive abnormal findings occur at lower doses in combination therapy compared to monotherapy.
5) Studies on rats have shown that ezetimibe is excreted into breast milk. In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe is excreted into human breast milk. Therefore, ezetimibe should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

[USE IN SPECIFIC POPULATION]

Paediatric population

Administration of this drug is not recommended in paediatric population because the safety and efficacy for pediatric population is not established.

▪ Rosuvastatin

The evaluation of linear growth (height), weight, BMI (body mass index) by Tanner staging in pediatric patients 10 to 17 years of age taking rosuvastatin is limited to a year period.

▪ Ezetimibe

Efficacy and safety of ezetimibe in patients 6 to10 years of age with heterozygous familial or non-familial hypercholesterolemia have been evaluated in a 12-week placebo-controlled clinical trial. In this study, there was generally no detectable effect on growth or sexual maturation in pediatric population. However, effects of ezetimibe for treatment periods > 12 weeks have not been studied in this age group.

Elderly

Pre-disposing factors for myopathy are increased in the elderly (≥ 65 years) and care should be taken when administration to elderly. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic Impairment

This drug is not recommended in patients with active liver disease or a persistent elevation of serum transaminase which cause is unknown (see section general caution).

Renal Impairment

A history of renal impairment may be a risk factor for the development of rhabdomyolysis. These patients may be closely monitored for skeletal muscle effects (see section general caution).

▪ Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; CrCl ≤ 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.

[OVERDOSE]

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver function and CPK levels should be monitored.

▪ Ezetimibe

1) A few cases of overdosage with ezetimibe have been reported, most have not been associated with adverse reactions. Reported adverse reactions have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.
2) 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.

[PRECAUTIONS FOR STORAGE AND HANDLING]

1) Keep out of reach of children.
2) Store in the original package in order to maintain quality and prevent accidents.

[OTHERS]

▪ Rosuvastatin

1) Preclinical data reveal no special hazard for humans based on conventional studies of pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity potential.
   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.
2) 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. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

▪ Ezetimibe

1) Carcinogenicity: 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 x the human exposure at 10 mg daily based on AUC0-24hr 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 x the human exposure at 10 mg daily based on AUC0-24hr for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.
2) Mutagenicity: No evidence of mutagenicity was observed in vitro in a microbial mutagenicity 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.
3) Reproductive toxicity: In fertility studies conducted in rats taking ezetimibe orally, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 x the human exposure at 10 mg daily based on AUC0-24hr for total ezetimibe).

[Storage condition] Store at temperature not exceeding 30°C. Protect from light

[Caution] Food, Drugs, Devices and Cosmetic Act prohibits Dispensing without prescription

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

[Packaging unit] 30 tablets (10T/blistersx3)

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