Version 0.1, 12/2022

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Crezet film-coated tablet 10/5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Crezet film-coated tablet 10/5mg contains 5.2 mg Rosuvastatin Calcium (5 mg as Rosuvastatin) & Ezetimibe 10.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Crezet film-coated tablet 10/5 mg: Pink, oblong, film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypercholesterolemia
CREZET is administered as an adjunct to a diet to elevate total cholesterol (total-C), LDL-cholesterol (LDL-C), apo-B protein (Apo B), triglycerides (TG), and non-HDL-cholesterol, and to increase HDL-cholesterol (HDL-C) in patients with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia.
Many risk factors should be considered when administering lipid modifiers to patients with an increased risk of atherosclerotic vascular disease due to hypercholesterolemia. Lipid modifiers should be used in conjunction with an appropriate diet (including saturated fat and cholesterol restriction) and should be used in cases of insufficient response to diet and other non-pharmacological measures.
Prior to administration of CREZET, other secondary causes of dyslipidemia (e.g., diabetes, hypothyroidism, obstructive hepatic disease, chronic renal failure, drugs that increase LDL-cholesterol and drugs that decrease HDL-cholesterol [progestin, anabolic steroid, and corticosteroid]), and if necessary, secondary causes should be treated. The lipid test should include total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. If triglyceride levels are 400 mg/dL or more (>4.5 mmol/L), the LDL-cholesterol concentration should be determined by ultracentrifugation. In the case of hospitalization due to an acute coronary accident, lipids should be measured at the time of admission or within 24 hours after admission. This measurement can be used as a reference for initiating LDL-lowering therapy before or at the time of patient's discharge.

4.2 Posology and method of administration

CREZET is administered once a day regardless of meals.
Prior to or under CREZET, patients must continue on a standard cholesterol-lowering diet. The dosage of CREZET should be adjusted according to the patient's baseline LDL-cholesterol level, the recommended therapeutic target, and the patient's response.

Primary hypercholesterolemia
The dosage range of CREZET is 10/5 mg to 10/20 mg per day. A starting dose of 10/5 mg per day is recommended. For patients who require more LDL-cholesterol reduction, the dosage may be adjusted. After starting CREZET or after titrating the dose, check the blood lipid level at an interval of at least 4 weeks and adjust the dose accordingly. The dose can be increased to a maximum of 10/20 mg per day.

Patients who are taking ezetimibe and rosuvastatin in combination may switch to CREZET (fix-dose combination with the same content of each API) for their convenience.
Paediatric population: The safety and efficacy of Rosuvastatin/Ezetimibe in children below the age of 18 years has not yet been established.
Rosuvastatin/Ezetimibe is not suitable for initial therapy.

4.3 Contraindications

1) Patients with hypersensitivity to the main APIs or components of CREZET
2) Patients with active liver disease or patients with persistently elevated serum aminotransferase levels of unknown cause (see Section 'General Precautions')
3) Patients with myopathy
4) Patients receiving cyclosporine concomitantly
5) Patients with severe renal impairment (creatinine clearance (ClCr) < 30mL/min)
6) Pregnancy, breast-feeding and women of childbearing potential not using appropriate contraceptive measures. (see Section 'Use in Pregnant and Lactating Women')
7) Dosage of rosuvastatin 40 mg is contraindicated in patients prone to myopathy and/or rhabdomyolysis. These factors are as follows.
(1) Moderate renal impairment (creatinine clearance < 60ml/min)
(2) Hypothyroidism
(3) A history of genetic myopathy or a family history
(4) A history of muscle toxicity to other statins (HMG-CoA reductase inhibitors) or fibrates
(5) Alcoholism
(6) Situations where plasma concentrations may increase
(7) Asian patients
(8) Concomitant administration of fibrates
8) Since CREZET contains lactose, it should not be administered to patients with genetic problems such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

4.4 Special warnings and precautions for use

Warnings

Rhabdomyolysis accompanying secondary acute renal failure due to myoglobinuria has been rarely reported with rosuvastatin and other drugs in the same class. Therefore, treatment with CREZET should be temporarily withheld or discontinued in patients with acute server myopathy or patients with risk factors for secondary renal failure due to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and/or electrolyte disorders, uncontrolled seizures) (see Section ' General Precautions').

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

Based on its mechanism of action, efficacy of enavogliflozin depends on renal function.
Serum creatinine may be increased or eGFR may be decreased with this treatment. Renal function should be evaluated and patients with renal impairment should be monitored thoroughly. Assessment of renal function is recommended as follows:
- Prior to enavogliflozin initiation and thereafter periodically
- Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function
- In patients with eGFR of less than 60 mL/min/1.73m^2, more frequently.

The following patients should be administered carefully

1) Patients with alcoholic or hepatic diseases
2) Patients with moderate or severe hepatic disorders: Administration of CREZET is not recommended in patients with moderate or severe hepatic disorders as systemic exposure to rosuvastatin and ezetimibe may increase resulting unexpected effects.
3) Patients with the following factors that are prone to myopathy/rhabdomyolysis
- History of renal damage or renal disorders
- Hypothyroidism
- History of hereditary myopathy or family history
- History of muscle toxicity to statins or fibrates
- History of hepatic diseases or ingestion of significant amounts of alcohol
- An elderly over 70 years old with a factor of rhabdomyolysis
- In case plasma drug concentration may increase
4) Patients co-administering fibrates
5) Acutely severe conditions suggestive of exacerbation of secondary renal failure by myopathy or rhabdomyolysis (e.g., sepsis, hypotension, major surgery, wounds, severe metabolic, endocrine, and/or electrolyte disorders, uncontrolled epileptic seizures)

General Precautions

1) Myopathy & Rhabdomyolysis
In patients with a predisposition to myopathy/rhabdomyolysis (see Section '3. The following patients should be administered carefully'), the CPK level should be measured before administration and should be administered with caution. In these patients, the risks of treatment should be considered along with the benefits, and clinical monitoring is recommended.
The CPK level should not be measured after strenuous exercise or when there are other potential factors that may cause CPK elevation, as interpretation of CPK levels is difficult. If the CPK level has significantly increased from the baseline to more than 5 times the upper limit of normal, it should be measured again after 5-7 days to confirm the results.
If the CPK level has significantly increased from baseline to more than 5 times the upper limit of normal even after 5 to 7 days, treatment with CREZET should not be initiated.
Patients should be informed of the risk of myopathy when initiating CREZET, and patients should be instructed to report to their doctor immediately if muscle pain accompanied by malaise or fever, muscle spasms, or muscle weakness occurs while taking CREZET. In addition, if these symptoms occur, the CPK level should be measured, and if the CPK level increases significantly (>5 times the upper limit of normal), CREZET should be discontinued. Even if the CPK level is less than 5 times the upper limit of normal, if muscle symptoms are severe and daily discomfort occurs, CREZET should be discontinued. When symptoms improve and CPK levels return to normal, and re-administration of CREZET or other statin-containing preparations are administered, administer the lowest dose while closely monitoring the patient.

○ Rosuvastatin
As with other statins, effects on skeletal muscle, such as myalgia and myopathy, and rarely rhabdomyolysis, have been reported in patients receiving rosuvastatin. Immune-mediated necrotizing myopathy has been reported in patients taking or discontinued statins, including rosuvastatin. Immune-mediated myopathy is clinically characterized by proximal muscle weakness and an increase of plasma CPK level, and the symptoms persist even after discontinuation of administration.
In clinical trials, there is no evidence of an increased effect on skeletal muscle in a small number of patients treated with rosuvastatin in combination with other drugs. However, in the case of other statins, the incidence of myositis and myopathies increased in patients who were co-administered with fibric acid derivatives (including gemfibrozil), cyclosporin, nicotinic acid, azole antifungals, protease inhibitors, and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when used in combination with statins. Therefore, concomitant use of rosuvastatin and gemfibrozil is not recommended. The benefits and risks of co-administration of rosuvastatin with fibrate or niacin should be carefully evaluated. A dose of 40 mg of rosuvastatin is contraindicated when co-administered with fibrates.

○ Ezetimibe

The risk of musculoskeletal toxicity increases when there are factors such as co-administration with high-dose statins, the geriatrics (over 65 years old), hypothyroidism, renal failure, the type of administered statin, and co-administration with other drugs.
Myopathy and rhabdomyolysis have been reported post-marketing with ezetimibe. Most of the patients who developed rhabdomyolysis were taking statins prior to ezetimibe administration. However, rhabdomyolysis was also reported when ezetimibe was administered alone. Rhabdomyolysis has also been reported when co-administered with drugs that increase the risk of rhabdomyolysis, such as ezetimibe and fibric acid derivatives.
If myopathy is diagnosed or suspected when ezetimibe and fenofibrate are co-administered, ezetimibe and fenofibrate should be discontinued immediately. If the CPK level increases more than 10 times the upper limit of normal along with muscle symptoms, it can be considered myopathy.

2) Liver enzyme
Liver enzyme tests should be performed prior to initiation of CREZET treatment, and liver function tests should be repeated in patients with clinical signs or symptoms of liver damage. Patients with elevated transaminases should be monitored until symptoms improve. If transaminase continues to increase more than 3 times the upper limit of normal, it is recommended to reduce the dose or discontinue treatment of CREZET.
As a result of post-marketing surveillances in patients taking statins including rosuvastatin, fatal and nonfatal liver failure has rarely been reported.
If severe liver damage and/or hyperbilirubinemia or jaundice develops along with clinical symptoms during treatment with CREZET, immediately discontinue treatment of CREZET. If no other etiology is identified, do not re-administer CREZET.
CREZET should be administered with caution when administering to patients with alcohol overdose and/or a history of liver disease. CREZET should not be administered to patients with active liver disease or persistent elevations of unexplained serum transaminases. (see Section '2. Do not administer to the following patients')

○ Ezetimibe
In a controlled clinical trial, the incidence of persistent elevation of hepatic transaminase levels (more than 3 times the upper limit of normal) was similar in the ezetimibe group (0.5%) and the placebo group (0.3%). In a controlled clinical trial on the co-administration of ezetimibe and statins, the incidence of persistent elevation of hepatic aminotransferase levels (more than 3 times the upper limit of normal) was 0.6% in the ezetimibe and statin co-administration group. This elevation of aminotransferase was generally asymptomatic, not associated with biliary stasis, and returned to baseline after discontinuation of administration or even during continued administration.

3) Endocrine function
Increased HbA1c and fasting blood glucose levels have been reported in patients treated with statins including rosuvastatin. However, the benefit of reducing vascular risk by administration of statins outweighs the risk of hyperglycemia.

4) Interstitial lung disease
For some statins, unusual cases such as interstitial lung disease have been reported, especially during long-term administration. Symptoms that develop may include dyspnoea, unproductive cough, and deterioration of general health (fatigue, weight loss and fever). If a patient is suspected of having interstitial lung disease, treatment with statins should be discontinued.

5) Diabetes
There is some evidence that statins may cause hyperglycemia requiring appropriate diabetes treatment in some patients at high risk for future diabetes. However, since the vascular risk reduction effect of statins outweighs this risk, it cannot be a reason for discontinuing statins. Both clinical and laboratory level monitoring should be performed with patients at risks (fasting blood glucose of 5.6~6.9 mmol/L, BMI>30 kg/m^2, elevated triglyceride level, hypertension) according to the guidelines.

6) Co-administration with other drugs
(1) Anticoagulants: The INR should be appropriately monitored when CREZET is added to patients receiving warfarin, other coumarin anticoagulants, or fluindione. In addition, when administering CREZET

to a patient who is taking coumarin anticoagulants, the prothrombin time should be measured before administration and frequently enough at the beginning of treatment to confirm that the prothrombin time does not change significantly. Once a stable prothrombin time is established, it can be monitored periodically. If the dose of CREZET is changed or discontinued, the same procedure as above should be repeated.

(2) Fibrates: Fibrates may cause cholelithiasis by increasing cholesterol excretion into bile. If cholelithiasis is suspected in a patient co-administering CREZET and a fibrate, a gallbladder examination should be performed and an alternative therapy for lipid lowering should be considered.

(3) Bile acid-binding resin: CREZET should be administered 2 hours before or 4 hours after administration of the bile acid-binding resin.

(4) Fusidic acid: Since muscle-related adverse events, including rhabdomyolysis, have been reported in post-marketing surveillances after co-administration of rosuvastatin and fusidic acid, concomitant administration of rosuvastatin and fusidic acid is not recommended.

(5) Rosuvastatin act as a substrate for some transporter proteins, such as the hepatic absorption drug transporter OATP1B1 and the efflux transporter BCRP. Caution should be exercised when co-administering CREZET with an inhibitor of this transporter protein, as the plasma concentration of CREZET may increase resulting an increase of the risk of myopathy. (see Section '6. Drug Interactions').

7) Genetic polymorphism: Genotypes of SLCO1B1(OATP1B1)c. 521CC or ABCG2(BCRP) c.421AA have been reported to be associated with increased exposure (AUC) of rosuvastatin compared to SLCO1B1 c.521TT and ABCG2 c.421CC. Although the safety and efficacy of THID DRUG according to the genetic polymorphisms have not been established, it is necessary to adjust the dose according to the patient's therapeutic response and tolerability.

8) Women of childbearing potential
Women of childbearing potential should use appropriate contraception while taking CREZET.

9) Effect on driving and operating machinery: Although there have been no studies on the effect on driving and operating machinery, it should be considered that dizziness may occur in patients receiving CREZET.

10) Serious skin adverse events: Serious skin adverse events that may be life-threatening or fatal, such as Stevens-Johnson syndrome (SJS) or eosinophilia and drug response syndrome with systemic symptoms (DRESS), have been reported with rosuvastatin. When prescribing, patients should be advised for symptoms and signs of severe skin reactions, and closely monitored. If symptoms and signs suggestive of these skin reactions occur, CREZET should be immediately discontinued, and alternative treatments should be considered.
If a patient develops a severe reaction, such as Stevens-Johnson syndrome (SJS) or eosinophilia drug response syndrome with systemic symptoms (DRESS), due to the use of CREZET, treatment with CREZET should not be resumed at any time.

Pediatric Use
Since the safety and efficacy of CREZET in pediatrics have not been established, its administration is not recommended.

Geriatric Use
Old age (over 65 years old) is one of the factors prone to myopathy, so caution should be exercised when administering CREZET to the geriatrics. No dose adjustment is necessary in the geriatrics.

Use in Patients with Hepatic Disorders
CREZET should not be administered to patients with active liver disease or persistently high levels of hepatic aminotransferases of unknown cause (see Sections ‘2, Do not administer to the following patients’, and ‘5. General precautions’).

Use in Patients with Renal Disorders

A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Close monitoring of skeletal muscle effects may be helpful in these patients (see Section '5. General Precautions').

○ Ezetimibe
After administration of ezetimibe 10 mg once daily to patients with severe renal impairment (n=8, creatinine clearance ≤ 30 ml/min/1.73 m^2), the mean AUC of total ezetimibe was increased approximately 1.5 times compared to healthy subjects (n=9). These results are not clinically significant, and no dose adjustment is required for patients with renal impairment.

Others
○ Rosuvastatin
1) According to preclinical data based on general pharmacology studies, repeated dose toxicity studies, genotoxicity studies, and carcinogenicity studies, there is no special risk to humans. In prenatal and postnatal development studies in rats, reproductive toxicity such as a decrease in the size of the twins, a decrease in the weight of the twins, and a decrease in the survival of the next generation were observed. This effect was observed when a dose equivalent to several times the therapeutic dose was systemically administered to the mother.
2) According to the pharmacokinetic studies, the median AUC and C_{max} were approximately doubled in Asians (Japan, China, Philippines, Vietnam, and Korea) compared with Caucasians. According to the demographic pharmacokinetic analysis, there was no clinically significant pharmacokinetic differences between Caucasians and African Americans.

○ Ezetimibe
1) Carcinogenicity: A carcinogenicity test was conducted by orally administering up to the maximum dose of ezetimibe to male and female rats, 1500 mg/kg/day and 500 mg/kg/day (about 20 times the human exposure when administered at 10 mg/day based on $AUC_{0\text{-}24hr}$ of total ezetimibe), respectively, for 104 weeks. Another carcinogenicity test was conducted by orally administering up to the maximum dose of 500 mg/kg/day of ezetimibe (150 times or more of the human exposure when administered at 10 mg/day based on $AUC_{0\text{-}24hr}$ of total ezetimibe) to mice for 104 weeks. There was no statistically significant increase in tumor expression in rats and mice treated with the drug.

2) Mutagenicity: No mutagenicity was observed in the *in vitro* reversion mutation test for *Salmonella typhimurium* and *Escherichia coli* regardless of metabolic activity. In the *in vitro* chromosomal aberration test of cultured human peripheral blood lymphocytes, no chromosomal abnormalities were observed regardless of metabolic activity. In addition, no genotoxicity was observed in the *in vivo* micronucleus test in mice.

3) Reproductive toxicity: No reproductive toxicity was observed in a reproductive toxicity study in which ezetimibe was orally administered up to a maximum dose of 1000 mg/kg/day (about 7 times the human exposure when administered at 10 mg/day based on $AUC_{0\text{-}24hr}$ of total ezetimibe) in female and male rats.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant pharmacokinetic interactions were observed when ezetimibe and rosuvastatin, the main APIs of CREZET, were co-administered. Although studies on drug interactions between other drugs and the fixed-dose combination of rosuvastatin/ezetimibe were not conducted, studies on individual drugs of rosuvastatin and ezetimibe were conducted as follows.

○ Rosuvastatin
1) Effect of other drugs on rosuvastatin
According to the results of *in vitro* and *in vivo* studies, rosuvastatin does not show clinically significant interactions (acting as a substrate, inhibitor, or inducer) with cytochrome P450.
Rosuvastatin act as a substrate for some transporter proteins, such as the hepatic absorption drug transporter OATP1B1 and the efflux transporter BCRP. Concomitant use of inhibitors of this transporter protein and rosuvastatin may increase the plasma level of rosuvastatin resulting an increase of the risk of myopathy. (see the following Table).

<Effect of other drugs on exposure (AUC) of rosuvastatin (based on published clinical results)>

Concomitant Drug Therapy	Administration of Rosuvastatin	Change of Rosuvastatin AUC
Cyclosporin 75~200 mg, twice a day for 6 months	10 mg once a day for 10 days	Increased by 7.1 times
Darolutamide 600 mg, twice a day for 5 days	Single administration of 5 mg	Increased by 5.2 times
Regorafenib 160 mg, Once a day for 14 days	Single administration of 5 mg	Increased by 3.8 times
Atazanavir 300 mg / Ritonavir 100 mg, once a day for 8 days	Single administration of 10 mg	Increased by 3.1 times
Velpatasvir 100 mg, once a day	Single administration of 10 mg	Increased by 2.7 times
Ombitasvir 25 mg / Paritaprevir 150 mg / Ritonavir 100 mg, once a day / Dasabuvir 400 mg, twice a day for 14 days	Single administration of 5 mg	Increased by 2.6 times
Grazoprevir 200 mg / Elbasvir 50 mg, once a day for 11 days	Single administration of 10 mg	Increased by 2.3 times
Glecaprevir 400 mg / Pibrentasvir 120 mg, once a day for 7 days	5 mg, once a day for 7 days	Increased by 2.2 times
Lopinavir 400 mg / Ritonavir 100 mg, twice a day for 17 days	20 mg, once a day for 7 days	Increased by 2.1 times
After administration of a tolerance dose of 300 mg of Clopidogrel, administration of 75 mg 24 hours later	Single administration of 20 mg	Increased by 2 times
Gemfibrozil 600 mg, twice a day for 7 days	Single administration of 80 mg	Increased by 1.9 times
Single administration of Eltrombopag 75 mg for 5 days	Single administration of 10 mg	Increased by 1.6 times
Darunavir 600 mg / Ritonavir 100 mg, twice a day for 7 days	10 mg, once a day for 7 days	Increased by 1.5 times
Tipranavir 500 mg / Ritonavir 200 mg, twice a day for 11 days	Single administration of 10 mg	Increased by 1.4 times
Dronedarone 400 mg, twice a day	10 mg	Increased by 1.4 time
Itraconazole 200 mg, once a day for 5 days	Single administration of 10 mg Single administration of 80 mg	Increased by 1.4 times Increased by 1.3 times
Ezetimibe 10 mg, once a day for 14 days	10 mg, once a day for 14 days	Increased by 1.2 times
Fosamprenavir 700 mg / Ritonavir 100 mg, twice a day for 8 days	Single administration of 10 mg	No significant difference
Aleglitazar 0.3 mg for 7 days	40 mg for 7 days	No significant difference
Silymarin 140 mg, 3 times a day for 5 days	Single administration of 10 mg	No significant difference
Fenofibrate 67 mg, 3 times a day for 7 days	10 mg for 7 days	No significant difference
Rifampin 450 mg, once a day for 7 days	Single administration of 20 mg	No significant difference
Ketoconazole 200 mg, twice a day for 7 days	Single administration of 80 mg	No significant difference
Fluconazoe 200 mg, once a day for 11 days	Single administration of 80 mg	No significant difference
Erythromycin 500 mg, 4 time a day for 7 days	Single administration of 80 mg	Reduction of 20%
Baicalin 50 mg, 3 times a day for 14 days	Single administration of 20 mg	Reduction of 47%

Effects of Other Drugs

(1) Antacid: As a result of co-administration of an antacid containing aluminum hydroxide or magnesium hydroxide with rosuvastatin, the plasma concentration of rosuvastatin decreased by about 50%. However, this effect was alleviated when the antacid was administered 2 hours after administration of rosuvastatin. The clinical relevance of this interaction has not been studied.

(2) Fusidic acid: No studies have been conducted on the interaction between rosuvastatin and fusidic acid. As with other statins, muscle-related adverse events including rhabdomyolysis have been reported when rosuvastatin and fusidic acid were used in combination in post-marketing surveillances. Therefore, concomitant use of rosuvastatin and fusidic acid is not recommended. Temporary discontinuation of rosuvastatin administration is recommended if possible, and close monitoring should be performed if administration is unavoidable.

2) Effect of Rosuvastatin on other drugs

(1) Warfarin: When used in combination with rosuvastatin, warfarin has no significant pharmacokinetic effects. However, as with other statins, when rosuvastatin and warfarin are administered in combination, the INR may increase compared to when warfarin is administered alone. INR monitoring is recommended when starting, discontinuing, or adjusting the dose of rosuvastatin in patients receiving vitamin K antagonists (e.g., warfarin).
(2) Cyclosporine: Co-administration of rosuvastatin and cyclosporine does not affect the plasma concentration of cyclosporin.
(3) Fenofibrate/fibric acid derivatives: Although pharmacokinetic interactions between fenofibrate and rosuvastatin were not observed, pharmacokinetic interactions may occur. Gemfibrozil, fenofibrate, other fibrates, and nicotinic acid in lipid-lowering doses (at least 1 g per day) can cause myopathy when administered alone, increasing the risk of myopathy when administered in combination with statins. In case of co-administration of fibrates and rosuvastatin, 40 mg of rosuvastatin is contraindicated, and the starting dose should be 5 mg.
(4) Oral contraceptives: When administered in combination with oral contraceptives, the AUCs of ethinyl oestradiol and norgestrel were increased by 26% and 34%, respectively. This increase in plasma concentration should be taken into account when selecting the dose of oral contraceptives. Since there are no pharmacokinetic data on patients using rosuvastatin and HRT in combination, similar effects should not be excluded, but co-administration was often used in women and tolerability was excellent in clinical trials.
(5) Effect on other drugs: No clinically significant interaction was observed with digoxin or ezetimibe.

○ Ezetimibe
1) Cholestyramine: When ezetimibe and cholestyramine were administered in combination, the mean AUC of total ezetimibe decreased by about 55%. Due to this interaction, the combined action on LDL-C lowering expected from co-administration of cholestyramine and ezetimibe may be reduced.

2) Fibrates: The safety and efficacy of co-administration of ezetimibe and fenofibrate in clinical trials were evaluated. Co-administration of ezetimibe with other fibrates has not been studied. Fibrates can cause gallstones by increasing cholesterol excretion into bile. Ezetimibe increased gallbladder bile cholesterol in a preclinical study in dogs. Although the relevance of these preclinical results to humans is unknown, co-administration of ezetimibe and fibrates (except fenofibrate) is not recommended until the results of studies in patients are available.
(1) Gemfibrozil: In a pharmacokinetic study, co-administration of ezetimibe and gemfibrozil increased the total ezetimibe concentration by about 1.7-fold, but it was not clinically significant. Relevant clinical data are not yet available.
(2) Fenofibrate: If cholelithiasis is suspected in patients treated with ezetimibe and fenofibrate in combination, the gallbladder should be examined and other lipid-lowering treatments should be considered. In a pharmacokinetic study, co-administration of ezetimibe and fenofibrate increased the total ezetimibe concentration by about 1.5-fold, but it was not clinically significant.

3) Statins: No clinically significant pharmacokinetic interactions were observed when ezetimibe were co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

4) Cyclosporine: Caution should be exercised when co-administering ezetimibe to patients receiving cyclosporine. If ezetimibe and cyclosporine are co-administered, the concentration of cyclosporine should be monitored. When a stable dose of cyclosporine (75-150 mg twice daily) and ezetimibe were co-administered to 8 patients with mild renal impairment or normal renal function (creatinine clearance > 50 mL/min) who have received a kidney transplant, the mean AUC and C_{max} of total ezetimibe increased by 3.4-fold (range of 2.3-7.9 times) and 3.9-fold (range of 3.0-4.4 times), respectively, compared to a healthy historical control group (n=17). In another clinical study, in one patient with severe renal impairment (creatinine clearance = 13.2 mL/min/1.73 m^2) who has received a kidney transplant, administration of several drugs, including cyclosporine, resulted in a 12-fold increase in total ezetimibe exposure. In a 2-period crossover study involving 12 healthy volunteers, after administration of 20 mg of ezetimibe once a day for 8 days and single administration of 100 mg of cyclosporine on Day 7, the AUC of cyclosporine was increased by an average of 15% (range of 10% reduction to 51% elevation) compared to the single administration of 100 mg of cyclosporine alone, the control group.

5) Anticoagulants: When ezetimibe and warfarin, other coumarin anticoagulants, or fluindione are co-administered, the prothrombin time (International Normalized Ratio (INR)) should be appropriately

monitored. In a clinical study involving 12 healthy adult males, co-administration of warfarin and ezetimibe (10 mg per day) did not significantly affect the bioavailability of warfarin and the prothrombin time. There have been reports of increased INR in patients treated with ezetimibe and warfarin or fluindione in combination post-marketing. Most of these patients were also receiving other medications.

4.6 Fertility, pregnancy and lactation

1) ROSUVASTATIN / EZETIMIBE is contraindicated in pregnancy and breast-feeding. Women of childbearing potential should use appropriate contraceptive measures.

2) Pregnancy

- Rosuvastatin: Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of ROSUVASTATIN/ EZETIMIBE, treatment should be discontinued immediately.
- Ezetimibe: No clinical data are available on the use of ezetimibe during pregnancy. Animal studies on the use of Ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development.

3) Breast-feeding

- Rosuvastatin: Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion of Rosuvastatin in milk in humans.
- Ezetimibe: Studies on rats have shown that Ezetimibe is secreted into milk. It is not known if Ezetimibe is secreted into human breast milk.

4) Fertility

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

4.7 Effects on ability to drive and use machines

Symptoms of hypoglycemia may occur. Patients should be advised to take precautions to avoid hypoglycemia while driving and using machines.

4.8 Undesirable effects

Summary of Safety Profile

- The adverse reactions seen with Rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4 % of Rosuvastatin - treated patients were withdrawn due to adverse reactions.
- In clinical studies of up to 112 weeks duration, Ezetimibe 10 mg daily was administered alone in 2396 patients, or with a statin in 11,308 patients or with fenofibrate in 185 patients. Adverse reactions were usually mild and transient. The overall incidence of side effects was similar between Ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between Ezetimibe and placebo.
- According to available data 1200 patients took Rosuvastatin and Ezetimibe combination in clinical studies. As reported in the published literature, the most frequent common adverse events related to Rosuvastatin Ezetimibe combination treatment in hypercholesterolemic patients are increased hepatic transaminases, gastrointestinal problems and muscle pain. These are known undesirable effects of the active substances. However, a pharmacodynamic interaction, in terms of adverse effects, between Rosuvastatin and Ezetimibe cannot be ruled out.
- Adverse drug reactions previously reported with one of the individual components (Ezetimibe or Rosuvastatin) may be potential undesirable effects with ROSUVASTATIN / EZETIMIBE.
- Tabulated list of adverse reactions
  - The frequencies of adverse events are ranked according to the following: Common (> 1/100 to 1

/ 1,000 to 1 / 10,000 to

MedDRA system organ class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Thrombocytopenia		Thrombocytopenia
Immune system disorders			Hypersensitivity reactons including angioedema		Hypersensitivity (including rash, urticaria, anaphylaxis and angioedema)
Endocrine disorders	Diabetes mellitus				
Metabolism and Nutrition Disorders		Decreased appetite			
Psychiatric disorders					Depression
Nervous system disorders	Headache, dizziness	paresthesia		Polyneuropathy, memory loss	Peripheral neuropathy, sleep disturbances (including insomnia and nightmares), dizziness, paresthesia
Vascular Disorders		Hot flush, hypertension			
Respiratory, thoracic and mediastinal disorders		cough			Cough, dyspnoea
Gastrointestinal disorders	Constipation, nausea, abdominal pain, diarrhoea, flatulence	Dyspepsia, gastrooesophageal reflux disease, nausea, dry mouth, gastritis	pancreatitis		Diarrhoea, pancreatitis, Constipation
Hepatobilliary disorders			Increased hepatic transaminases	Jaundice, hepatitis	Hepatitis, Choledocholithiasis, cholecystitis,
Skin and subcutaneous tissue diisorders		Pruritus, rash, urticaria			Steven-Johnsons syndrome, erythema multiforme
Musculoskeletal and connective tissue disorders	myalgia	Arthralgia, muscle spasm, neck pain, back pain, muscular, weakness, pain in extremity	Myopathy (including myositis), rhabdomyolisis	arthralgia	Immune-mediated necrotizing myopathy, tendon disorders, sometimes complicated by rupture, arthralgia, myalgia, myopathy, rhabdomyolysis

Renal and urinary disorders				Hematuria	
Reproductive system and breast disorders				Gynecomastia	
General disorders and administration site condition	Asthenia, fatigue	Chest pain, pain, asthenia oedema peripheral			Oedema, asthenia
Investigations	ALT and/or AST increased	ALT and/or AST increased, blood CPK increased, gamma-glutamyl-transferase increased, liver function test abnormal			

- 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
- 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), the treatment should be discontinued.
- Liver Effects: As with other HMG - CoA reductase inhibitors , a dose - related increase in transaminases has been observed in a small number of patients taking Rosuvastatin; the majority of cases were mild, asymptomatic and transient.
- The following adverse events have been reported with some statins:
  - Sexual dysfunction
  - Exceptional cases of interstitial lung disease, especially with long term therapy
- The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) are higher at the 40 mg rosuvastatin dose.
- Laboratory values: In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and / or AST 3XULN, 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.
- In clinical trials, CPK > 10X 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).
- Paediatric population: The safety and efficacy of ROSUVASTATIN / EZETIMIBE in children below the age of 18 years has not yet been established.

○ Rosuvastatin/Ezetimibe fixed-dose combination

1) The safety of CREZET was evaluated in a rosuvastatin-controlled clinical trial in 377 patients with primary hypercholesterolemia. This clinical trial consists of an 8-week treatment period and a 12-week extension period, and the 12-week extension treatment was conducted in 295 patients who have completed the 8-week treatment period and whose LDL-C levels have reached the treatment goal according to the risk of cardiovascular disease.

(1) Adverse events collected during the 8-week treatment period
The most commonly reported adverse events during this period were nasopharyngitis (3.2%), dyspepsia (1.6%), ALT elevation (1.3%), edema (1.1%), and myalgia (1.1%). Adverse events related to CREZET were 4 cases of ALT elevation, 2 cases of CPK elevation, 2 cases of AST elevation, 2 cases of headache, 1 case of acute pyelonephritis, 1 case of dry mouth, 1 case of liver enzyme elevation, 1 case of liver function test abnormality, 1 case of increase in blood lactate dehydrogenase, 1 case of edema, and 1 case of pruritus, all of which were mild or moderate. and blood There were 1 case of increased lactate dehydrogenase, 1 case of edema, and 1 case of pruritus, all of which were mild or moderate.
(2) Adverse events collected over an extended period of 12 weeks
The most commonly reported adverse events during this period were nasopharyngitis (3.73%), ALT elevation (3.05%), AST elevation (3.05%), dyspepsia (1.36%), upper respiratory tract infection (1.36%), increased plasma glucose (1.36%), increased plasma lactate dehydrogenase (LDH) (1.36%), increased plasma CPK (1.02%), increased liver enzymes (1.02%), chest discomfort (1.02%), and pruritus (1.02%). The incidence of other adverse events was less than 1%. As in the 8-week rosuvastatin-controlled clinical trial, no specific adverse events of CREZET were observed.

<Table 1> Adverse events reported in ≥ 1% of patients during the 8-week treatment period

	Rosuvastatin Treatment Group (N=187)			CREZET Treatment Group (N=190)			Total Treatment Group
AE by SOC	5mg (N=62) N	10mg (N=62) N	20mg (N=63) N	10/5mg (N=63) N	10/10mg (N=64) N	10/20mg (N=63) N	(N=377) N (%)
Infection & Infestation Nasopharyngitis	2	0	1	4	1	4	12 (3.25%)
Gastrointestinal system Indigestion	0	1	1	1	2	1	6 (1.6%)
Investigation ALT elevation	0	1	0	0	1	3	5 (1.3%)
General disorders & Administration site conditions Edema	1	1	0	0	0	2	4 (1.1%)
Musculoskeletal & Connective tissue disorders Myalgia	1	0	1	0	2	0	4 (1.1%)

2) Results of post-marketing surveillance (PMS) in Korea following re-examination
For re-examination in Korea, 6 post-marketing surveillances on fixed-dose combination of ezetimibe/rosuvastatin were conducted in a total of 10,317 subjects for 6 years. The incidences of adverse events for each PMS regardless of causal relationship were 11.11% (71/639 subjects, 101 cases), 11.61% (529/4556 subjects, 790 cases), and 15.85% (100/631 subjects, 156 cases), 11.73% (306/2,608 subjects, 412 cases), 6.76% (85/1,258 subjects, 117 cases), and 6.88% (43/625 subjects, 59 cases), respectively. Among these, serious adverse drug reactions in which causality cannot be excluded and unexpected adverse drug reactions in which causality cannot be excluded have been reported as shown in the following table.

System Organ Class (SOC)	Serious Adverse Event	Unexpected Adverse Drug Reaction
General disorders & Administration site conditions	Chest pain (1 subject)	Facial edema (3 subjects), Strange feeling (2 subjects), Drug intolerance (1 subject)
Gastrointestinal disorders	Colon polyp (1 subject)	Irritable bowel syndrome (2 subjects), Colon polyps (1 subject), Esophagitis (1 subject)
Nervous system disorders	Dizziness (1 subject)	Lethargy (1 subject), Neurodegenerative disorder (1 subject), Postural dizziness (1 subject), Migraine (1 subject)
Metabolism & Nutrition disorders	Diabetes (1 subject)	Glucose tolerance disorder (1 subject)
Psychiatric disorders	Depression (1 subject)	
Infections & Infestations		Bronchitis (5 subjects), Rhinitis (2 subjects),

		Cystitis (2 subjects), Onychodermatophytosis (1 subject), Cellulitis (1 subject)
Hepatobiliary disorders		Hepatic steatosis (3 subjects), Hepatic disorder (2 subjects), Liver toxicity (1 subject), Acute hepatitis (1 subject), Toxic hepatitis (1 subject)
Investigations		Increased γ-glutamyltransferase (2 subjects), Increased plasma cholesterol (2 subjects), Increased plasma alkaline phosphatase (1 subject), Irregular heart rate (1 subject)
Musculoskeletal & Connective tissue disorders		Bronchitis (1 subject), Osteoporosis (1 subject), Musculoskeletal stiffness (1 subject), Musculoskeletal discomfort (1 subject), Muscle weakness (1 subject)
Skin & Subcutaneous tissue disorders		Cold sweat (1 subject), Dermatitis (1 subject), Skin burning (1 subject), Skin disorders (1 subject), Alopecia (1 subject)
Respiratory, Thoracic & Mediastinal disorders		Oropharyngeal pain (2 subjects), Stuffy nose (1 subject), Respiratory disorders (1 subject)
Reproductive system & Breast disorders		Pelvic pain (1 subject), Breast cyst (1 subject)
Eye disorders		Blepharoptosis (1 subject), Diabetic retinopathy (1 subject)
Ear & Labyrinth disorders		Ear discomfort (1 subject)
Renal & Urinary disorders		Renal dysfunction (1 subject)
Neoplasms benign, Malignant and Unspecified (incl. cysts and polyps)		Benign esophageal neoplasm (1 subject)

* The number of incidences of serious adverse drug reactions and unexpected adverse drug reactions listed in the table above are the aggregated results of each post-marketing surveillances (PMSs).

The following information is based on data collected from clinical trials and post-marketing surveillances of the individual components of rosuvastatin and ezetimibe.

○ Information collected from Rosuvastatin

1) The reported adverse events were generally mild and transient. Patients who discontinued the study due to adverse events in the Rosuvastatin treatment group were less than 4%.

The incidence of adverse events was classified as follows.

Common (>1/100, <1/10);
Uncommon (>1/1,000, <1/100);
Rare (>1/10,000, <1/1,000);
Very rare (<1/10,000).
Unknown (cannot be inferred from available data.)

<Table 2> Adverse events that occurred after administration of Rosuvastatin

Onset System	Incidence by Symptoms		
	Common	Uncommon	Rare
Immune system			Hypersensitivity reactions including angioedema
Endocrine system	Diabetes[1)]		
Nervous system	Headache, Dizziness		
Gastrointestinal system	Constipation, Nausea, Abdominal pain		Pancreatitis
Skin & Subcutaneous tissue		Itching, Rash, Hives	
Musculoskeletal system & Connective tissue	Myalgia		Myopathy (including myositis), rhabdomyolysis
General system	Asthenia		
Footnote 1: The most frequently reported adverse event in patients with fasting blood glucose of 5.6 to 6.9 mmol/L in the JUPITER clinical study (2.8% for Rosuvastatin treatment group and 2.3% for placebo group, respectively)			

As with other statins, adverse events tended to increase with increasing dose.

2) Effect on kidney: Proteinuria, mostly tubular origin, detected by Dipstick test was observed. The conversion of urine protein from negative or trace amounts to more than ++ was observed in less than 1% in 10 and 20 mg and about 3% in 40 mg. A slight increase of urine protein from negative or trace amounts to + was also observed in 20 mg dose. Proteinuria decreased or spontaneously disappeared during treatment in most cases and is not a predictor of acute or progressive renal failure. Hematuria was observed in patients treated with rosuvastatin and in clinical trial data, but the incidence was low.

3) Effect on musculoskeletal system: Effect on musculoskeletal system with or without acute renal failure (e.g., myalgia, myopathy (including myositis), rarely rhabdomyolysis, etc.) has been reported in patients treated with rosuvastatin in all doses (especially 20 mg or more). There was a dose-dependent increase in creatinine kinase (CK) levels in the patient group receiving rosuvastatin. Most cases were mild, asymptomatic, and transient. If the creatinine kinase (CK) level significantly increases (more than 5 times the upper limit of normal), treatment should be temporarily stopped.

4) Effect on liver: As with other statins, transaminase levels increased in a dose-dependent manner in a small number of patients treated with rosuvastatin. Most cases were mild, asymptomatic, and transient.

5) Post-marketing surveillances in overseas
In addition to the above adverse events, the following adverse events were reported during post-marketing surveillances (PMSs).
- Nervous system: Very rarely polyneuropathy, amnesia, peripheral neuropathy (incidence unknown)
- Respiratory system & Chest: Cough, dyspnea (incidence unknown)
- Gastrointestinal system: Diarrhea (incidence unknown)
- Hematological disorders: Thrombocytopenia (incidence unknown)
- Hepatobiliary system: Very rarely jaundice and hepatitis, rarely increased transaminase
- Skin & Subcutaneous tissue disorders: Stevens-Johnson syndrome (incidence unknown), drug response syndrome with eosinophilia and systemic symptoms (DRESS) (incidence unknown)
- Musculoskeletal system: Rarely lupus-like syndrome and muscle rupture, very rarely arthralgia and immune-mediated necrotizing myopathy (incidence unknown)
- Kidney: Very rarely hematuria
- Others: Edema (incidence unknown)

The following adverse events have been reported with some statins.
- Mental nervous system: Depression, Sleep disorders (including insomnia and nightmares) (incidence unknown)
- Respiratory system: Exceptional cases such as interstitial lung disease, especially during long-term administration
- Urogenital system: Sexual dysfunction, Gynecomastia (incidence unknown)
- Hepatobiliary system: Fatal and nonfatal liver failure

There have been rare reports of post-marketing cognitive impairments associated with statin use (e.g., hypomnesis, amnesia, loss of memory, memory impairment, confusion). These cognitive impairments have been reported with all statins. These reports are generally not serious and are reversible after discontinuation of drug use, and the time of symptom onset (1 day to several years) and symptom improvement (median value of 3 weeks) vary.

6) Results of post-marketing surveillances in Korea
As a result of a use result surveillance conducted on 3,081 subjects for 6 years for re-examination in Korea, the incidence rate of adverse events was 10.06% (310 subjects, 415 cases), regardless of the causal relationship. The reported adverse events were mainly headache 0.78% (24 subjects, 24 cases), dizziness. 0.75% (23 subjects, 23 cases), ALT elevation 0.58% (18 subjects, 18 cases), and chest pain, cough, and muscle pain 0.49% (15 subjects, 15 cases), respectively, of which 2.92% (90 subjects, 106 cases) were adverse drug reactions that could not exclude a causal relationship with rosuvastatin.
Among the reported adverse drug reactions, ALT elevation was the most by 0.55% (17 subjects, 17 cases), followed by myalgia 0.42% (13 subjects, 13 cases), headache 0.39% (12 subjects, 12 cases), increased CK 0.29% (9 subjects, 9 cases), dizziness 0.26% (8 subjects, 8 cases), constipation and AST elevation 0.16%

respectively (5 subjects, 5 cases), asthenia and joint pain 0.13% respectively (4 subjects, 4 cases), fatigue and numbness 0.10% respectively (3 subjects, 3 cases), paresthesia, chest discomfort, nausea, abdominal pain, diarrhea, anorexia, abdominal distension, itching, and liver function test abnormality 0.06% respectively (2 subjects, 2 cases), syncope, generalized pain, muscle spasm, gout, and erectile dysfunction 0.03% respectively (1 subject, 1 case). Among them, myalgia, and joint pain in 1 subject were serious adverse drug reactions. Unexpected adverse drug reactions that did not appear before marketing were joint pain 0.13% (4 subjects, 4 cases), fatigue and numbness 0.10% respectively (3 subjects, 3 cases), paresthesia, chest discomfort, anorexia, abdominal distension, liver function test abnormality 0.06% respectively (2 subjects, 2 cases), syncope, generalized pain, muscle spasm, gout, and erectile dysfunction 0.03% respectively (1 subject, 1 case), and 1 case of joint pain was reported as a suspected unexpected serious adverse reaction (SUSAR).
During the re-examination period, 98 cases were reported voluntarily, of which 2 cases of acute renal failure, 1 case each of oliguria, thrombocytopenia, and increased blood creatinine were reported as suspected unexpected serious adverse reactions (SUSARs).

○ Information collected from Ezetimibe
The safety of ezetimibe was evaluated in clinical trials conducted on more than 4,700 patients. As a result of clinical trials on ezetimibe (either administered alone or in combination with an HMG-CoA reductase inhibitor), ezetimibe was generally well tolerated. The total incidence of adverse events reported with ezetimibe was similar to that reported with placebo, and the rate of discontinuation due to adverse events was also similar to that of placebo.

1) Single administration
<Table 3> shows adverse events reported in more than 2% of patients treated with ezetimibe regardless of causality evaluation and reported at a higher rate than in the placebo group in placebo-controlled clinical trials.

<Table 3*> Clinical adverse events reported in ≥2% of patients treated with CREZET regardless of causality evaluation and reported at a higher rate than in the placebo group

AE by SOC	Placebo (%) n = 795	Ezetimibe 10 mg (%) n = 1691
General system		
Fatigue	1.8	2.2
Digestive system		
Abdominal pain	2.8	3.0
Diarrhea	3.0	3.7
Infection		
Virus infection	1.8	2.2
Pharyngitis	2.1	2.3
Sinusitis	2.8	3.6
Musculoskeletal system		
Joint pain	3.4	3.8
Lumbago	3.9	4.1
Respiratory system abnormalities		
Cough	2.1	2.3

* Includes the patients under sing administration of placebo or CREZET reported in <Table 4>
The incidence rates of other adverse events with lower incidence than the above adverse events were similar between the ezetimibe group and the placebo group (see Table 4).

2) Co-administration with HMG-CoA reductase inhibitor
The safety of ezetimibe was evaluated in more than 2,000 patients in a co-administration clinical study. Adverse reactions after co-administration of ezetimibe and HMG-CoA reductase inhibitor were generally similar to those after administration of HMG-CoA reductase inhibitor alone. However, the incidence of aminotransferase level elevation was slightly higher in patients treated with ezetimibe and an HMG-CoA reductase inhibitor in combination compared to patients who received HMG-CoA reductase inhibitor alone.
<Table 4> shows adverse events reported in more than 2% regardless of causality evaluation and reported at a higher rate than in the placebo group in 4 placebo-controlled clinical trials in which ezetimibe was administered alone or administration of ezetimibe was initiated in combination with various HMG-CoA reductase inhibitors.

<Table 4*> Clinical adverse events reported in more than 2% of patients regardless of causality evaluation and reported at a higher rate than in the placebo group in clinical trials in which ezetimibe and stains were administered in combination

AE by SOC	Placebo (%) n = 259	Ezetimibe 10 mg (%) n = 262	Statins** (%) n = 936	Ezetimibe + statins (%) n = 925
General system				
Chest pain	1.2	3.4	2.0	1.8
Dizziness	1.2	2.7	1.4	1.8
Fatigue	1.9	1.9	1.4	2.8
Headache	5.4	8.0	7.3	6.3
Digestive system				
Abdominal pain	2.3	2.7	3.1	3.5
Diarrhea	1.5	3.4	2.9	2.8
Infection				
Pharyngitis	1.9	3.1	2.5	2.3
Sinusitis	1.9	4.6	3.5	3.5
Upper respiratory tract infection	10.8	13.0	11.8	11.8
Musculoskeletal system				
Joint pain	2.3	3.8	3.4	3.4
Lumbago	3.5	3.4	4.3	4.3
Myalgia	4.6	5.0	4.5	4.5

* Includes 4 placebo-controlled concomitant trials in which administration of ezetimibe was initiated concurrently with an HMG-CoA reductase inhibitor.
** Statins = All doses of all HMG-CoA reductase inhibitors

3) Co-administration with fenofibrate
A multicenter, double-blind, placebo-controlled clinical trial was conducted on 625 patients with mixed hyperlipidemia up to 12 weeks and on 576 patients with mixed hyperlipidemia up to a year. This study is not designed to compare rarely occurred adverse events between treatment groups. The incidence (95% CI) of clinically significant elevations of serum transaminases (≥3 times the upper limit of normal, sustained) was 4.5% (1.9, 8.8) in the fenofibrate alone administered group and 2.7% (1.2, 5.4) in the ezetimibe and fenofibrate co-administered group when the exposure was adjusted. The incidence of cholecystectomy was 0.6% (0.0, 3.1) in the fenofibrate alone administered group and 1.7% (0.6, 4.0) in the ezetimibe and fenofibrate co-administered group. There was no case in which creatine phosphokinase (CPK) increased more than 10 times the upper limit of normal in each administration group in this study.

4) Commonly reported adverse events (≥1/100, <1/10) related with the investigational product in the group treated with ezetimibe alone (n=1691), group treated with ezetimibe and statins in combination (n=1675), or group treated with ezetimibe and fenofibrate in combination (n=185) are as follows;
• Group treated with ezetimibe alone: Headache, abdominal pain, diarrhea
• Group treated with ezetimibe and statins in combination: Headache, fatigue, abdominal pain, constipation, diarrhea, flatulence, nausea, AST elevation, ALT elevation, myalgia
• Group treated with ezetimibe and fenofibrate in combination: Abdominal pain

5) Adverse events after post-marketing
The following adverse events were reported post-marketing regardless of causality evaluation;
Anaphylaxis, urticaria, hypersensitivity reactions including rash and angioedema, erythema multiforme, arthralgia, myalgia, elevated creatine phosphokinase levels, myopathy/rhabdomyolysis, elevated liver aminotransferase levels, hepatitis, abdominal pain, thrombocytopenia, nausea, pancreatitis, dizziness, paresthesia, depression, headache, cholelithiasis, cholecystitis

6) Results of post-marketing surveillance in Korea
As a result of a post-marketing survey in 3,536 patients for 6 years for re-examination in Korea, the incidence of adverse events was reported to be 7.27% (257/3,536 patients, 422 cases) regardless of causal relationship. The most commonly reported adverse event (≥1.0%) was fatigue by 1.05% (37/3,536 patients, 37 cases).
The incidence rate of adverse drug reactions, which is an adverse event that cannot exclude a causal relationship with ezetimibe, was 1.95% (69/3,536 patients, 108 cases). ALT elevation and AST elevation were the most common at 0.28% (10/3,536 patients, 10 cases) respectively, followed by diarrhea at 0.17% (6/3,536 patients, 6 cases), indigestion and dizziness at 0.14% (5/3,536 patients, 5 cases) respectively, and

nausea at 0.11% (4/3,536 patients, 4 cases). Other adverse drug reactions reported less than 0.1% by system organ class are as follows;
- General system: Fatigue, chest pain, chest discomfort, edema, asthenia, generalized edema
- Nervous system: Headache, diabetic neuropathy, tremor
- Digestive system: Epigastric pain, vomiting, abdominal pain, gastritis, constipation, dry mouth, stomach discomfort, belching, gastrointestinal disorder, gastroesophageal reflux disease (GERD), tongue disease
- Cardiovascular system: Palpitations, congestive heart failure, myocardial ischemia, flushing
- Respiratory system: Cough, sputum, runny nose
- Musculoskeletal system: Extremity pain, joint pain
- Metabolism and Nutrition: Diabetes, hypoglycemia
- Blood system: Anemia, splenomegaly
- Skin: Urticaria, hyperhidrosis, rash, itching
- Infection: Upper respiratory tract infection
- Eye: Conjunctival hyperemia
- Urinary system: Renal failure (renal disease)
- Hepatobiliary system: Hepatic dysfunction
- Laboratory tests: Increased blood creatinine, increased blood pressure, increased blood urea, increased CPK, abnormal in hepatic function test

7) Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Pusat Farmakovigilans/MESO Nasional

Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif

Badan Pengawas Obat dan Makanan

Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079

Website: https://e-meso.pom.go.id/ADR

4.9 Overdose

There is no specific treatment recommended for overdosage with CREZET. In case of an overdose of CREZET, treatment according to the symptoms and appropriate supportive care should be provided. In addition, liver function tests and serum CPK levels should be monitored.

○ Ezetimibe
1) There have been several reports of overdose with ezetimibe. Most were not accompanied by adverse events, and even the reported adverse events were not serious. In case of overdose, general symptomatic and supportive care should be used.
2) In clinical trials, when 50 mg of ezetimibe per day was administered to 15 healthy subjects for up to 14 days or when 40 mg of ezetimibe per day was administered to 18 patients with primary dyslipidemia up to day 56, the tolerability was generally excellent.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clinical efficacy and safety

In clinical studies, randomization and double-blindness were used to prevent bias in the study conduct and result analysis. In addition, all subjects underwent placebo run-in period for a certain period to minimize the bias in the results.

Percent change of LDL-C from baseline was the primary efficacy endpoint in two studies (including extension study) in patients with dyslipidemia.

LDL-C is a key index to evaluate the efficacy in clinical studies in patients with dyslipidemia and was used as an efficacy endpoint. Based on difference of the percent change between Crezet group and rosuvastatin group, the efficacy was confirmed. The test was conducted at baseline, Weeks 4 and 8 in subjects of rosuvastatin 5 mg, 10 mg and 20 mg groups and Crezet 10/20 mg, 10/10 mg and 10/5 mg groups. Later, in subjects participating in the extension study, test was conducted at Weeks 12 (4 weeks of extension treatment), Week 16 (8 weeks of extension treatment) and Week 20 (12 weeks of extension treatment).

LS mean of percent change of LDL-C at Week 4 from baseline was -58.50±1.34% in Crezet group and -48.38±1.36% in rosuvastatin group, showing significantly greater decrease in Crezet group, compared to rosuvastatin group (p<0.0001). In comparison of individual dose groups, all of Dose Groups 1, 2 and 3 showed significantly greater decrease in Crezet group, compared to rosuvastatin group (p<0.0001, p=0.0022, p=0.0089 for each).

Percent change of LDL-C at Week 8 from baseline was -61.60±1.44% in Crezet group and -50.50±1.45% in rosuvastatin group, showing significantly greater decrease in Crezet group, compared to rosuvastatin group (p<0.0001). In comparison of individual dose groups, all of Dose Groups 1, 2 and 3 showed significantly greater decrease in Crezet group, compared to rosuvastatin group (p<0.0001, p=0.0039, p=0.0033 for each).

Table 5. Mean±Standard Deviation of LDL-C in Pooled Dose Group at Each Measurement Time Point_Main Study

LDL-C		pooled			percent change (%)		
		Crezet	Rosuvastatin	*p*-value	Crezet	Rosuvastatin	*p*-value
Baseline (mg/dL)	n	185	181				
	Mean±SD	158.77±29.03	162.73±32.07				
Week 4 (mg/dL)	n	185	181		185	181	
	Mean±SD	64.87±22.98	82.95±26.56		-58.46±15.32	-48.75±14.36	
	LS Mean±SE				-58.50±1.34	-48.38±1.36	<0.0001
Week 8 (mg/dL)	n	185	181		185	181	
	Mean±SD	60.20±20.17	80.19±30.24		-61.17±15.27	-50.56±16.58	
	LS Mean±SE				-61.60±1.44	-50.50±1.45	<0.0001

Table 6. Mean±Standard Deviation of LDL-C by Dose and the Percent Change at Measurement Time Point_Main Study

LDL-C		Dose Group 1		Dose Group 2		Dose Group 3	
		Crezet 5/10 mg	RSV 5 mg	Crezet 10/10 mg	RSV 10 mg	Crezet 20/10 mg	RSV 20 mg
Baseline (mg/dL)	Mean±SD	161.18±29.55	163.07±27.98	157.39±26.83	164.21±31.23	157.71±30.86	160.79±37.08
Week 4 (mg/dL)	Mean±SD	70.37±17.34	94.77±25.60	66.26±23.42	79.85±21.79	58.00±25.92	73.83±28.02
percent change	LS Mean±SE	-55.55±1.98	-40.81±1.87	-58.33±1.97	-51.02±2.04	-62.34±2.83	-53.92±2.95
	p-value	<0.0001		0.0022		0.0089	
Week 8 (mg/dL)	Mean±SD	65.77±15.41	90.13±27.49	62.23±21.99	79.10±29.00	52.63±20.49	70.91±31.58
percent change	LS Mean±SE	-58.56±2.02	-43.61±1.90	-61.11±2.37	-52.83±2.46	-65.63±2.95	-55.76±3.07
	p-value	<0.0001		0.0039		0.0033	

5.2 Pharmacokinetic properties

Rosuvastatin

Rosuvastatin is a HMG-CoA Reductase Inhibitor, which inhibits cholesterol synthesis in the liver by competitively inhibiting HMG-CoA reductase, an enzyme that acts in the rate-limiting step of cholesterol biosynthesis where HMG-CoA is converted to mevalonic acid.

Ezetimibe
Ezetimibe is a selective cholesterol absorption inhibitor which suppresses absorption of cholesterol from dietary intake and from bile in the enterohepatic circulation by acting on NPC1L1 protein, a cholesterol absorption receptor in the villi of small intestine, without effect on absorption of bile acid, lipid acid, triglyceride and fat soluble vitamins

Phase 1study evaluated the pharmacokinetic properties of Crezet (combination of rosuvastatin 20 mg and ezetimibe 10 mg), versus co-administration of rosuvastatin 20 mg and ezetimibe 10 mg.
This was designed as a randomized, open, single-dose, 2-way crossover study of Crezet with control drugs of Crestor 20 mg (rosuvastatin calcium) and Ezetrol Tablet (ezetimibe) in healthy adult males.

(1) Primary endpoints
Mean AUClast and Cmax of rosuvastatin were 338.53 h*ng/mL and 39.28 ng/mL with Crezet (a combination of rosuvastatin 20 mg and ezetimibe 10 mg) alone and 332.99 h*ng/mL and 38.17 ng/mL with co-administration of single agents of rosuvastatin 20 mg and ezetimibe 10 mg.
Mean AUClast and Cmax of ezetimibe were 55,988.88 h*pg/mL and 3,112.12 pg/mL with Crezet (a combination of rosuvastatin 20 mg and ezetimibe 10 mg) alone and 55,446.26 h*pg/mL and 3,251.57 pg/mL with co-administration of single agents of rosuvastatin 20 mg and ezetimibe 10 mg.

5.3 Preclinical safety data

Repeated-Dose Toxicity
This test was conducted to investigate the effects and toxicokinetic behavior when oral administration of the test substance Crezet to Sprague-Dawley rats was repeated for 13 weeks, and verify the changes that occurred during the 4-week recovery period, thereby to assess the toxicity of the test substance.
There was a test substance treatment group in which Crezet was administered in 2, 6, 18 mg/kg/day and a single substance treatment group in which Crezet was administered as its ingredients – rosuvastatin calcium 12.16 mg/kg/day and ezetimibe 5.84 mg/kg/day. In addition, a vehicle control group to which only 0.5 % MC was administered was selected. Each group was composed of 10 females and 10 males. However, a recovery group of five females and five males was added to the vehicle control group, high-dose test substance group, and the single substance treatment group.
The observation and test items were clinical signs observation, weighing, food and water consumption measurement, urinalysis and hematological and blood biochemistry tests, organ weighing, necropsy findings observation, and histopathological examinations. The results were compared to those of the vehicle control group. In addition, a toxicokinetics analysis was performed and the results were as follows:

1. [Clinical Signs]
   No clinical signs determined to be caused by the test substance were observed.
2. [Weight]
   No significant changes determined to be caused by the test substance were observed.
3. [Food Consumption]
   No significant changes determined to be caused by the test substance were observed.
4. [Water Consumption]
   No significant changes determined to be caused by the test substance were observed.
5. [Ophthalmologic Examination]
   There were no abnormal findings in all test subject animals.
6. [Urinalysis]
   No significant changes determined to be caused by the test substance were observed.

7. [Hematological Test]
No significant changes determined to be caused by the test substance were observed.
8. [Blood Biochemistry Test]
No significant changes determined to be caused by the test substance were observed.
9. [Oragan Weight]
Females in the high-dose test substance treatment group showed a significant increase in absolute weight of the liver. However, it was not a toxicologically significant change.
10. [Necropsy Findings]
No significant changes determined to be caused by the test substance were observed.
11. [Histopathological Examination]
Periportal hepatocellular hypertrophy and erosions in the non-glandular stomach were observed in both males and females. However, they were determined to have no toxicological significance.
12. [Toxicokinetics Analysis]
In the case of systemic exposure to rosuvastatin, there were no differences between females and males, single agent or combination, linear kinetics was shown, and there was no accumulation in all dose groups.
In the case of systemic exposure to total ezetimibe, there were no differences between females and males, single agent or combination, linear kinetics was shown, and there was no accumulation in all dose groups.

To sum up the results above, when oral administration of the test substance Crezet to Sprague-Dawley rats was repeated for 13 weeks, periportal hepatocellular hypertrophy and erosions in the non-glandular stomach were observed. However, they were determined to have no toxicological significance.
In the case of systemic exposure to rosuvastatin and total ezetimibe, there were no differences between females and males, single agent or combination, linear kinetics was shown, and there was no accumulation in all dose groups.
Thus, the No Observed Adverse Effect Level(NOAEL) of the test substances under the conditions of this test was 18 mg/kg/day, and no target organ was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

A. Crezet film coated tablet 10/5 mg

Tablet core

Hydroxypropyl cellulose, Low-substituted
Dibasic Calcium Phosphate Dihydrate
Lactose monohydrate
Croscarmellose sodium
Hydroxypropylcellulose
Magnesium stearate

Film coating

Opadry Pink 03B54445

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

1) Store in airtight container at room temperature (1~ 30°C)
2) Keep out of reach of children.
3) Be careful not to put it in another container as it may cause an accident or is not desirable in terms of quality maintenance.

6.5 Nature and contents of container

The type of container and closure used for Crezet 10/5 mg are blister packing.
Blister packing is composed of soft aluminum foil and hard aluminum foil. Each blister packaging unit contains 10 tablets per PTP plate and 3 plates are packaged in a box (total 30 tablets). PTP is an inert substance that does not react with the finished product and is widely used for orally administered pharmaceutical products. In addition, as it is effective in blocking light and humidity, pharmaceutical products can be stably stored.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

7. INFORMATION OF MANUFACTURER

Daewoong Pharmaceutical Co., Ltd., Cheongju-si, Republic of Korea

8. MARKETING AUTHORISATION HOLDER

PT. Daewoong Infion, Pasuruan, Indonesia

Imported and marketed by:
PT. AstraZeneca Indonesia, Jakarta, Indonesia

9. MARKETING AUTHORISATION NUMBER(S)

CREZET 10/5 Film-Coated Tablets, Box of 3 blisters @ 10 film-coated tablets Reg. No.
DKIXXXXXXXXXXXX

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Mar. 11, 2023

HARUS DENGAN RESEP DOKTER

Lembar Informasi untuk Pasien

CREZET 10/5mg TABLET SALUT SELAPUT

Ezetimibe / Rosuvastatin Calcium

Bacalah brosur ini dengan seksama sebelum Anda menggunakan obat ini karena berisi informasi yang penting bagi Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan kepada orang lain. Obat tersebut dapat membahayakan mereka, meskipun gejala penyakitnya sama dengan Anda.
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Ini termasuk segala bentuk efek samping yang tidak tercantum dalam brosur ini.

Contents of this brochure:

1. Nama Produk

Crezet 10/5

2. Bentuk Sediaan

Crezet 10/5 Tablet Salut Selaput

3. Deskripsi Produk

Crezet Tablet Salut Selaput 10/5 mg: tablet salut selaput berwarna merah muda, berbentuk lonjong.

4. Apa saja kandungan obat ini?

Crezet mengandung zat aktif rosuvastatin kalsium dan ezetimibe.

5. Kekuatan

Tiap tablet salut selaput Crezet 10/5 mg mengandung 5,2 mg Rosuvastatin kalsium (5 mg sebagai Rosuvastatin) & Ezetimibe 10,0 mg

6. Untuk apa produk ini digunakan?

CREZET merupakan obat yang digunakan pada pasien dewasa untuk menurunkan tingkat kolesterol total, kolesterol " jahat " (kolesterol LDL) dan zat lemak yang disebut trigliserida dalam darah. Selain itu, obat ini juga meningkatkan kadar kolesterol "baik" (kolesterol HDL). Obat ini berkhasiat untuk mengurangi kadar kolesterol Anda dengan dua cara, yaitu dengan mengurangi jumlah kolesterol yang diserap dalam saluran pencernaan Anda dan mengurangi jumlah kolesterol yang diproduksi oleh tubuh Anda sendiri.

Bagi kebanyakan orang, kolesterol tinggi tidak mempengaruhi apa yang mereka rasakan karena tidak menimbulkan gejala apa pun. Namun, jika tidak diobati, timbunan lemak dapat menumpuk di dinding pembuluh darah Anda sehingga menyebabkan penyempitan pembuluh darah. Kadang - kadang, pembuluh darah yang menyempit ini dapat tersumbat sehingga menghambat suplai darah ke jantung atau otak yang mengarah ke serangan jantung atau stroke. Dengan menurunkan kadar kolesterol Anda, Anda dapat mengurangi resiko terkena serangan jantung, stroke, atau masalah kesehatan lainnya yang terkait.

Obat ini digunakan pada pasien yang mempunyai kadar kolesterol yang tidak dapat terkontrol hanya oleh diet penurun kolesterol saja. Anda harus tetap menjalani diet penurun kolesterol walaupun sedang mengkonsumsi obat ini.

CREZET digunakan sebagai terapi tambahan pada diet untuk mengurangi peningkatan kolesterol total, kolesterol LDL, apolipoprotein B (ApoB), kolesterol non-HDL, dan trigliserida (TG) dan untuk menaikkan kolesterol HDL pada pasien dengan hiperlipidemia primer (heterozigous dan homozigous familial) atau dislipidemia campuran. .

7. Seberapa banyak dan seberapa sering Anda harus menggunakan obat ini? Apa yang harus Anda lakukan jika Anda lupa minum satu dosis?

Gunakan obat sesuai petunjuk dokter.
Dosis dan cara pemberian: Obat diminum satu tablet sekali sehari.

CREZET tidak boleh digunakan sebagai terapi awal.

Dosis awal: Terapi Anda dengan CREZET harus dimulai dengan dosis 10/5 mg.
Pemilihan dosis awal untuk Anda akan tergantung pada:

- Kadar kolesterol Anda.
- Tingkat risiko Anda untuk mengalami serangan jantung atau stroke.
- Apakah Anda memiliki faktor yang membuat Anda lebih sensitif akan kemungkinan efek samping.

Menaikkan dosis dan dosis harian maksimum: Dokter Anda mungkin memutuskan untuk menaikkan dosis obat Anda. Hal ini dilakukan supaya Anda mendapat dosis CREZET yang tepat untuk Anda. Akan terdapat rentang empat minggu di antara setiap dosis penyesuaian. Dosis harian maksimum CREZET adalah 10/20 mg.

CREZET dapat diminum baik dengan ataupun tanpa makanan.

Usahakan untuk meminum tablet CREZET Anda pada waktu yang sama setiap harinya untuk membantu Anda mengingatnya.

Jika Anda lupa minum satu dosis, minum obat sesuai dosis yang dianjurkan saat Anda mengingatnya.

Jangan meminum dosis dobel untuk menggantikan dosis yang terlupakan.

Pemeriksaan kolesterol berkala: Penting untuk kembali ke dokter Anda untuk pemeriksaan kolesterol rutin, untuk memastikan kolesterol Anda mencapai dan tetap pada kadar yang tepat. Dokter Anda mungkin memutuskan untuk meningkatkan atau menurunkan dosis CREZET Anda sehingga Anda mengonsumsi jumlah CREZET yang sesuai untuk Anda.

8. Kapan Anda tidak boleh menggunakan produk ini?

Konsultasikan dengan dokter Anda sebelum meminum Crezet.
Obat ini tidak dianjurkan untuk pasien dengan kondisi berikut:
1) Pasien yang memiliki alergi terhadap bahan aktif obat ini atau komponen lain dari obat ini
2) Pasien dengan penyakit hati aktif
3) Pasien dengan miopati (penyakit nyeri otot)
4) Jika Anda memiliki faktor-faktor berikut yang membuat Anda lebih rentan menderita nyeri otot (miopati) atau ganguan jaringan otot rangka (rhabdomyolisis):

- Gangguan ginjal berat dengan bersihan kreatinin
- Kelainan kadar hormon tiroid di bawah normal
- Riwayat diri atau keluarga dengan kelainan otot bawaan
- Pernah mengalami keluhan pada otot karena konsumsi obat kolesterol golongan statin lainnya atau obat fibrate
- Mengonsumsi alkohol dalam jumlah berlebih (penyalahgunaan alkohol)
- Ras Asia
- Sedang menggunakan obat fibrate

5) Pasien yang sedang menerima pengobatan dengan siklosporin
6) Pasien dengan gangguan ginjal berat dengan klirens kreatinin <30 mL/menit
7) Pasien dengan intoleransi laktosa
8) Pasien yang sedang hamil atau menyusui
9) Pasien anak-anak
10) Jika Anda wanita usia subur yang tidak menggunakan alat kontrasepsi yang tepat

9. Apa yang harus diperhatikan saat Anda menggunakan produk ini?

Konsultasikan dengan dokter sebelum menggunakan Crezet.

- Jika Anda mengonsumsi alkohol atau memiliki penyakit hati.
- Jika Anda memiliki gangguan fungsi hati sedang atau berat.
- Jika Anda sedang menjalani pengobatan dengan fibrat
- Jika Anda memiliki faktor-faktor berikut:
  • Riwayat kerusakan ginjal atau gangguan ginjal
  • Hipotiroidisme Riwayat miopati bawaan
  • Riwayat toksisitas otot akibat statin atau fibrat

• Riwayat penyakit hati atau akibat konsumsi alkohol berlebihan
- Lansia di atas 70 tahun yang memiliki faktor rhabdomyolysis (kondisi ketika jaringan otot rusak dan melepaskan zat ke dalam aliran darah yang dapat membahayakan ginjal)
- Jika Anda memiliki kemungkinan hamil
- Anak dan remaja: CREZET tidak dianjurkan untuk anak dan remaja berusia di bawah 18 tahun. Keamanan dan manfaat obat ini pada anak dan remaja belum ditetapkan

10. Apa saja obat atau makanan lain yang harus dihindari selama penggunaan obat ini?

Obat ini harus diberikan dengan hati-hati kepada pasien yang juga menerima pengobatan dengan:

- Obat antikoagulan
- Obat fibrat
- Obat resin pengikat asam empedu
- Obat asam fusidat

Beritahukan dokter Anda atau apoteker jika Anda sedang meminum, baru saja meminum atau mungkin akan meminum obat-obatan lain. Jika Anda meminum/ menggunakan salah satu obat berikut:

Cyclosporine (obat untuk mencegah penolakan organ setelah cangkok organ)
Bebearapa obat untuk infeksi virus (atazanavir, lopinavir, ritonavir, darunavir, tipranavir)
Clopidogrel (obat untuk mengurangi pembekuan darah) Eltrombopag (obat untuk kondisi hitung keping darah rendah)
Obat penurun kadar lemak darahlainnya, seperti gemfibrozil
Dronedarone (obat untuk kelainan irama jantung) Itraconazole (obat untuk infeksi jamur)
Fusidic acid (obat untuk infeksi kulit)

Beritahukan dokter Anda sebelum meminum CREZET karena obat-obatan tersebut dapat meningkatkan efek dari CREZET dan kemungkinan efek samping yang tidak diinginkan. Dokter Anda akan memutuskan jika Anda harus diterapi dengan CREZET dan jika Anda harus diawasi.

Jika Anda meminum salah satu obat berikut:

Antasida (obat pereda sakit lambung)
Colestyramine (obat penurun kadar lemak darah lainnya)

Jika ada poin di atas yang berkaitan dengan Anda, beritahu dokter Anda sebelum meminum CREZET karena efek CREZET dapat berkurang. Dokter Anda akan memutuskan jika Anda harus diterapi dengan CREZET dan jika Anda harus diawasi.

Jika Anda meminum salah satu obat berikut:

Warfarin (obat untuk mengurangi pembekuan darah)
Kontrasepsi oral (pil KB)

Beritahukan dokter Anda sebelum meminum CREZET karena CREZET dapat meningkatkan efek dari obat-obat tersebut dan kemungkinan efek samping yang tidak diinginkan. Dokter Anda akan memutuskan jika Anda harus diterapi dengan CREZET dan jika Anda harus diawasi.

11. Kehamilan dan Menyusui

Jangan menggunakan CREZET jika Anda sedang hamil, sedang program kehamilan atau Anda merasa ada kemungkinan hamil. Jika Anda hamil saat menggunakan obat ini, segera hentikan menggunakan obat ini dan beritahukan Dokter Anda. Pasien wanita harus menggunakan kontrasepsi selama terapi dengan obat ini. Jangan menggunakan CREZET, jika Anda sedang menyusui, karena belum diketahui keamanannya apakah obat tersebut dapat masuk ke dalam ASI.

12. Berkendara dan menggunakan mesin

Berkendara dan menggunakan mesin: Obat ini belum diketahui apakah mengganggu kemampuan Anda untuk mengemudi atau menggunakan mesin. Namun demikian harus diperhitungkan bahwa beberapa orang menjadi pusing setelah menggunakan obat ini. Jika Anda pusing, Anda tidak boleh mengemudi atau menggunakan mesin.

13. Apa saja efek samping yang mungkin terjadi akibat penggunaan produk ini?

Efek samping umumnya ringan dan bersifat sementara.

- Sistem saraf: sangat jarang terjadi polineuropati, amnesia, neuropati perifer
- Sistem pernapasan: batuk, kesulitan bernapas
- Sistem pencernaan: diare
- Hematologi: trombositopenia
- Sistem hepatobilier: penyakit kuning dan hepatitis yang sangat jarang serta peningkatan transaminase
- Kelainan kulit dan subkutan: Sindrom Stevens-Johnson
- Sistem muskuloskeletal: jarang terjadi sindrom mirip lupus
- Gangguan ginjal: hematuria sangat jarang
- Lainnya: membengkak

Layaknya semua obat, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.
Penting untuk Anda mewaspadai efek-efek samping yang dapat terjadi. Efek-efek samping tersebut biasanya ringan dan menghilang dalam waktu singkat.
Hentikan meminum CREZET dan segera cari pertolongan medis jika Anda mengalami reaksi-reaksi alergi berikut:

Kesulitan bernapas, dengan atau tanpa pembengkakan wajah, bibir, lidah dan/atau tenggorokan Pembengkakan wajah, bibir, lidah dan/atau tenggorokan yang dapat menyebabkan kesulitan menelan
Gatal-gatal di kulit yang berat (dengan benjolan menonjol)

Selain itu, hentikan meminum CREZET dan segera konsultasi dengan dokter jika Anda mengalami rasa sakit atau nyeri yang tidak biasa pada otot Anda yang dirasakan lebih lama dari yang Anda perkirakan. Seperti yang dialami pada konsumsi obat-obat statin lainnya, sejumlah kecil orang mengalami efek-efek tidak menyenangkan pada otot dan jarang yang berkembang menjadi kerusakan otot yang berpotensi mengancam nyawa yang dikenal sebagai rabdomiolisis.

Efek samping lainnya:
Efek samping yang umum (dapat terjadi hingga 1 dari 10 orang)

Sakit kepala Sembelit Merasa sakit Nyeri otot
Merasa lemah, pusing

Hal ini lebih mungkin jika Anda memiliki kadar gula dan lemak yang tinggi dalam darah Anda, kelebihan berat badan dan memiliki tekanan darah tinggi. Dokter Anda akan memantau Anda saat Anda menggunakan obat ini.
Sakit perut Diare
Perut kembung (kelebihan gas dalam saluran usus) Merasa lelah
Peningkatan pada beberapa tes darah laboratorium untuk fungsi hati (transaminase)

Efek samping yang tidak umum (dapat terjadi hingga 1 dari 100 orang)
Ruam, gatal, sangat gatal
Peningkatan pada beberapa tes darah laboratorium untuk fungsi otot (tes Creatine Kinase)
Batuk
Gangguan pencernaan
Mulas
Nyeri sendi Kejang otot Sakit leher
Kurang nafsu makan Nyeri
Nyeri dada Panas
Tekanan darah tinggi Sensasi kesemutan Mulut kering
Radang lambung Sakit punggung Lemah otot
Rasa sakit di lengan dan kaki Pembengkakan, terutama di tangan dan kaki

Efek samping yang jarang (dapat terjadi hingga 1 dari 1.000 orang)
Radang pankreas, yang menyebabkan nyeri perut berat yang dapat meluas ke punggung
Pengurangan trombosit darah

Efek samping yang sangat jarang (dapat terjadi hingga 1 dari 10.000 orang)
Penyakit kuning (kulit dan mata menguning) Peradangan hati (hepatitis)
Terdapat darah dalam urin
Kerusakan pada saraf kaki dan lengan Anda (seperti mati rasa)
Hilang ingatan
Pembesaran payudara pada pria (ginekomastia)

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia)
Sesak napas
Edema (pembengkakan)
Gangguan tidur, termasuk insomnia dan mimpi buruk Kesulitan seksual
Depresi
Masalah pernapasan termasuk batuk terus - menerus dan/atau sesak napas atau demam Cedera tendon
Lemah otot yang tetap
Batu empedu atau radang kantong empedu (yang dapat menyebabkan sakit perut, mual, muntah)

14. Apa yang harus saya lakukan jika saya mengonsumsi lebih dari dosis yang dianjurkan?

Tidak ada pengobatan khusus untuk overdosis obat ini. Konsultasikan dengan dokter Anda jika Anda mengonsumsi lebih dari dosis yang dianjurkan.

15. Bagaimana cara menyimpan obat ini?

Simpan pada suhu di bawah 30°C dalam wadah kedap udara. Jauhkan dari jangkauan anak-anak.

16. Zat Tambahan Obat

Hidroksipropilselulosa (*low-substituted*)
Kalsium fosfat dibasa dihidrat
Laktosa monohidrat
Croscarmellose sodium
Hidroksipropilselulosa
Magnesium stearat
Alkohol
Opadry Pink 03B54445
Air murni

17. Nomor izin edar (NIE)

CREZET 10/5 Tablet Salut Selaput, Dus, 3 blister @ 10 tablet salut selaput; No. Reg. DKIXXXXXXXXXXXXX

18. Nama dan alamat produsen dan pemegang izin edar (

Diproduksi oleh:
Daewoong Pharmaceutical Co., Ltd., Cheongju-si, Republik Korea

Didaftarkan oleh:
PT. Daewoong Infion, Pasuruan, Indonesia

Diimpor dan dipasarkan oleh:
PT. AstraZeneca Indonesia, Jakarta, Indonesia

19. Tanggal Revisi Leaflet Pasien

28 Oktober 2024

HARUS DENGAN RESEP DOKTER