Proposed packaging material		
Code	Crestor 5mg, 10 mg, 20 mg, and 40 mg (30s) FCT-PI-04.03	
Submission	☐NDA ☐Renewal ☒Variation changes detail no.: RO-Change Event-0036915	
Code of previous version	Crestor 5mg, 10 mg, 20 mg, and 40 mg (30s) FCT-PI-03.02	
Changes	New indication: CV Prevention	
Reference	☒CDS version: Doc ID-001371104 ☐CPIL version:	☐SmPC ☐country/version/date: GRL approval:
Name & Date	YS	

CRESTOR®

rosuvastatin

Film-coated tablets

Qualitative and quantitative composition

Each film-coated tablet contains 5 mg, 10 mg, 20 mg or 40 mg of rosuvastatin as rosuvastatin calcium.

For excipients, see *List of excipients*

Pharmaceutical form

Film-coated tablet.
5 mg tablet: Round, yellow coloured tablets, intagliated with ‘ZD4522’ and ‘5’ on one side and plain on the reverse.
10 mg tablet: Round, pink coloured tablets, intagliated with 'ZD4522' and '10' on one side and plain on the reverse.
20 mg tablet: Round, pink coloured tablets, intagliated with 'ZD4522' and '20' on one side and plain on the reverse.
40 mg tablet: Oval, pink coloured tablets, intagliated with 'ZD4522' on one side and '40' on the reverse.

Therapeutic indications

CRESTOR is indicated for patients with primary hypercholesterolaemia, (type IIa, including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and exercise is inadequate.

CRESTOR reduces elevated LDL-cholesterol, total cholesterol, triglycerides and ApoB, and increases HDL-cholesterol.

CRESTOR is also indicated in patients with homozygous familial hypercholesterolemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL aphaeresis).

Prevention of Cardiovascular Events

Crestor is indicated to reduce the risk of cardiovascular events (reduce the risk of stroke, myocardial infarction, and arterial revascularization procedures) in adult patients with an increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular disease risk markers such as hypertension, low HDL-C, smoking or a family history of premature coronary heart disease.

Posology and method of administration

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines.

CRESTOR may be given at any time of day, with or without food.

The recommended start dose is 5 mg or 10 mg orally once daily in both statin naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. A dose adjustment to the next dose level can be made after 4 weeks, if necessary (see *Pharmacodynamic properties*). In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses (see *Undesirable effects*), a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed (see *Special warnings and precautions for use*). Specialist supervision is recommended when the 40 mg dose is initiated.

Prevention of cardiovascular events

The usual start dose of CRESTOR is 10 mg once a day.
The dose range is 10-40 mg orally once a day. The dosage of CRESTOR should be individualised according to the goal of therapy and patient response. The majority of patients are controlled at the start dose. However, if necessary, dose adjustment can be made at 2 to 4 week intervals.
For patients with aggressive lipid targets, a start dose of 20 mg may be considered.

Use in children
Safety and efficacy have not been established in children. Paediatric experience is limited to a small number of children (aged 8 years or above) with homozygous familial hypercholesterolaemia. Therefore, CRESTOR is not recommended for paediatric use at this time.

Use in the elderly
A start dose of 5 mg is recommended in patients >70 years (see *Special warnings and precautions for use*). No other dose adjustment is necessary in relation to age.

Dosage in patients with renal insufficiency

No dose adjustment is necessary in patients with mild to moderate renal impairment**.** For patients with severe renal impairment (CL_{cr} <30 ml/min/1.73m^2) not on haemodialysis, dosing of CRESTOR should be started at 5 mg once daily and not to exceeded 10 mg once daily (see Pharmacokinetic properties).

Dosage in patients with hepatic impairment

There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9 (see *Pharmacokinetic properties*). In these patients an assessment of renal function should be considered and the dose of CRESTOR should not exceed 20 mg once daily (see *Special warnings and precautions for use*). There is no experience in subjects with Child-Pugh scores above 9. CRESTOR is contraindicated in patients with active liver disease (see *Contraindication*).

Race

A 5 mg starting dose of CRESTOR should be considered for Asian patients. Increased plasma concentration of rosuvastatin has been seen in Asian subjects (see *Special warnings and precautions for use* and *Pharmacokinetic properties*). The increased systemic exposure should be taken into consideration when treating Asian patients whose hypercholesterolemia is not adequately controlled at doses up to 20 mg/day.

Dosage in patients with pre-disposing factors to myopathy

The recommended start dose is 5 mg in patients with predisposing factors to myopathy (see *Special warnings and precautions for use*).

Concomitant therapy

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when CRESTOR is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir and/or tipranavir; see *Special warnings and precautions for use* and *Interaction with other medicinal products and other forms of interaction*). It is recommended that prescribers consult the relevant product information when considering administration of such products together with CRESTOR. Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing CRESTOR therapy. In situations where co- administration of these medicinal products with CRESTOR is unavoidable, the benefit and the risk of concurrent treatment and CRESTOR dosing adjustments should be carefully considered (see *Interaction with other medicinal products and other forms of interaction*).

Contraindications

CRESTOR is contraindicated in patients:

- with hypersensitivity to rosuvastatin or to any of the excipients.
- with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3x the upper limit of normal (ULN).
- with myopathy.
- receiving concomitant cyclosporine.

- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

Special warnings and precautions for use

Renal effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of CRESTOR, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease (see *Undesirable effects*). An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Skeletal muscle effects

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in CRESTOR-treated patients with all doses and in particular with doses > 20 mg. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with CRESTOR in post- marketing use is higher at the 40 mg dose.

Statins may in rare instances induce or aggravate myasthenia gravis or ocular myasthenia (see section 4.8 Undesirable effects) including reports of recurrence when the same or a different statin was administered. CRESTOR should be used with caution in patients with these conditions and should be discontinued if they are induced or aggravated.

Creatine kinase measurement

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

Before treatment

CRESTOR, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- renal impairment
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- age >70 years
- situations where an increase in plasma levels may occur (see *Posology and method of administration*, *Interaction with other medicinal products and other forms of interaction* and *Pharmacokinetic properties*)
- concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (>5 x ULN) treatment should not be started.

Whilst on treatment
Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5 x ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are
≤ 5 x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing CRESTOR or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted.

There have been very rare reports of an immune-mediated necrotizing myopathy clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including rosuvastatin. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with CRESTOR and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. The benefit of further alterations in lipid levels by the combined use of CRESTOR with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40 mg dose is contraindicated with concomitant use of a fibrate (see *Interaction with other medicinal products and other forms of interaction* and *Undesirable effects*).

CRESTOR should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Liver effects
As with other HMG-CoA reductase inhibitors, CRESTOR should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease. It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. CRESTOR should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with CRESTOR.

Diabetes mellitus
As with other HMG-CoA reductase inhibitors, increases in HbA1c and serum glucose levels have been observed in patients treated with rosuvastatin, and in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus, primarily in patients already at high risk for developing diabetes (see *Undesirable effects*).

Race
Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see *Posology and method of administration* and *Pharmacokinetic properties*).

Interactions with other medicinal products and other forms of interaction

Effect of co-administered medicinal products on rosuvastatin

Transporter protein inhibitors: *In vitro* and *in vivo* data indicate that rosuvastatin has no clinically significant cytochrome P450 interactions (as a substrate, inhibitor or inducer).

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of CRESTOR with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see Table 1, *Posology and method of administration* and *Special warnings and special precautions for use*).

Ciclosporin: During concomitant treatment with CRESTOR and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1). CRESTOR is contraindicated in patients receiving concomitant ciclosporin (see *Contraindications*). Concomitant administration did not affect plasma concentrations of ciclosporin.

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see Table 1). For instance, in a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold increase in rosuvastatin AUC. The concomitant use of CRESTOR and some protease inhibitor combinations may be considered after careful consideration of CRESTOR dose adjustments based on the expected increase in rosuvastatin exposure (Table 1).

Gemfibrozil and other lipid-lowering products: Concomitant use of CRESTOR and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC. Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. The 40 mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5 mg dose.

Ezetimibe: Concomitant use of CRESTOR and ezetimibe resulted in no change to AUC for either drug when administered to healthy volunteers. There was a 1.2 fold increase in AUC of rosuvastatin when 10 mg CRESTOR and 10 mg ezetimibe was administered in hypercholesterolaemic subjects (Table 1). A pharmacodynamic interaction, in terms of adverse effects, between CRESTOR and ezetimibe cannot be ruled out.

Antacid: The simultaneous dosing of CRESTOR 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 CRESTOR. The clinical relevance of this interaction has not been studied.

Fusidic Acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with rosuvastatin and fusidic acid given concurrently. Patients should be closely monitored and temporary suspension of rosuvastatin treatment may be appropriate.

Erythromycin: Concomitant use of CRESTOR and erythromycin resulted in a 20% decrease in AUC and a 30% decrease in Cmax of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes: Results from *in vitro* and *in vivo* studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

Interactions requiring rosuvastatin dose adjustments (see also Table 1)
When it is necessary to co-administer CRESTOR with other medicinal products known to increase exposure to rosuvastatin, doses of CRESTOR should be adjusted. It is recommended that prescribers consult the relevant product information when considering administration of such products together with CRESTOR.

If medicinal product is observed to increase rosuvastatin AUC approximately 2 fold or higher, the starting dose of CRESTOR should not exceed 5 mg once daily. The maximum daily dose of CRESTOR should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of CRESTOR taken without interacting medicinal products, for example a 20 mg dose of CRESTOR with gemfibrozil (1.9-fold increase), a 10 mg dose of CRESTOR with combination ritonavir/atazanavir (3.1-fold increase), and a 5 mg dose of CRESTOR with ciclosporin (7.1 fold increase in exposure).

If medicinal product is observed to increase rosuvastatin AUC less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the CRESTOR dose above 20mg.

Protease Inhibitors: Coadministration of rosuvastatin with certain protease inhibitors or combination of protease inhibitors may increase the rosuvastatin exposure, (AUC) up to 7-fold (see Table1). Dose adjustment are needed depending on the level of effect on rosuvastatin exposure (see sections posology and administration, and special warning and precautions)

Table 1 Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials		
2-fold or greater than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Sofosbuvir/velpatasvir/voxilaprevir (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) once daily for 15 days	10mg single dose	7.39 -fold ↑
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Darolutamide 600 mg BID, 5 days	5mg, single dose	5.2-fold ↑
Regorafenib 160 mg OD, 14 days	5 mg single dose	3.8 -fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Simeprevir 150 mg OD, 7 days	10 mg, single dose	2.8-fold ↑
Velpatasvir 100 mg OD	10 mg single dose	2.69 -fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg/dasabuvir 400 mg BID	5mg single dose	2.59-fold ↑
Teriflunomide	Not Available	2.51-fold↑
Grazoprevir 200 mg/elbasvir 50 mg OD	10mg single dose	2.26-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD for 7 days	5mg once daily	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Capmatinib 400mg BID	10 mg, single dose	2.08-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Fostamatinib 100 mg twice daily	20 mg, single dose	1.96-fold ↑
Febuxostat 120mg OD	10 mg single dose	1.9-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Less than 2-fold increase in AUC of rosuvastatin		

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg or 80 mg, single dose	1.4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	1.2-fold ↑
Decrease in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓

*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as % change represent % difference relative to rosuvastatin alone.
Increase is indicated as "↑", decrease as "↓".
AUC = area under curve; OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

Effect of rosuvastatin on co-administered medicinal products

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

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of CRESTOR and an oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant CRESTOR 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.

Genetic polymorphisms

Genotypes of SLCO1B1 (OATP1B1) c.521CC and ABCG2 (BCRP) c.421AA have been shown to be associated with an increase in rosuvastatin exposure (AUC) compared to SLCO1B1 c.521TT and ABCG2 c.421CC. For patients known to have the c.521CC or c.421AA genotype, a maximum once daily dose of 20 mg of CRESTOR is recommended (see *Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction* and *Pharmacokinetic properties*).

Pregnancy and lactation
CRESTOR is contraindicated during pregnancy or lactation as the safety of CRESTOR during pregnancy and whilst breast-feeding has not been established. Women of child- bearing potential should use appropriate contraceptive measures. Since cholesterol and other products of cholesterol biosyntheses 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 (see *Preclinical safety data*). If a patient becomes pregnant during the 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 (see *Contraindications*).

Effects on ability to drive and use machines
Studies to determine the effect of CRESTOR on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, CRESTOR is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

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

The frequencies of adverse events are ranked according to the following: Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Rare (>1/10,000, <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Immune system disorders
Rare: hypersensitivity reactions including angioedema

Endocrine disorders
Common: diabetes mellitus[12]

Nervous system disorders
Common: headache, dizziness

Gastrointestinal disorders
Common: constipation, nausea, abdominal pain
Rare: pancreatitis

Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash and urticaria

Musculoskeletal, connective tissue and bone disorders
Common: myalgia
Rare: myopathy (including myositis) and rhabdomyolysis

General disorders
Common: asthenia

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

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 CRESTOR. 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 and is not predictive acute or progressive renal disease.

Skeletal muscle effects: Rare cases of rhabdomyolysis which were occasionally associated with the impairment of renal function have been reported with rosuvastatin and with other marketed statins.

Laboratory effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases and CK have been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5 x ULN), treatment should be discontinued. Increases in HbA1c have also been observed in patients treated with rosuvastatin (see section Special warnings and precautions for use and *Pharmacodynamic properties*).

Post marketing experience:
In addition to the above, the following adverse events have been reported during post marketing experience for CRESTOR:

Eye disorders: Frequency unknown: ocular myasthenia.

Haematological disorders: Frequency unknown: thrombocytopenia.

Hepatobiliary disorders: Very rare: jaundice, hepatitis; *rare:* increased hepatic transaminases.
Musculoskeletal disorders: Frequency unknown: immune- mediated necrotising myopathy;
very rare: arthralgia.

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose.

Nervous system disorders: Very rare: polyneuropathy, memory loss, frequency unknown:
peripheral neuropathy, myasthenia gravis

Psychiatric disorders: Frequency unknown: depression, sleep disorders (including insomnia and nightmares).

Reproductive system and breast disorders: Frequency unknown: gynaecomastia.

Skin and subcutaneous tissue disorders: Frequency unknown: drug reaction with eosinophilia and systemic symptoms (DRESS), lichenoid drug eruption

Reporting 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 at:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id/ADR

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

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors ATC code: C10A A07

Mechanism of action

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Pharmacodynamic effects

CRESTOR reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 2).

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

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

Dose	N	LDL-C	Total-C	HDL-C	TG	NonHDL-C	ApoB	ApoA-1
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

A therapeutic response to CRESTOR is evident within 1 week of commencing therapy and 90% of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Clinical efficacy

CRESTOR is effective in adult patient populations with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolaemia.

From pooled phase III data CRESTOR has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesteraemia (mean baseline LDL-C about 4.8 mmol/l) to recognized European Atherosclerosis Society (EAS:1998) guideline targets; about 80% of patients treated with CRESTOR 10mg reached the EAS targets for LDL-C levels (<3 mmol/l).

In a large study of patients with heterozygous familial hypercholesterolaemia, 435 subjects were given CRESTOR from 20 mg to 80 mg in a force-titration design. All doses of CRESTOR showed a beneficial effect on lipid parameters and treatment to target goals.
Following titration to 40mg (12 weeks of treatment), LDL-C was reduced by 53%. 33% of patients reached EAS guidelines for LDL-C levels (<3 mmol/l).

In a force-titration, open label trial, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to CRESTOR 20 - 40 mg. In the overall population, the mean LDL-C reduction was 22%.

In clinical studies with a limited number of patients, CRESTOR has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin (see *Special warnings and precautions for use*).
In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of CRESTOR (rosuvastatin calcium) on the occurrence of major atherosclerotic cardiovascular (CV) disease events was assessed in 17,802 men (≥50 years) and women (≥60 years) who had no clinically evident cardiovascular disease, LDL-C levels <3.3 mmol/L (130 mg/dL) and hs-CRP levels ≥2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.6% over 10 years based on the Framingham risk criteria and included a high percentage of patients with additional risk factors such as hypertension (58%), low HDL-C levels (23%), cigarette smoking (16%) or a family history of premature CHD (12%). Study participants had a median baseline LDL-C of 2.8 mmol/L (108 mg/dL) and hsCRP of 4.3 mg/L. The average age of study participants was 66 years. Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily

(n=8901) and were followed for a mean duration of 2 years. The JUPITER study was stopped early by the Data Safety Monitoring Board due to meeting predefined stopping rules for efficacy in rosuvastatin-treated subjects.

The primary endpoint was a composite endpoint consisting of the time-to-first occurrence of any of the following CV events: CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina or an arterial revascularisation procedure.

Rosuvastatin significantly reduced the risk of CV events (252 events in the placebo group vs. 142 events in the rosuvastatin group) with a statistically significant (p<0.001) relative risk reduction of 44%; absolute risk reduction of 1.2% (see Figure 1 and Table 3). The benefit was apparent within the first 6 months of treatment (HR 0.62; 95% CI 0.40-0.96; p=0.029). The risk reduction was consistent across multiple predefined population subsets based on assessments of age, sex, race, smoking status, family history of premature CHD, body mass index, LDL-C, HDL-C or hsCRP levels at the time of entry into the study.

In JUPITER, there was a statistically significant increase in the frequency of diabetes mellitus reported by investigators; 2.8% of patients in the rosuvastatin group and 2.3% of patients in the placebo group (HR: 1.27, 95% CI: 1.05-1.53, p=0.015). The difference between treatment groups (rosuvastatin versus placebo) in mean HbA1c change from baseline was approximately 0.1%. The number of patients with HbA1c >6.5% at the end of the trial was significantly higher in rosuvastatin-treated versus placebo-treated patients.

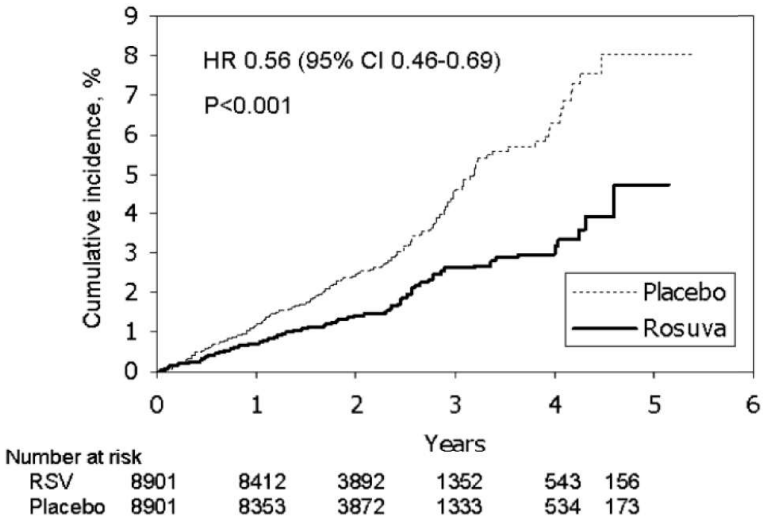
Table 3 Summary of Risk Reductions from JUPITER trial

Endpoint	Placebo N (%)	RSV 20 mg N (%)	HR (95% CI)	RRR*(%)	ARR*(%)
Primary (major cardiovascular event)	252 (2.8)	142 (1.6)	0.56 (0.46-0.69) p<0.001	44	1.2
Secondary					
CV death, stroke and MI	158 (1.8)	83 (0.9)	0.52 (0.40-0.68)	48	0.9
Fatal or non-fatal MI	68 (0.8)	31 (0.3)	0.46 (0.30-0.70)	54	0.3
Fatal or non-fatal stroke	64 (0.7)	33 (0.4)	0.52 (0.34-0.79)	48	0.3
Total mortality	247(2.8)	198 (2.2)	0.80 (0.67-0.97)	20	0.6
Venous thromboembolism	46 (0.5)	26 (0.3)	0.57 (0.35-0.91)	43	0.2

HR = Hazard Ratio; RRR = Relative Risk Reduction; ARR = Absolute Risk Reduction
* Calculated values were at 1.9 years median follow-up

There were no statistically significant reductions in the rate of noncardiovascular death or the incidence of bone fractures in the rosuvastatin treated group compared to placebo.

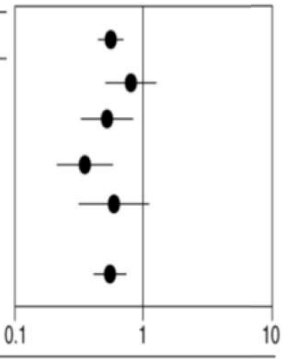
Figure 1 Time to occurrence of major cardiovascular events in JUPITER



The individual components of the primary end point are presented in Figure 2. Rosuvastatin significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularisation procedures. There were no significant treatment differences between the rosuvastatin and placebo groups for death due to cardiovascular causes or hospitalisations for unstable angina.

Figure 2 Major CV events by treatment group in JUPITER

End point	Number of events: Rosuva 20 mg (n=8901) n (rate*)	Placebo 20 mg (n=8901) n (rate*)	HR (95% CI)	P value
Primary end point (MCE)	142 (7.6)	252 (13.6)	0.56 (0.46, 0.69)	<0.001
Cardiovascular death**	35 (1.9)	44 (2.4)	0.80 (0.51, 1.24)	0.315
Nonfatal Stroke	30 (1.6)	58 (3.1)	0.52 (0.33, 0.80)	0.003
Nonfatal MI	22 (1.2)	62 (3.3)	0.35 (0.22, 0.58)	<0.001
Hospitalilzed unstable Angina	16 (0.9)	27 (1.5)	0.59 (0.32, 1.10)	0.093
Arterial revascularization	71 (3.8)	131 (7.1)	0.54 (0.41, 0.72)	<0.001



* event rate/1000-patient years
** Cardiovascular death included fatal MI, fatal stroke, sudden death, and other adjudicated causes of CV death

In a post-hoc subgroup analysis of JUPITER subjects (n =1405; rosuvastatin = 725, placebo = 680) with a hsCRP ≥2 mg/L and no other traditional risk factors (smoking, BP ≥140/90 or taking antihypertensives, low HDL-C) other than age, after adjustment for high HDL-C, there was no significant treatment benefit with rosuvastatin treatment. At one year, rosuvastatin increased HDL-C (1.41 vs 1.34 mmol/L) and reduced LDL-C (1.59 mmol/L vs. 2.82 mmol/L), hsCRP (2.20 vs. 3.50 mg/L), total cholesterol and serum triglyceride levels (p<0.001 for all versus placebo).

The Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) was a randomized, double-blind, placebo controlled study in 5011 subjects with chronic symptomatic systolic heart failure treated with rosuvastatin 10 mg (n=2514) or placebo (n=2497) for a mean treatment duration of 2.5 years. The study results showed that rosuvastatin 10 mg did not lead to a significant difference compared to placebo in reducing cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke (time to first event: HR: 0.922, 95%CI: 0.831, 1.023, p=0.1237).

LUNAR was a 12-Week, Randomized, Open-Label, 3-Arm, Parallel Group, Multicenter, Phase IIIb Study Comparing the Efficacy and Safety of Rosuvastatin 20 mg and 40 mg with that of Atorvastatin 80 mg in Patients with Acute Coronary Syndromes over 6 to 12 weeks of once daily treatment. The study results showed that rosuvastatin 20 mg can reduce LDL-C levels similarly to atorvastatin (p = 0.3870), while rosuvastatin 40 mg demonstrated a more significant reduction in LDL-C levels compared to atorvastatin (p = 0.0219).

The Heart Outcomes Prevention Evaluation (HOPE)-3 study, was pragmatic, multicenter, long-term, multinational, double-blind, randomized, placebo-controlled trial at 228 centers in 21 countries. A 2-by-2 factorial design was used for the trial. The trial included 12,705 people (age, ≥65 for women, and ≥55 for men) without known cardiovascular (CV) disease who had at least one of the following cardiovascular risk factors: elevated waist-to-hip ratio, HDL cholesterol level <39 mg/dL (men) or <50 mg/dL (women), current or recent smoking, dysglycemia (impaired fasting glucose, impaired glucose tolerance or uncomplicated diabetes treated with diet only), family history of premature coronary disease, and mild renal dysfunction. Most participants had at least two risk factors. The study results showed that the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in the rosuvastatin group were significantly lower than in the placebo group (HR: 0.76 (95% CI: 0.64 – 0.91), p=0.002).

Pharmacokinetic properties

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

Distribution: Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Metabolism: Rosuvastatin undergoes limited metabolism (approximately 10%) mainly to the N-desmethyl metabolite and the lactone metabolite. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

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

Special populations:
Age and sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults.

Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC in Asian subjects compared with Caucasians. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups.

Renal insufficiency: In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentrations of rosuvastatin.
However, subjects with severe impairment (CrCl <30 ml/min) had a 3-fold increase in plasma concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

Hepatic impairment: In a study with subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin other than in the 2 subjects with the most severe liver disease (Child-Pugh scores of 8 and 9). In these subjects systemic exposure was increased by at least 2-fold compared to subjects with lower Child- Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

Genetic polymorphisms: Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with an approximate 1.7-fold higher rosuvastatin exposure (AUC) or 2.4-fold higher exposure, respectively, compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes. This specific genotyping is not established in clinical practice, but for patients who are known to have these types of polymorphisms, a lower daily dose of CRESTOR is recommended.

Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity potential. In a rat pre and post-natal study, reproductive toxicity was evident from reduced litter sizes, litter weight and pup survival. These effects were observed at maternally toxic doses at systemic exposures several times above the therapeutic exposure level.

List of excipients
Tablet core:
Crospovidone Lactose monohydrate
Microcrystalline cellulose Calcium phosphate Magnesium stearate

Tablet coat:
Titanium dioxide (E171) Ferric oxide, red (E172) Ferric oxide, yellow (E172) Glycerol triacetate
Lactose monohydrate Hypromellose

Incompatibilities
None applicable

Shelf life
Please refer to expiry date on outer carton

Special precautions for storage
Do not store above 30°C

Pack Size
5 mg tablets : Box of 2 blisters @ 15 film-coated tablets (Reg. No.: DKI1435300817A1)
10 mg tablets : Box of 2 blisters @ 15 film-coated tablets (Reg. No.: DKI1435300817B1)
20 mg tablets : Box of 2 blisters @ 15 film-coated tablets (Reg. No.: DKI1435300817C1)
40 mg tablets : Box of 3 blisters @ 10 film-coated tablets (Reg. No.: DKI1435300817D1)

Instructions for use/handling
No special instructions

Golongan Obat Keras
HARUS DENGAN RESEP DOKTER

Manufactured by:
IPR Pharmaceuticals Inc, Puerto Rico
For AstraZeneca UK Limited, Macclesfield, Cheshire, SK10 2NA, United Kingdom

Packed and released by:
AstraZeneca Pharmaceutical Co. Ltd
No. 2 Huangshan Road, Wuxi, Jiangsu, China

Imported by:
PT AstraZeneca Indonesia
Cikarang, Bekasi - Indonesia

Date of Revision : 12 Juni 2025
Document Number : VV-RIM-06087217

ID : EREG10042212400112,
EREG10042212400113,
EREG10042212400114,
EREG10042212400115.

DISETUJUI OLEH BPOM : 16/07/2025

DISETUJUI OLEH BPOM : 16/07/2025

ID : EREG10042212400112,
EREG10042212400113,
EREG10042212400114,
EREG10042212400115.

Proposed packaging material		
Code	Crestor-FCT-PIL-04.01	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: RO-Change Event-0036915	
Code of previous version	Crestor-FCT-PIL-03.01	
Changes	Additional of Indication CV Prevention	
Reference	☐CDS version: ☒CPIL version: VV-RIM-04905361	☐SmPC country/version/date: ☐GRL approval:
Name & Date	YS	

Informasi untuk pasien
Crestor
Rosuvastatin
Tablet salut selaput 5 mg, 10 mg, 20 mg, dan 40 mg

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisi hal-hal penting untuk Anda.

- Simpanlah leaflet ini. Anda mungkin perlu membacanya di kemudian hari
- Apabila Anda memiliki pertanyaan lebih lanjut, tanyakanlah dokter, apoteker, atau perawat Anda
- Obat ini telah diresepkan khusus untuk Anda. Dilarang memberikan obat ini untuk orang lain karena hal ini dapat membahayakan mereka, meskipun tanda dan gejala penyakit mereka sama dengan yang Anda alami.
- Apabila Anda mengalami efek samping, komunikasikanlah pada dokter atau apoteker Anda. Perhatikan pula kemungkinan efek samping yang tidak terdaftar dalam leaflet ini.

Informasi yang terkandung dalam leaflet ini:

1. Crestor dan kegunaannya
2. Hal yang perlu Anda ketahui sebelum mengkonsumsi Crestor
3. Cara pemakaian Crestor
4. Efek samping yang mungkin terjadi
5. Cara penyimpanan Crestor
6. Informasi lebih lanjut

Bahan aktif dalam CRESTOR adalah rosuvastatin. Tablet salut selaput CRESTOR mengandung rosuvastatin 5 mg, 10 mg, 20 mg, atau 40 mg.

Tablet ini juga mengandung sejumlah bahan tidak aktif yang digunakan untuk membentuknya, antara lain:
laktosa monohidrat, mikrokristal selulosa, kalsium fosfat, krospovidon, magnesium stearat, hipromelose, gliserol triasetat, titanium dioksida (E171), besi oksida merah (E172), besi oksida kuning (E172).

1. CRESTOR DAN KEGUNAANNYA

CRESTOR merupakan obat golongan Inhibitor HMG-CoA reduktase (diketahui pula sebagai "statin"). Pada orang dewasa, obat ini digunakan untuk menurunkan kadar lemak darah yang tinggi, yang disebut sebagai lipid, yang biasanya terjadi ketika

diet dan olahraga gagal. Jika kadar lipid yang tinggi dibiarkan tanpa pengobatan, deposit lemak dapat tertimbun pada dinding pembuluh darah tubuh, yang mana seiring berjalannya waktu dapat mempersempit pembuluh darah tersebut. Hal ini merupakan salah satu penyebab kelainan jantung paling umum. Dengan menurunkan kadar lipid dalam darah Anda, CRESTOR dapat memperlambat atau menunda penimbunan deposit lemak pada dinding pembuluh darah. Oleh karena itu, CRESTOR dapat mengurangi risiko kejadian kardiovaskular (seperti serangan jantung, stroke, dan prosedur revaskularisasi arteri).

CRESTOR tersedia dalam kemasan blister yang berisi 30 tablet.

Empat dosis tablet yang tersedia, yaitu:
CRESTOR tablet salut selaput 5 mg berwarna kuning, bulat, dan bertanda 'ZD4522' dan '5'
CRESTOR tablet salut selaput 10 mg berwarna merah muda, bulat, dan bertanda 'ZD4522' dan '10'
CRESTOR Tablet salut selaput 20 mg berwarna merah muda, bulat, dan bertanda 'ZD4522' dan '20' CRESTOR Tablet salut selaput 40 mg berwarna merah muda, oval, dan bertanda 'ZD4522' dan '40'

2. HAL YANG PERLU ANDA KETAHUI SEBELUM MENGGUNAKAN CRESTOR

Jangan menggunakan CRESTOR apabila:

- Anda memiliki alergi terhadap CRESTOR atau bahan-bahan lain yang terkandung dalam obat ini.
- Apabila Anda sedang hamil, berusaha untuk kehamilan, atau sedang menyusui
- Apabila saat ini Anda sedang memiliki gangguan hati dan ginjal

Jika Anda mengalami salah satu kondisi di atas, bicarakan dengan dokter Anda.
Jika Anda hamil saat mengonsumsi CRESTOR, Anda harus segera menghentikan konsumsi dan memberitahukan dokter Anda.

Peringatan dan pencegahan:
Diskusikan dengan dokter atau apoteker Anda apabila:

- Anda pernah diberitahu bahwa Anda memiliki masalah pada hati atau ginjal
- Anda pernah mengalami nyeri atau sakit otot yang tidak dapat dijelaskan atau memiliki riwayat nyeri otot
- Anda rutin meminum alkohol dalam jumlah banyak
- Anda memiliki gula darah tinggi atau mengalami peningkatan HbA1c.
- Anda menderita atau pernah menderita miastenia gravis (penyakit dengan kelemahan otot umum termasuk otot mata dan pada beberapa kasus otot yang digunakan saat bernapas) karena statin dapat memperburuk kondisi. Kadang-kadang, hal ini juga dapat menyebabkan terjadinya miastenia gravis.

Selama mengonsumsi tablet, beritahukan dokter atau apoteker Anda jika:

- Anda mengalami nyeri atau sakit otot yang tidak dapat dijelaskan
- Anda mengalami kelemahan otot secara terus menerus. Uji dan obat tambahan mungkin dibutuhkan untuk mendiagnosis dan mengobati kejadian ini.

Tablet ini mengandung laktosa, yang mana dapat menyebabkan masalah pada beberapa pasien yang memiliki alergi terhadap laktosa.

Jika anda mengalami sakit parah atau dirawat di rumah sakit, beritahu staf medis yang merawat

Anda bahwa anda mengonsumsi CRESTOR, yang mungkin akan lebih baik jika dihentikan dalam jangka waktu pendek.

Mengonsumsi obat lain
Beritahu dokter atau apoteker Anda jika Anda sedang mengonsumsi obat-obatan lain, termasuk obat yang Anda beli secara bebas. Secara rinci, beritahukan dokter Anda jika Anda mengonsumsi salah satu obat-obat berikut:

- siklosporin (digunakan, misalnya, setelah transplantasi organ),
- warfarin, klopidogrel (atau obat-obatan lain yang digunakan untuk mengencerkan darah),
- gemfibrozil, ezetimibe (digunakan untuk menurunkan kadar lipid darah),
- fosfatamatinib (digunakan untuk mengobati jumlah trombosit rendah),
- Eltrombopag (digunakan untuk mengobati jumlah trombosit rendah),
- febuxostat (digunakan untuk mengobati atau kadar asam urat tinggi),
- teriflunomide (digunakan untuk mengobati Multiple Sklerosis kambuhan),
- atau obat antivirus, baik tunggal maupun kombinasi seperti darunavir, tipranavir, lopinavir, atazanavir, ritonavir, sofosbuvir, simeprevir, velpatasvir, voxilaprevir, grazoprevir, elbasvir, ombitasvir, paritaprevir, dasabuvir, glecaprevir, pibrentasvir (digunakan untuk melawan infeksi, termasuk infeksi HIV),
- capmatinib, regorafenib, darolutamide (digunakan untuk mengobati kanker),
- dronedarone, baicalin, itrakonazol, eritromisin, antasida, asam fusidat, dan kontrasepsi oral.

Hamil dan Menyusui
Tidak boleh digunakan pada wanita hamil dan menyusui

Berkendara dan mengoperasikan mesin
CRESTOR belum dilakukan studi terkait pengaruh Crestor terhadap kemampuan mengemudi dan menggunakan mesin. Namun Crestor dapat menyebabkan sakit kepala, sehingga tidak disarankan untuk mengemudi dan menggunakan mesin saat mengonsumsi Crestor.

3. CARA PEMAKAIAN CRESTOR

Ikuti petunjuk dokter Anda mengenai kapan dan bagaimana menggunakan obat ini. BACALAH LABEL PADA KEMASAN. Tanyakan pada dokter atau apoteker Anda jika Anda tidak yakin mengenai hal ini.

Pada orang dewasa, pengobatan menggunakan CRESTOR biasanya dimulai dengan dosis tablet 5 mg atau 10 mg satu kali per hari. Dosis awal diberikan sesuai dengan hasil pengujian kadar kolesterol dan resiko penyakit jantung. Jika diperlukan penyesuaian dosis dapat dilakukan setelah 4 minggu pemberian. Dosis harian maksimal hanya diberikan pada pasien dewasa dengan kadar kolesterol tinggi kategori berat dan beresiko tinggi terkena penyakit jantung (yang tidak sembuh pada pemberian dosis 20 mg) dan perlu dilakukan pemeriksaan rutin (perlu dilakukan pengawasan pada pasien yang diberikan dosis 40 mg).

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DISETUJUI OLEH BPOM : 16/07/2025

Jika Anda berisiko tinggi terkena penyakit jantung atau pernah mengalami kejadian kardiovaskular (stroke, serangan jantung atau myocardial infarction (MI), angina tidak stabil, atau revaskularisasi arteri), pengobatan menggunakan CRESTOR biasanya diawali dengan dosis 10 mg sekali sehari. Kisaran dosisnya adalah 10-40 mg per oral sekali sehari. Dosis CRESTOR harus disesuaikan secara individual sesuai dengan tujuan terapi dan respon pasien. Mayoritas pasien dikontrol pada dosis awal. Namun bila perlu, penyesuaian dosis dapat dilakukan dengan interval 2 hingga 4 minggu. Untuk pasien dengan target lipid agresif, dosis awal 20 mg dapat dipertimbangkan.

Telan setiap tablet utuh dengan segelas air. Anda dapat meminum obat Anda kapan saja, dengan atau tanpa makanan. Akan tetapi, cobalah untuk meminum obat Anda pada waktu yang sama setiap harinya agar dapat membantu Anda untuk mengingat jadwal meminumnya.

Jangan berhenti meminum obat Anda, walaupun Anda merasa sudah membaik, tanpa anjuran dokter atau kecuali Anda hamil.

Jika Anda lupa minum obat
Jangan khawatir jika Anda lupa minum obat. abaikan dosis yang terlewat dan minum dosis berikutnya seperti biasa. Jangan minum dosis ganda untuk mengganti dosis yang terlewat.

Jika Anda minum CRESTOR melebihi jumlah yang seharusnya
Jika Anda minum lebih dari jumlah yang seharusnya, hubungi dokter atau rumah sakit terdekat.

4. EFEK SAMPING YANG MUNGKIN TERJADI

Seperti obat-obatan pada umumnya, efek-efek yang tidak diinginkan terkadang terjadi ketika menggunakan CRESTOR. Efek-efek ini biasanya ringan dan hilang dalam waktu singkat. Efek yang tidak diinginkan yang paling umum adalah sakit kepala, nyeri otot, sakit perut, kelemahan, konstipasi, pusing, dan merasa tidak enak badan. Selain itu, peningkatan HbA1c, penanda kadar gula darah, ditemukan terjadi pada pasien yang meminum CRESTOR. Dalam beberapa kasus, peningkatan ini memenuhi diagnosis diabetes mellitus, terutama pada pasien yang berisiko tinggi untuk mengalami kondisi ini.

Efek yang tidak diinginkan yang kurang umum adalah ruam kulit, gatal-gatal, dan melepuh. Sangat jarang orang yang mengalami penyakit kuning, kondisi hati yang disebut hepatitis, nyeri sendi atau kehilangan memori, protein dalam urin melebihi nilai normal (proteinuria). Pada kejadian langka, beberapa orang mungkin mengalami sakit perut parah (radang pankreas) atau reaksi alergi parah. Efek yang tidak diinginkan tambahan dengan frekuensi kejadian tidak diketahui yang mungkin dapat terjadi adalah depresi dan gangguan tidur, termasuk kesulitan untuk tidur atau mimpi buruk, perbesaran payudara pada pria dan wanita (ginekomastia), ruam yang mungkin terjadi pada kulit atau luka di bagian dalam mulut (erupsi obat likenoid), lemah otot yang terus menerus dan mati rasa, sensasi kesemutan atau nyeri pada lengan atau kaki (neuropati perifer), kelemahan otot umum termasuk pada beberapa orang kasus otot yang digunakan saat bernapas (miastenia gravis), kelemahan otot mata (ocular miastenia gravis), kekurangan trombosit (trombositopenia), dan sindrom DRESS. Hentikan penggunaan CRESTOR dan segera dapatkan bantuan medis jika salah satu dari hal di bawah ini (reaksi alergi) terjadi:

- Jika Anda mengalami sulit bernapas, disertai atau tanpa pembengkakan wajah, bibir, lidah dan/atau tenggorokan

- Jika Anda mengalami pembengkakan wajah, bibir, lidah, dan/atau tenggorokan, yang menyebabkan kesulitan menelan
- Jika Anda mengalami kulit gatal-gatal yang parah (disertai dengan munculnya benjolan yang terangkat)
- Jika Anda mengalami ruam yang menyebar, suhu tubuh tinggi, dan pembesaran kelenjar getah bening (Sindrom DRESS atau sindrom hipersensitivitas obat).

Sebagai tambahan, efek tidak menyenangkan pada otot terjadi pada sejumlah kecil pasien yang diberikan CRESTOR. Oleh karena itu, sebagai pencegahan, jika Anda merasakan sakit atau nyeri pada otot yang tidak Anda ketahui penyebabnya atau berlangsung lebih lama daripada yang Anda kira, Anda harus mengonsultasikan hal ini kepada dokter Anda secepat mungkin. Dokter Anda mungkin akan melakukan tes darah untuk memeriksa kondisi otot Anda.

Jangan khawatir dengan daftar kejadian yang mungkin Anda alami. Kemungkinan besar Anda tidak akan mengalami hal-hal tersebut.

Pelaporan efek samping

Beritahukan dokter atau apoteker Anda jika Anda merasa Anda mengalami hal-hal di atas atau masalah lainnya ketika menggunakan CRESTOR. Anda juga dapat melaporkan efek samping secara langsung ke kontak industri farmasi pada bagian "**Informasi Lebih Lanjut**". Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. CARA PENYIMPANAN CRESTOR

- Seperti obat-obatan pada umumnya, SIMPAN OBAT ANDA PADA TEMPAT YANG AMAN, di mana anak-anak tidak dapat meraih obat tersebut. Obat Anda dapat membahayakan mereka
- Jangan simpan obat Anda pada suhu di atas 30^0C
- Simpan obat Anda di dalam kemasannya
- Jika dokter Anda memutuskan untuk menghentikan penggunaan obat Anda, buang obat Anda dengan cara mengembalikannya ke apoteker Anda
- Jangan meminum obat Anda setelah melewati batas kedaluarsa yang tertera di kemasan. Buang obat Anda dengan cara mengembalikannya ke apoteker Anda

6. INFORMASI LEBIH LANJUT

PT AstraZeneca Indonesia
Perkantoran Hijau Arkadia Tower G, 16th floor Jl. TB. Simatupang Kav. 88, Jakarta – 12520 Tel: +62 21 2997 9000

HARUS DENGAN RESEP DOKTER

Pemegang Hak Pemasaran dan Produsen
Diproduksi oleh:
IPR Pharmaceutical, Inc, Puerto Rico
Untuk AstraZeneca UK Limited, Macclesfield, Cheshire, SK10 2NA, United Kingdom

ID : EREG10042212400112, EREG10042212400113, EREG10042212400114, EREG10042212400115.
DISETUJUI OLEH BPOM : 16/07/2025

Dikemas dan dirilis oleh:
AstraZeneca Pharmaceutical Company
Ltd. No. 2 Huangshan Road Jiangsu,
Wuxi China
Diimpor oleh:
PT AstraZeneca Indonesia,
Cikarang, Bekasi - Indonesia

Nomor izin edar :
Crestor tablet 5 mg: Dus, 2 blister @ 15 Tablet Salut Selaput
(Reg. No: DKI1435300817A1)
Crestor tablet 10 mg: Dus, 2 blister @ 15 Tablet Salut Selaput
(Reg. No: DKI1435300817B1)
Crestor tablet 20 mg: Dus, 2 blister @ 15 Tablet Salut Selaput
(Reg. No: DKI1435300817C1)
Crestor tablet 40 mg: Dus, 3 blister @ 10 Tablet Salut Selaput
(Reg. No: DKI1435300817D1)

Leaflet ini terakhir direvisi : 19 Juni 2025
Document Number : VV-RIM-06296615