

SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

CRESTOR™ 10 mg, 20 mg, 40 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rosuvastatin calcium corresponding to 10 mg, 20 mg or 40 mg rosuvastatin.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Round, pink coloured (10 mg and 20 mg); oval, pink coloured (40 mg).

4. CLINICAL PARTICULARS

4.1 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 hypercholesterolaemia, either alone or as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis).

4.2 Posology and method of administration

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

The usual start dose is CRESTOR 10 mg once daily and the majority of patients are controlled at this dose. A dose adjustment to 20 mg can be made after 4 weeks, if necessary (see Section 5.1 Pharmacodynamic properties). CRESTOR 40 mg should only be used in patients with severe hypercholesterolaemia (including those with familial hypercholesterolaemia) who do not achieve their treatment goal on 20 mg.

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

Use in Children

Paediatric experience is limited to a small number of children (aged 8 years or above) with homozygous familial hypercholesterolaemia. Use in children should be supervised by specialists.

Use in the elderly

No dose adjustment is necessary.

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 (CrCl <30 ml/min) the dose of CRESTOR should not exceed 10 mg once daily (see Section 5.2 Pharmacokinetic properties).

Dosage in patients with hepatic impairment

No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Increased systemic exposure to rosuvastatin has been observed in patients with severe hepatic impairment therefore the dose of CRESTOR should not exceed 20 mg once daily (see Section 5.2 Pharmacokinetic properties).

Interactions requiring dose adjustments

Gemfibrozil: Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant CRESTOR and gemfibrozil. Patients taking this combination should not exceed a dose of CRESTOR 10 mg once daily. (see Section 4.4 Special warnings and special precautions for use, Section 4.5 Interactions with other medicaments and other forms of interaction.)

4.3 Contraindications

CRESTOR is contraindicated in patients:

- with hypersensitivity to any component of this product.
- with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal.
- with myopathy.
- receiving concomitant cyclosporin.

4.4 Special warnings and special precautions for use

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 with CRESTOR. CRESTOR should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal.

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle e.g. uncomplicated myalgia and myopathy, have been reported in CRESTOR treated patients. Patients should be asked to report inexplicable muscle pain or weakness immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. CRESTOR therapy should be discontinued if CK levels are markedly elevated (>10xULN) or, if on clinical grounds, myopathy is diagnosed or suspected.

In CRESTOR 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, cyclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. (see Section 4.8 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).

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. This is usually transient, and not predictive of acute or progressive renal disease (see Section 4.8 Undesirable effects).

4.5 Interaction with other medicinal products and other forms of interaction

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) may result in an increase in INR. Discontinuation or down-titration of CRESTOR may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Gemfibrozil: Concomitant use of CRESTOR and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC (see Section 4.2 Posology and method of administration).

Cyclosporin: During concomitant treatment with CRESTOR and cyclosporin, rosuvastatin plasma levels were on average 7 times higher than those observed in healthy volunteers (see Section 4.3 Contraindications).

Concomitant administration of CRESTOR and cyclosporin did not affect plasma concentrations of cyclosporin.

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.

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. No interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

Erythromycin: Concomitant use of CRESTOR and erythromycin resulted in a 20% decrease in AUC (0-t) and a 30% decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Oral Contraceptive: Concomitant use of CRESTOR and an oral contraceptive resulted in an increase in ethinyl oestradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses.

Other medications: There were no clinically relevant interactions with digoxin, fenofibrate, antihypertensive agents, antidiabetic agents and hormone replacement therapy.

4.6 Use during pregnancy and lactation

CRESTOR should not be used 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 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 (see Section 5.3 Preclinical safety data). If a patient becomes pregnant during use of this product, treatment should be discontinued immediately. Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.

4.7 Effects on ability to drive and use machines

CRESTOR is not expected to affect the ability to drive or use machines.

4.8 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); Rare (>1/10,000, <1/1000);

Nervous system disorders

Common: headache, dizziness

Gastrointestinal disorders

Common: constipation, nausea, abdominal pain

Musculoskeletal, connective tissue and bone disorders

Common: myalgia

Rare: myopathy

General disorders

Common: asthenia

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to increase with increasing dose.

Skeletal Muscle Effects: Rare cases of rhabdomyolysis have been reported in subjects receiving rosuvastatin 80 mg in investigational clinical trials which were occasionally associated with impairment of renal function. All cases improved on cessation of therapy.

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.

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 at some time during treatment with 10 and 20 mg were <1%, and approximately 3% 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 of acute or progressive renal disease.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

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

Table 1 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-I
Placebo	13	-7	-5	3	-3	-7	-3	0
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

The lowering of total cholesterol, LDL-cholesterol and apolipoprotein B has been shown to reduce the risk of cardiovascular events and mortality. Mortality and morbidity studies with CRESTOR have not yet been completed.

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 hypercholesterolaemia (mean baseline LDL-C about 4.8 mmol/l) to recognised European Atherosclerosis Society (EAS; 1998) guideline targets; about 80% of patients treated with CRESTOR 10 mg 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 40 mg (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 Section 4.4 Special warnings and special precautions for use).

5.2 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 and the remaining part is excreted in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses.

Special populations:

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

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

Hepatic insufficiency: In a study with subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin other than in the two 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.

5.3 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 postnatal 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Crospovidone
Lactose monohydrate
Microcrystalline cellulose
Calcium phosphate
Magnesium stearate

Tablet coat

Titanium dioxide (E171)
Iron oxide, red (E172)
Glycerol triacetate

Lactose monohydrate
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Blister packs: Do not store above 30°C.

HDPE bottles: Do not store above 30°C. Keep container tightly closed.

6.5 Nature and content of container

Blister packs of aluminium/aluminium foil of 7, 14, 15, 20, 28, 30, 42, 50, 56, 60, 84, 98 and 100 tablets and HDPE bottles of 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling, and disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

As appropriate nationally.

8 NUMBER(S) IN THE COUNTRY REGISTER OF MEDICINAL PRODUCTS

As appropriate nationally.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT