NAME OF MEDICINE
CRESTOR
rosuvastatin 5 mg, 10 mg, 20 mg or 40 mg tablets

PRESENTATION

CRESTOR 5 mg: A yellow, film-coated, round, biconvex, 7 mm tablet, impressed with “ZD4522 5”. Each tablet contains 5 mg rosuvastatin as rosuvastatin calcium.

CRESTOR 10 mg: A pink, film-coated, round, biconvex, 7 mm tablet, impressed with “ZD4522 10”. Each tablet contains 10 mg rosuvastatin as rosuvastatin calcium.

CRESTOR 20 mg: A pink, film-coated, round, biconvex, 9 mm tablet, impressed with “ZD4522 20”. Each tablet contains 20 mg rosuvastatin as rosuvastatin calcium.

CRESTOR 40 mg: A pink, film-coated, oval, biconvex, 11.4 x 6.9 mm tablet impressed with “ZD4522” on one side and “40” on the other side. Each tablet contains 40 mg rosuvastatin as rosuvastatin calcium.

INDICATIONS
CRESTOR should be used as an adjunct to diet when the response to diet and exercise is inadequate.

Prevention of Major Cardiovascular events
In adult patients without documented history of cardiovascular or cerebrovascular events, but with at least two conventional risk factors for cardiovascular disease, (see Clinical Efficacy) CRESTOR is indicated to:

- Reduce the risk of nonfatal myocardial infarction
- Reduce the risk of nonfatal stroke
- Reduce the risk of coronary artery revascularisation

Hypercholesterolaemia
CRESTOR is indicated to:

- Reduce elevated LDL-C, total cholesterol, triglycerides and to increase HDL-cholesterol in patients with primary hypercholesterolaemia (heterozygous familial and non familial) and mixed dyslipidaemia (Fredrickson Types IIa and IIb). CRESTOR also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG, the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I ratios and increases ApoA-I in these populations.

- Treat isolated hypertriglyceridaemia (Fredrickson Type IV hyperlipidaemia).
• Reduce total cholesterol and LDL-C in patients with homozygous familial hypercholesterolaemia, as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or alone if such treatments are unavailable.

Prior to initiating therapy with rosuvastatin, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinæmias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

**DOSE AND ADMINISTRATION**

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

**PREVENTION OF MAJOR CARDIOVASCULAR EVENTS**

A dose of 20 mg once daily has been found to reduce the risk of major cardiovascular events.

**HYPERCHOLESTEROLAEMIA**

The usual 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. (See ACTIONS).

A dose of 40 mg once a day should only be considered in patients who are still at high cardiovascular risk after their response to a dose of 20 mg once a day is assessed. It is recommended that the 40 mg dose is used only in patients in whom regular follow-up is planned. A dose of 40 mg must not be exceeded in any patient taking rosuvastatin.

Primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia and isolated hypertriglyceridaemia

The usual start dose is 10 mg once a day.

For patients with severe hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), a start dose of 20 mg may be considered.

**Homozygous familial hypercholesterolaemia**

For patients with homozygous familial hypercholesterolaemia a start dose of 20 mg once a day is recommended.

**USE IN CHILDREN**

In children and adolescents with homozygous familial hypercholesterolaemia experience is limited to a small number of patients (aged 8 years and above).
USE IN THE ELDERLY
The usual dose range applies.

DOSAGE IN PATIENTS WITH RENAL INSUFFICIENCY
The usual dose range applies in patients with mild to moderate renal impairment.

For patients with severe renal impairment the dose of CRESTOR should not exceed 10 mg once daily. (See PHARMACOKINETICS and CONTRAINDICATIONS).

DOSAGE IN PATIENTS WITH HEPATIC INSUFFICIENCY
The usual dose range applies in patients with mild to moderate hepatic impairment.

Patients with severe hepatic impairment should start therapy with CRESTOR 10 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above CRESTOR 10 mg should be carefully considered. (See PHARMACOKINETICS).

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 WARNINGS AND PRECAUTIONS and PHARMACOKINETICS). The increased systemic exposure should be taken into consideration when treating Asian patients whose hypercholesterolaemia is not adequately controlled at doses up to 20 mg daily.

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 WARNINGS AND PRECAUTIONS, INTERACTIONS, AND PHARMACOKINETICS).

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 WARNINGS AND PRECAUTIONS, AND INTERACTIONS). 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 INTERACTIONS).
CONTRAINDICATIONS

CRESTOR is contraindicated in patients with hypersensitivity to any component of this product.

CRESTOR is contraindicated in patients with active liver disease or persistent, unexplained elevations in transaminases.

CRESTOR is contraindicated during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures.

CRESTOR 40 mg is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- situations where an increase in rosuvastatin plasma levels may occur
- severe renal impairment (CrCl < 30 mL/min)
- Asian patients
- concomitant use of fibrates

WARNINGS AND PRECAUTIONS

LIVER:
Liver function tests should be performed before initiation of treatment and periodically thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended.

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.

SKELETAL MUSCLE:
As with other HMG-CoA reductase inhibitors, effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with rosuvastatin. As with other HMG-CoA reductase inhibitors, the reported rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. CRESTOR therapy should be discontinued if CK levels are markedly elevated (>10xULN) or if myopathy is diagnosed or suspected. 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 CRESTOR trials there was no evidence of increased skeletal muscle effects when CRESTOR was dosed with any 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 ciclosporin, fibracids derivitives, including gemfibrozil, nicotinic acid, azole antifungals and macrolide antibiotics.

CRESTOR should be prescribed with caution in patients with pre-disposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism, or situations where an increase in plasma levels may occur (see INTERACTIONS and PHARMACOKINETICS).

Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

CRESTOR should be temporarily withheld 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).

**DIABETES MELLITUS:**
There is sufficient evidence to support an association between statin use and new-onset type 2 diabetes mellitus; however the risk appears to be mainly in patients already at increased risk of developing type 2 diabetes. Risk factors for the development of type 2 diabetes include raised fasting blood glucose, history of hypertension, raised triglycerides and raised body mass index. Patients at risk should be monitored both clinically and biochemically according to national guidelines.

There is insufficient evidence to confirm or exclude an increased risk for any individual statin or a dose-response relationship and the cardiovascular benefits of statin therapy continue to outweigh the risk of developing type 2 diabetes.

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 ADVERSE EFFECTS and PHARMACODYNAMIC PROPERTIES).

**RACE:**
Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see DOSAGE AND ADMINISTRATION and PHARMACOKINETICS).

**INTERSTITIAL LUNG DISEASE:**
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see ADVERSE EFFECTS). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

**CHILDREN AND ADOLESCENTS 6 TO 17 YEARS OF AGE:**
The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric
patients taking CRESTOR is limited to a two year period (See PHARMACOLOGICAL PROPERTIES).

EFFECT ON ABILITY TO DRIVE AND USE MACHINES:
Pharmacology testing revealed no evidence of a sedative effect of CRESTOR. From the safety profile, CRESTOR is not expected to adversely affect the ability to drive or use machines.

PREGNANCY AND LACTATION:
The safety of CRESTOR during pregnancy and whilst breast feeding has not been established. Women of child-bearing potential should use appropriate contraceptive measures (see CONTRAINDICATIONS).

ADVERSE EFFECTS
CRESTOR is generally well tolerated. 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. This withdrawal rate was comparable to that reported in patients receiving placebo.

**Common** (>1/100, <1/10)  Headache, myalgia, asthenia, constipation, dizziness, nausea, abdominal pain, diabetes mellitus*.

**Uncommon** (>1/1000, <1/100)  Pruritus, rash and urticaria.

**Rare** (>1/10,000, <1/1000)  Myopathy (including myositis), hypersensitivity reactions (including angioedema), rhabdomyolysis, pancreatitis.

* Observed in the JUPITER study (reported overall frequency 2.8% in rosuvastatin and 2.3% in placebo) primarily in patients already at high risk for developing diabetes (See WARNINGS AND PRECAUTIONS and PHARMACODYNAMIC PROPERTIES).

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, which were occasionally associated with 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 liver transaminases and CK has been observed in a small number of patients taking rosuvastatin. Increases in HbA1c have also been observed in patients treated with rosuvastatin (See WARNINGS AND PRECAUTIONS - DIABETES MELLITUS and PHARMACODYNAMIC PROPERTIES). Abnormal urinalysis testing (Dipstick positive proteinuria) has been seen in a small number of patients taking CRESTOR and other HMG-CoA reductase inhibitors. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on continued therapy, and is not predictive of acute or progressive renal disease.
In the JUPITER study, occurrences of diabetes mellitus as a pre-specified secondary outcome were reported more frequently in the CRESTOR-treated patients (2.8%) than in placebo (2.3%) and a slight increase in the number of subjects whose fasting glucose levels increased to \( \geq 5.6 \text{ mmol/L (126 mg/dL)} \) was observed in subjects treated with CRESTOR. There was a 0.1% increase in mean HbA1c with CRESTOR compared to placebo.

**OTHER EFFECTS:**

In a long term controlled clinical trial CRESTOR was shown to have no harmful effects on the ocular lens.

In CRESTOR treated patients, there was no impairment of adrenocortical function.

**POST MARKETING EXPERIENCE:**

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

- **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: memory loss, frequency unknown: peripheral neuropathy.
- **Psychiatric disorders:** Frequency unknown: depression, sleep disorders (including insomnia and nightmares).
- **Reproductive system and breast disorders:** Frequency unknown: gynaecomastia

The following adverse events have been reported with some statins:
- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy.

**CHILDREN AND ADOLESCENTS 6 TO 17 YEARS OF AGE:**

The safety profile of CRESTOR is similar in children or adolescent patients and adults although CK elevations >10 x ULN and muscle symptoms following exercise or increased physical activity, which resolved with continued treatment, were observed more frequently in a clinical trial of children and adolescents. However, the same warnings and precautions for use in adults also apply to children and adolescents (See Warnings and Precautions).
**INTERACTIONS**

**EFFECT OF CO-ADMINISTERED MEDICINAL PRODUCTS ON ROSUVASTATIN**

*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, and DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Table 1: Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

<table>
<thead>
<tr>
<th>Interacting drug dose regimen</th>
<th>Rosuvastatin dose regimen</th>
<th>Change in rosuvastatin AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclosporin 75 mg BID to 200 mg BID, 6 months</td>
<td>10 mg OD, 10 days</td>
<td>7.1-fold ↑</td>
</tr>
<tr>
<td>Atazanavir 300 mg/ritonavir 100 mg OD, 8 days</td>
<td>10 mg, single dose</td>
<td>3.1-fold ↑</td>
</tr>
<tr>
<td>Simeprevir 150 mg OD, 7 days</td>
<td>10 mg, single dose</td>
<td>2.8-fold ↑</td>
</tr>
<tr>
<td>Lopinavir 400 mg/ritonavir 100 mg BID, 17 days</td>
<td>20 mg OD, 7 days</td>
<td>2.1-fold ↑</td>
</tr>
<tr>
<td>Clopidogrel 300 mg loading, followed by 75 mg at 24 hours</td>
<td>20 mg single dose</td>
<td>2-fold ↑</td>
</tr>
<tr>
<td>Gemfibrozil 600 mg BID, 7 days</td>
<td>80 mg, single dose</td>
<td>1.9-fold ↑</td>
</tr>
<tr>
<td>Eltrombopag 75 mg OD, 5 days</td>
<td>10 mg, single dose</td>
<td>1.6-fold ↑</td>
</tr>
<tr>
<td>Darunavir 600 mg/ritonavir 100 mg BID, 7 days</td>
<td>10 mg OD, 7 days</td>
<td>1.5-fold ↑</td>
</tr>
<tr>
<td>Tipranavir 500 mg/ritonavir 200 mg BID, 11 days</td>
<td>10 mg, single dose</td>
<td>1.4-fold ↑</td>
</tr>
<tr>
<td>Dronedarone 400 mg BID</td>
<td>Not available</td>
<td>1.4-fold ↑</td>
</tr>
<tr>
<td>Itraconazole 200 mg OD, 5 days</td>
<td>10 mg or 80 mg, single dose</td>
<td>1.4-fold ↑</td>
</tr>
<tr>
<td>Ezetimibe 10 mg OD, 14 days</td>
<td>10 mg, OD, 14 days</td>
<td>1.2-fold ↑</td>
</tr>
<tr>
<td>Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 days</td>
<td>10 mg, single dose</td>
<td>↔</td>
</tr>
<tr>
<td>Aleglitazar 0.3 mg, 7 days</td>
<td>40 mg, 7 days</td>
<td>↔</td>
</tr>
<tr>
<td>Silymarin 140 mg TID, 5 days</td>
<td>10 mg, single dose</td>
<td>↔</td>
</tr>
<tr>
<td>Fenofibrate 67 mg TID, 7 days</td>
<td>10 mg, 7 days</td>
<td>↔</td>
</tr>
<tr>
<td>Rifampicin 450 mg OD, 7 days</td>
<td>20 mg, single dose</td>
<td>↔</td>
</tr>
<tr>
<td>Ketoconazole 200 mg BID, 7 days</td>
<td>80 mg, single dose</td>
<td>↔</td>
</tr>
</tbody>
</table>
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<th>Rosuvastatin dose regimen</th>
<th>Change in rosuvastatin AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole 200 mg OD, 11 days</td>
<td>80 mg, single dose</td>
<td>↔</td>
</tr>
<tr>
<td>Erythromycin 500 mg QID, 7 days</td>
<td>80 mg, single dose</td>
<td>20% ↓</td>
</tr>
<tr>
<td>Baicalin 50 mg TID, 14 days</td>
<td>20 mg, single dose</td>
<td>47% ↓</td>
</tr>
</tbody>
</table>

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. Start with a 5 mg once daily dose of CRESTOR if the expected increase in exposure (AUC) is approximately 2-fold or higher. 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 5 mg dose of CRESTOR with ciclosporin (7.1-fold increase in exposure), a 10 mg dose of CRESTOR with ritonavir/atazanavir combination (3.1-fold increase) and a 20 mg dose of CRESTOR with gemfibrozil (1.9-fold increase).

Other interacting medicinal products

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.

EFFECT OF ROSUVASTATIN ON CO-ADMINISTERED MEDICINAL PRODUCTS

Warfarin:
The pharmacokinetics of warfarin are not significantly affected following co-administration with CRESTOR. However, as with other HMG-CoA reductase inhibitors, co-administration of CRESTOR and warfarin may result in a rise in INR compared to warfarin alone. In patients taking vitamin K antagonists monitoring of INR is recommended both at initiation or cessation of therapy with CRESTOR or following dose adjustment.

Fenofibrates/fibric acid derivatives:
Although no pharmacokinetic interaction between rosuvastatin and fenofibrate was observed; a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate and other fibric acids, including nicotinic acid, may increase the risk of myopathy when
given concomitantly with HMG-CoA reductase inhibitors (see WARNINGS AND PRECAUTIONS).

**Ciclosporin:**
Co-administration of CRESTOR with ciclosporin resulted in no significant changes in ciclosporin plasma concentration.

**Other medications:**
There were no clinically significant interactions with an oral contraceptive, digoxin or fenofibrate.

In clinical studies CRESTOR was co-administered with antihypertensive agents, antidiabetic agents and hormone replacement therapy. These studies did not produce any evidence of clinically significant adverse interactions.

**OVERDOSEAGE**
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. Haemodialysis is unlikely to be of benefit.

**PHARMACOLOGICAL PROPERTIES**

**PHARMACODYNAMIC PROPERTIES**

**Mechanism of action:**
Rosuvastatin is a selective, potent and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver.

Rosuvastatin produces its lipid-modifying effects in two ways; it 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.

High density lipoprotein (HDL), which contains ApoA-I is involved, amongst other things, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

The involvement of LDL-C in atherogenesis has been well documented. Epidemiological studies have established that high LDL-C, TG, low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease. Intervention studies have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent data has linked the beneficial effects of HMG-CoA reductase inhibitors to lowering of non-HDL (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.
Clinical efficacy:
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 and Table 3).

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

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.

Table 2 - Dose Response in Patients with Primary Hypercholesterolaemia (Type IIa and IIb) (Adjusted mean % change from baseline)

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>LDL-C</th>
<th>Total-C</th>
<th>HDL-C</th>
<th>TG</th>
<th>NonHDL-C</th>
<th>ApoB</th>
<th>ApoA-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>13</td>
<td>-7</td>
<td>-5</td>
<td>3</td>
<td>-3</td>
<td>-7</td>
<td>-3</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>-45</td>
<td>-33</td>
<td>13</td>
<td>-35</td>
<td>-44</td>
<td>-38</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>17</td>
<td>-52</td>
<td>-36</td>
<td>14</td>
<td>-40</td>
<td>-48</td>
<td>-42</td>
<td>4</td>
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<tr>
<td>20</td>
<td>17</td>
<td>-55</td>
<td>-40</td>
<td>8</td>
<td>-23</td>
<td>-51</td>
<td>-46</td>
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<tr>
<td>40</td>
<td>18</td>
<td>-63</td>
<td>-46</td>
<td>10</td>
<td>-28</td>
<td>-60</td>
<td>-54</td>
<td>0</td>
</tr>
</tbody>
</table>

The data in Table 2 and Table 3 are confirmed by the broader clinical programme of over 5,300 patients given CRESTOR.

In a 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%.

In a force-titration open label study, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to CRESTOR 20 - 40 mg titrated at a 6 week interval. In the overall population, the mean LDL-C reduction was 22%. In the 27 patients with at least a 15% reduction by week 12 (considered to be the responder population), the mean LDL-C reduction was 26% at the 20 mg dose and 30% at the 40 mg dose. Of the 13 patients with an LDL-C of less than 15%, 3 had no response or an increase in LDL-C.

CRESTOR is effective in a wide variety of 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.
The first 12-weeks’ efficacy data from 5 Phase III efficacy trials (Trials 24 to 28) were pooled to investigate the overall effect of rosuvastatin 10 mg, and to look at comparisons with atorvastatin 10 mg (Trials 24 to 26), pravastatin 20 mg and simvastatin 20 mg (Trials 27 and 28). Table 4 presents key findings from these pools of data.

Overall, treatment with rosuvastatin at these doses resulted in a substantially better improvement in the atherogenic lipid profile than did treatment with the comparator statins.

### Table 4: Efficacy of rosuvastatin 10 mg versus atorvastatin 10 mg, pravastatin 20 mg and simvastatin 20 mg in subjects with Types IIa and IIb dyslipidaemia

<table>
<thead>
<tr>
<th>Trial number/time</th>
<th>Treatment</th>
<th>N</th>
<th>LS mean of % change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LDL-C</td>
</tr>
<tr>
<td>Rosuvastatin overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 to 28 pooled/12 weeks</td>
<td>Rosuvastatin 5 mg</td>
<td>630</td>
<td>-41.4a</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin 10 mg</td>
<td>615</td>
<td>-47.2a</td>
</tr>
<tr>
<td>Rosuvastatin versus atorvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 to 26 pooled/12 weeks</td>
<td>Rosuvastatin 5 mg</td>
<td>390</td>
<td>-41.9***</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin 10 mg</td>
<td>389</td>
<td>-46.7***</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin 10 mg</td>
<td>393</td>
<td>-36.4</td>
</tr>
<tr>
<td>Rosuvastatin versus pravastatin and simvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 and 28 pooled/12 weeks</td>
<td>Rosuvastatin 5 mg</td>
<td>240</td>
<td>-40.6***,###</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin 10 mg</td>
<td>226</td>
<td>-48.1***,###</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 20 mg</td>
<td>252</td>
<td>-27.1</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20 mg</td>
<td>249</td>
<td>-35.7</td>
</tr>
</tbody>
</table>

* Mean of % change from baseline; LS mean = Least squares mean; N = Number of subjects.
** p<0.01 versus atorvastatin; *** = p<0.001 versus atorvastatin; + = p<0.05 versus pravastatin; ++ = p<0.01 versus pravastatin; +++ = p<0.001 versus pravastatin; # = p<0.05 versus simvastatin; ## = p<0.01 versus simvastatin; ### = p<0.001 versus simvastatin.

The percentage of subjects who achieved joint European recommendations for LDL-C following 12 weeks of treatment with rosuvastatin (for the trial data pools) is shown in Table 5.
### Table 5  % of subjects reaching EAS targets for LDL-C levels at Week 12

<table>
<thead>
<tr>
<th>Trial number/time</th>
<th>Treatment</th>
<th>Risk category</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Other</td>
<td>High</td>
</tr>
<tr>
<td>Rosuvastatin versus atorvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 to 26 pooled/12 weeks</td>
<td>Rosuvastatin 5 mg</td>
<td>77</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin 10 mg</td>
<td>88</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin 10 mg</td>
<td>69</td>
<td>23</td>
</tr>
<tr>
<td>Rosuvastatin versus pravastatin and simvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 and 28 pooled/12 weeks</td>
<td>Rosuvastatin 5 mg</td>
<td>63</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin 10 mg</td>
<td>84</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 20 mg</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20 mg</td>
<td>56</td>
<td>22</td>
</tr>
</tbody>
</table>

*** p<0.001 versus atorvastatin; +++ p<0.001 versus pravastatin and simvastatin

Active-Controlled Study: CRESTOR was compared with the HMG-CoA reductase inhibitors atorvastatin, simvastatin and pravastatin in a multicenter, open-label, dose-ranging study of 2,239 patients with Type IIa and IIb hypercholesterolaemia. After randomization, patients were treated for 6 weeks with a single daily dose of either CRESTOR, atorvastatin, simvastatin or pravastatin (
Figure 1 and Table 6). The primary endpoint for this study was the percent change from baseline in LDL-C at week 6.
Figure 1. Percent LDL-C Change by Dose of CRESTOR, Atorvastatin, Simvastatin and Pravastatin at Week 6 in Patients With Type IIa/IIb Dyslipidaemia

Box plots are a representation of the 25th, 50th, and 75th percentile values, with whiskers representing the 10th and 90th percentile values.

Mean baseline LDL-C: 189 mg/dL.

Table 6. LS Mean§ % change in LDL-C from baseline to Week 6 for each statin treatment group. N = number of patients at each dose of each statin.

<table>
<thead>
<tr>
<th>TREATMENT DAILY DOSE</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>N</td>
<td>Mean (95%CI)</td>
<td>N</td>
<td>Mean (95%CI)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>156</td>
<td>-46 (-48, -44)</td>
<td>160</td>
<td>-52 (-54, -50)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>158</td>
<td>-37 (-39, -35)</td>
<td>154</td>
<td>-43 (-45, -41)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>160</td>
<td>-20 (-22, -18)</td>
<td>164</td>
<td>-24 (-26, -22)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>165</td>
<td>-28 (-30, -26)</td>
<td>162</td>
<td>-35 (-37, -33)</td>
</tr>
</tbody>
</table>

* Rosuvastatin 10 mg reduced LDL-C significantly more than atorvastatin 10 mg; pravastatin 10 mg, 20 mg, and 40 mg; simvastatin 10 mg, 20 mg, and 40 mg. (p<0.002)
† Rosuvastatin 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg, and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. (p<0.002)
‡ Rosuvastatin 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg, and 80 mg (p<0.002)
§ Corresponding standard errors are approximately 1.00

The percent change from baseline in HDL-C at week 6 is shown in
Figure 2 below:
Figure 2. Mean (LS mean) Percent Change from Baseline in HDL-C to Week 6

\[
\begin{array}{cccc}
\text{Rosuvastatin} & \text{Atorvastatin} & \text{Pravastatin} & \text{Simvastatin} \\
7.7 & 5.7 & 5.3 & 6.8 \\
9.5 & 4.8 & 6.0 & 5.2 \\
9.6 & 4.4 & 5.6 & 6.8 \\
\end{array}
\]

p < 0.002 Rosuvastatin 10 mg vs Pravastatin 10 mg
p < 0.002 Rosuvastatin 20 mg vs Atorvastatin 20 mg, 40 mg, 80 mg; Pravastatin 20 mg, 40 mg; Simvastatin 40 mg
p < 0.002 Rosuvastatin 40 mg vs Atorvastatin 40 mg, 80 mg; Pravastatin 40 mg; Simvastatin 40 mg

Data presented as LS means ± SE

The mean percent change in HDL-C from baseline to Week 6 for each statin treatment group represented in
Figure 2 is summarised with 95% CI in Table 7.

Table 7. LS mean % change in HDL-C from baseline to Week 6 for each statin treatment group. N = number of patients at each dose of each statin.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>10 mg N</th>
<th>Mean (95%CI)</th>
<th>20 mg N</th>
<th>Mean (95%CI)</th>
<th>40 mg N</th>
<th>Mean (95%CI)</th>
<th>80 mg N</th>
<th>Mean (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>156</td>
<td>8 (6,9)</td>
<td>160</td>
<td>9 (8,11)</td>
<td>157</td>
<td>10 (8,11)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>158</td>
<td>6 (4,7)</td>
<td>154</td>
<td>5 (3,7)</td>
<td>156</td>
<td>4 (3,6)</td>
<td>165</td>
<td>2 (0,4)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>160</td>
<td>3 (2,5)</td>
<td>164</td>
<td>4 (3,6)</td>
<td>161</td>
<td>6 (4,7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>165</td>
<td>5 (4,7)</td>
<td>162</td>
<td>6 (4,8)</td>
<td>158</td>
<td>5 (4,6)</td>
<td>163</td>
<td>7 (5,8)</td>
</tr>
</tbody>
</table>

Hypertriglyceridaemia (Fredrickson Type IIb & IV)

In a double blind, placebo-controlled dose-response study in patients with baseline TG levels from 273 to 817 mg/dL, CRESTOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels (}
Table 8).
Table 8. Dose-Response in Patients With Primary Hypertriglyceridaemia Over 6 Weeks
Dosing Median (Min, Max) Percent Change From Baseline

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo N=26</th>
<th>Rosuvastatin 5 mg N=25</th>
<th>Rosuvastatin 10 mg N=23</th>
<th>Rosuvastatin 20 mg N=27</th>
<th>Rosuvastatin 40 mg N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>1 (-40, 72)</td>
<td>-21 (-58, 38)</td>
<td>-37 (-65, 5)</td>
<td>-37 (-72, 11)</td>
<td>-43 (-80, -7)</td>
</tr>
<tr>
<td>NonHDL-C</td>
<td>2 (-13, 19)</td>
<td>-29 (-43, -8)</td>
<td>-49 (-59, -20)</td>
<td>-43 (-74, -12)</td>
<td>-51 (-62, -6)</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>2 (-36, 53)</td>
<td>-25 (-62, 49)</td>
<td>-48 (-72, 14)</td>
<td>-49 (-83, 20)</td>
<td>-56 (-83, 10)</td>
</tr>
<tr>
<td>Total-C</td>
<td>1 (-13, 17)</td>
<td>-24 (-40, -4)</td>
<td>-40 (-51, -14)</td>
<td>-34 (-61, -11)</td>
<td>-40 (-51, -4)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>5 (-30, 52)</td>
<td>-28 (-71, 2)</td>
<td>-45 (-59, 7)</td>
<td>-31 (-66, 34)</td>
<td>-43 (-61, -3)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-3 (-25, 18)</td>
<td>3 (-38, 33)</td>
<td>8 (-8, 24)</td>
<td>22 (-5, 50)</td>
<td>17 (-14, 63)</td>
</tr>
</tbody>
</table>

High Risk Hypercholesterolaemic Patients
In a 26 week double-blind forced titration study, 871 high risk hypercholesterolaemic patients with established CHD or multiple risk factors for CHD, were randomised to receive either rosuvastatin or atorvastatin. Patients in the rosuvastatin arm were titrated to 40 mg, while in the atorvastatin arm patients were titrated to 80 mg. The primary objective of the study was to compare rosuvastatin 40 mg with atorvastatin 80 mg in high risk patients, by measuring the percentage change in LDL-C from baseline to Week 8. Table 9 summarises the results for the mean percentage change from baseline at 8 weeks in lipid and lipoprotein variables.

Table 9: Summary of the mean percentage changes in lipid and lipoprotein variables in high risk hypercholesterolaemic patients after 8 weeks treatment with either rosuvastatin 40 mg or atorvastatin 80 mg.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean % change‡ RSV 40 mg n=432</th>
<th>Mean % change‡ ATV 80 mg n=439</th>
<th>Difference in ls mean% changes</th>
<th>95% CI§</th>
<th>p value ¥</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>-55.89</td>
<td>-52.18</td>
<td>-3.71</td>
<td>-5.61 to –1.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>9.58</td>
<td>4.35</td>
<td>5.23</td>
<td>3.04 to 7.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC</td>
<td>-40.40</td>
<td>-39.27</td>
<td>-1.13</td>
<td>-2.63 to 0.36</td>
<td>0.138 a</td>
</tr>
<tr>
<td>non-HDL-C</td>
<td>-50.75</td>
<td>-48.27</td>
<td>-2.48</td>
<td>-4.25 to –0.72</td>
<td>0.006 b</td>
</tr>
<tr>
<td>Apo B</td>
<td>-44.64</td>
<td>-42.29</td>
<td>-2.35</td>
<td>-4.17 to –0.52</td>
<td>0.012</td>
</tr>
<tr>
<td>Apo AI</td>
<td>4.20</td>
<td>-0.47</td>
<td>4.67</td>
<td>2.71 to 6.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG</td>
<td>-22.21</td>
<td>-27.02</td>
<td>4.81</td>
<td>1.10 to 8.53</td>
<td>0.011*</td>
</tr>
</tbody>
</table>

‡ Mean % change from baseline
§ 95% confidence interval for the difference between the least squares means
¥ p< 0.05 was statistically significant
a statistically significant in favour of atorvastatin
b ns = not significant
RSV = rosuvastatin; ATV = atorvastatin; Is = least squares

Atherosclerosis
In a multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk <10% over 10 years), with a mean LDL-C of 4.0 mmol/l (154.5 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomised to 40 mg rosuvastatin once daily or placebo for 2 years. Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -0.0093; p<0.0001]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for rosuvastatin
compared to a progression of +0.0131 mm/year (1.12%/year (p<0.0001)) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of Crestor 40mg. The 40mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk (see DOSAGE AND ADMINISTRATION).

Prevention of Major Cardiovascular Events

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 established cardiovascular disease, LDL-C levels < 3.3 mmol/l and hs-CRP levels ≥2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.3% 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 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 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, unstable angina or an arterial revascularization procedure.

Rosuvastatin significantly reduced the risk of CV events (252 events in the placebo group vs. 142 events in the rosvastatin group) with a statistically significant (p<0.001) relative risk reduction of 44% (see Figure 3Error! Reference source not found.). The benefit was apparent within the first 6 months of treatment. 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. There was a statistically significant 48% reduction in the combined endpoint of CV death, stroke and myocardial infarction (HR: 0.52, 95% 95% CI: 0.40-0.68, p<0.001), a 54% reduction in fatal or nonfatal myocardial infarction (HR: 0.46, 95% CI: 0.30-0.70) and a 48% reduction in fatal or nonfatal stroke. Total mortality was reduced 20% in the rosvastatin group (HR: 0.80, 95% CI: 0.67-0.97, p=0.02).
Figure 3: Time to occurrence of major cardiovascular events in JUPITER

The safety profile for subjects taking rosuvastatin 20 mg was generally similar to that of subjects taking placebo. There were 1.6% of rosuvastatin and 1.8% of placebo subjects who withdrew from the trial due to an adverse event, irrespective of treatment causality. The most common adverse reactions that led to treatment discontinuation were: myalgia (0.3% rosuvastatin, 0.2% placebo), abdominal pain (0.03% rosuvastatin, 0.02% placebo) and rash (0.03% rosuvastatin, 0.03% placebo). Adverse reactions reported in ≥2% of patients and at a rate greater than or equal to placebo were myalgia (7.6% rosuvastatin, 6.6% placebo), constipation (3.3% rosuvastatin, 3.0% placebo) and nausea (2.4% rosuvastatin, placebo, 2.3%).

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%. A post hoc analysis of this study suggests that the risk of development of diabetes on rosuvastatin therapy is limited to patients already at high risk of developing diabetes. The cardiovascular and mortality benefits of rosuvastatin therapy exceeded the diabetes hazard in the trial population as a whole as well as in participants at increased risk of developing diabetes (see WARNINGS AND PRECAUTIONS and ADVERSE EFFECTS).

Children and Adolescents with Hypercholesterolaemia
In a double-blind, randomised, multi-centre, placebo-controlled, 12-week study (n = 176, 97 male and 79 female) followed by a 40-week (n = 173, 96 male and 77 female), open label, rosuvastatin dose titration phase, patients 10 – 17 years of age (Tanner stage II-V, females at least 1 year post-menarche) with heterozygous familial hypercholesterolaemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12
weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10 – 13 years and approximately 17%, 18%, 40% and 25% were Tanner stage II, III, IV and V respectively.

Rosuvastatin reduced LDL-C (primary end point), total cholesterol and ApoB levels. Results are shown in Table 10 below.

Table 10 Lipid-modifying effects of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia (least-squares mean percent change from baseline to week 12)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>N</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>Total-C</th>
<th>TG</th>
<th>Non-HDL-C</th>
<th>ApoB</th>
<th>ApoA-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>46</td>
<td>-0.7</td>
<td>6.9</td>
<td>-0.0</td>
<td>5.1</td>
<td>-0.9</td>
<td>-1.7</td>
<td>2.8</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>-38.3</td>
<td>4.2</td>
<td>-29.9</td>
<td>0.3</td>
<td>-36.1</td>
<td>-31.7</td>
<td>1.8</td>
</tr>
<tr>
<td>10</td>
<td>44</td>
<td>-44.6</td>
<td>11.2</td>
<td>-34.2</td>
<td>-13.6</td>
<td>-43.0</td>
<td>-38.1</td>
<td>5.4</td>
</tr>
<tr>
<td>20</td>
<td>44</td>
<td>-50.0</td>
<td>8.9</td>
<td>-38.7</td>
<td>-8.1</td>
<td>-47.5</td>
<td>-40.7</td>
<td>4.0</td>
</tr>
</tbody>
</table>

At the end of the 40 week, open label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 110 mg/dL (2.8 mmol/L).

After 52 weeks of study treatment, no effect on growth or sexual maturation was detected (See WARNINGS AND PRECAUTIONS).

Rosuvastatin was also studied in a 2-year open-label, titration-to-goal study in 198 children with heterozygous familial hypercholesterolaemia aged 6 to 17 years (88 male and 110 female, Tanner stage <II-V). The starting dose for all patients was 5 mg rosuvastatin once daily. Patients aged 6 to 9 years (n=64) could titrate to a maximum dose of 10 mg once daily and patients aged 10 to 17 years (n=134) to a maximum dose of 20 mg once daily.

After treatment, 74 of 197 patients (37.6%) in this study achieved the LDL-C goal of less than 110 mg/dL (2.8 mmol/L). All age groups showed statistically significant reductions in LDL-C from baseline values.

Rosuvastatin 5 mg, 10 mg, and 20 mg also achieved statistically significant mean changes from baseline for the following secondary lipid and lipoprotein variables: HDL-C, TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, non-HDL C/HDL-C, ApoB, ApoB/ApoA-1. These changes were each in the direction of improved lipid responses and were sustained over 2 years.

No effect on growth or sexual maturation was detected after 24 months of treatment.

PHARMACOKINETIC PROPERTIES

Crestor is administered orally in the active form with peak plasma levels occurring 5 hours after dosing. Absorption increases linearly over the dose range. The half life is 19 hours and does not increase with increasing dose. Absolute bioavailability is 20%. There is minimal accumulation on repeated once daily dosing.

Rosuvastatin undergoes first pass extraction in the liver which is the primary site of cholesterol synthesis and LDL-C clearance.
Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin. The parent compound accounts for greater than 90% of the circulating active HMG CoA reductase inhibitor activity.

Rosuvastatin undergoes limited metabolism (approximately 10%), mainly to the N-desmethyl form, and 90% is eliminated as unchanged drug in the faeces with the remainder being excreted in the urine.

**Special populations:**

**Age and sex:**
There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers.

**Race:**
Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) 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 little 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.

**Hepatic insufficiency:**
In a study in 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.

**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 1.6-fold higher rosuvastatin exposure (AUC) or 2.4-fold higher exposure, respectively, compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes.
PHARMACEUTICAL PARTICULARS

EXCIPIENTS

Tablet core:
- Crospovidone
- Lactose monohydrate
- Microcrystalline cellulose
- Calcium phosphate
- Magnesium stearate

Tablet coat:
- Titanium dioxide (E171)
- Ferric oxide, red (E172) (10 mg, 20 mg, 40 mg only)
- Ferric oxide, yellow (E172) (5 mg only)
- Glycerol triacetate
- Lactose monohydrate
- Hypromellose

STORAGE CONDITIONS
Blister Packs: Store below 30°C

SHELF-LIFE
3 years

MEDICINE CLASSIFICATION
Prescription Medicine

PACKAGE QUANTITIES
Blister packs containing 7 (CRESTOR 5 and 10 mg only) or 30 tablets.

FURTHER INFORMATION

PRE-CLINICAL SAFETY INFORMATION
Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity.

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