CRESTOR 5 mg, film-coated tablet
B/30 (CIP code: 369 853-8)
B/90 (CIP code: 391 690-0)

CRESTOR 10 mg, film-coated tablet
B/30 (CIP code: 391 694-6)
B/90 (CIP code: 391 696-9)

CRESTOR 20 mg, film-coated tablet
B/30 (CIP code: 391 697-5)
B/90 (CIP code: 391 699-8)

Applicant: ASTRAZENECA

rosuvastatin
ATC code: C10AA07

List I

Dates of initial (centralised) Marketing Authorisations:
CRESTOR 10 and 20 mg: 11 June 2003
CRESTOR 5 mg: 6 October 2005

Date of extension of indication: 21 June 2010

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use in the extension of indication: “Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors”.

Medical, Economic and Public Health Assessment Division
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
rosuvastatin

1.2. Indications
“Treatment of hypercholesterolaemia
Adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Prevention of cardiovascular events
Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event (see Pharmacokinetic properties section), as an adjunct to correction of other risk factors.”

1.3. Dosage
“Before treatment initiation the patient should be placed on an appropriate cholesterol-lowering diet that should continue throughout 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.

Prevention of cardiovascular events
In the cardiovascular events risk reduction study, the dose used was 20 mg daily (see Pharmacokinetics section).

Paediatric use: Paediatric use should only be carried out by specialists.
• Children and adolescents 10-17 years of age (boys Tanner stage II and above, and girls who are at least 1 year post-menarche): In children and adolescents with heterozygous familial hypercholesterolaemia the usual start dose is 5 mg daily. The usual dose range is 5-20 mg orally once daily. Titration should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations (see Section 4.4). Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment. Safety and efficacy of doses greater than 20 mg have not been studied in this population. The 40 mg dose is not suitable for use in paediatric patients.

• Children younger than 10 years: Experience in children younger than 10 years is limited to a small number of children (aged between 8 and 10 years) with homozygous familial hypercholesterolaemia. Therefore, CRESTOR is not recommended for use in children younger than 10 years.

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. The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance < 60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of CRESTOR in patients
with severe renal impairment is contraindicated for all doses (see Contraindications and Pharmacokinetic properties in the SPC).

**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 (see Special warnings and special 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 Contraindications).

**Race:** Increased systemic exposure has been seen in Asian subjects (see Special warnings and special precautions for use and Pharmacokinetic properties). The recommended start dose is 5 mg for patients of Asian ancestry. The 40 mg dose is contraindicated in these patients (see Contraindications and Pharmacokinetic properties).

**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 special precautions for use). The 40 mg dose is contraindicated in these patients (see Contraindications)."

### 2. SIMILAR MEDICINAL PRODUCTS

#### 2.1. ATC Classification (2004)
- C : Cardiovascular system
- C10 : Lipid modifying agents
- C10A : Cholesterol-lowering and triglyceride-lowering agents
- C10AA : HMG CoA reductase inhibitors
- C10AA07 : Rosuvastatin

#### 2.2. Medicines in the same therapeutic category
These are the other statins indicated in primary prevention of cardiovascular events:
- Pravastatin (ELISOR, VASTEN and generics), indicated in “Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolaemia and at high risk of a first cardiovascular event, as an adjunct to diet”.
- Simvastatin (LODALES, ZOCOR and generics), indicated in “Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy”
- Atorvastatin (TAHOR), indicated in “Reduction of coronary events in treated hypertensive patients with 3 risk factors in primary prevention, with or without associated hyperlipidaemia” and “Prevention of coronary and cerebrovascular events in type 2 diabetes patients with another risk factor, with or without associated hyperlipidaemia”.

#### 2.3. Medicines with a similar therapeutic aim
These are all the other medicines indicated in the management of patients in primary prevention of cardiovascular events.
3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy
The evaluation of the efficacy and tolerance of CRE STOR in this new indication is based on a clinical study (JUPITER)\(^1\).

**Aim:** to evaluate the efficacy and tolerance of rosuvastatin 20 mg/day compared to placebo in terms of reduction of the number of major cardiovascular events (CVE) in patients with low levels of LDL-c (<1.30 g/l) and high levels of high-sensitivity C-reactive protein (HS-CRP) (≥ 2 mg/l).

**Method:** placebo-controlled, randomised, double-blind phase III study carried out in 17,802 non-hypercholesterolaemic (LDL-c < 1.3 g/l) patients with high HS-CRP (≥ 2 mg/l) followed up for a period of 4 years.

According to the protocol, the final analysis was to be carried out after 520 validated observed events. The study was ended prematurely after a median follow-up duration of 1.9 years and 393 events.

**Inclusion criteria:** men aged 50 years or over and women aged 60 years or over, without a history of cardiovascular disease and with:
- LDL-c < 1.3 g/l,
- HS-CRP ≥ 2 mg/l
- a triglyceride (TG) level < 5 g/l.

**Note:** The choice of the HS-CRP level as a criterion for inclusion and selection of patients at high CV risk remains controversial. Firstly, the study did not compare patients with or without high HS-CRP, and secondly, a subgroup analysis showed an inverse correlation between HS-CRP levels and clinical benefit (the lower the HS-CRP, the greater the clinical benefit). Finally, considerable variability in measurement of this HS-CRP was identified.

**Cardiovascular risk (CVR) on inclusion:** The CVR (risk of having a CVE within 10 years) was calculated for each included patient on the basis of both the Framingham scale and the SCORE scale. These risk levels did not constitute inclusion criteria. The distribution of the patients included in the study as a function of their CVR is as follows:

**According to the Framingham\(^2\) scale:**
- 7217 (40.5%) patients were at low CVR (risk of CVE <15% at 10 years),
- 9001 (50.6%) patients were at medium CVR (risk of CVE 15-20% at 10 years),
- 1558 (8.8%) patients were at high CVR (risk of CVE > 20% at 10 years),
- 26 (0.1%) not calculated.

**According to the SCORE\(^2\) scale:**
- 8474 (47.6%) patients had a CVE risk < 5% at 10 years,
- 9302 (52.3%) patients had a CVE risk > 5% at 10 years,
- 26 (0.1%) not calculated.

On inclusion, 25% of the patients had a single CV risk factor (RF): age, 50% had more than two RFs, and 25% had more than three.

According to the results obtained with these scales, approximately 50% of the patients had a medium or high CVR and 50% a low CVR.

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Non-inclusion criteria: treatment with lipid-lowering agents in the 6 months prior to inclusion, or ongoing, a history of hypersensitivity (including myopathy) to statins, history of cardiovascular or cerebrovascular disease, hormone replacement therapy for the menopause, impaired liver function, CK > 3 times the upper limit, creatinine > 2 mg/dl, diabetes, uncontrolled hypertension, cancer in the last 5 years, uncontrolled hypothyroidism, inflammatory diseases treated with immunosuppressants (lupus, severe arthritis).

Treatment:
All the patients selected received placebo for 4 weeks, after which the patients included were randomised to two groups:
- CRESTOR 20 mg/day, n = 8901,
- Placebo, n = 8901.

Note: the rosuvastatin dose used in this study (20 mg/day) is debatable as the treatment should be initiated at a dose of 5 mg and only increased if the subject does not achieve the LDL-c goal set in advance according to the patient's CV risk factors. No data for lower-dose rosuvastatin, in this context of elevated CRP, are available at present.

Primary endpoint: occurrence of the first major cardiovascular event (MCE), a composite endpoint consisting of: non-fatal MI, non-fatal CVA, hospitalisation because of unstable angina, an arterial revascularisation procedure or death from CV causes.

RESULTS: intention-to-treat analysis.
The results for the composite primary endpoint are presented in Table 1.

On inclusion, the characteristics of the patients were comparable. The mean age of the patients included was 66 years, and the mean BMI 29. 41.4% of the patients had a metabolic syndrome, 57% had hypertension, and 16% were smokers. All the patients included (100%) had HS-CRP ≥ 2 mg/l.

**Table 1: Number and percentage of first MCEs observed after a median follow-up of 1.9 years**

<table>
<thead>
<tr>
<th></th>
<th>CRESTOR 20 mg/day n = 8901</th>
<th>Placebo n = 8901</th>
<th>Hazard ratio [95% CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite primary endpoint:</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- Non-fatal MI</td>
<td>142 (1.6%)</td>
<td>251 (2.9%)</td>
<td>0.56 [0.46; 0.69]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>- Non-fatal CVA</td>
<td>21</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Arterial revascularisation</td>
<td>30</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hospitalisation because of unstable angina</td>
<td>47</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Death from CV cause</td>
<td>29</td>
<td>37</td>
<td></td>
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</tr>
</tbody>
</table>

NB: Account was taken of only 1 MCE per patient. If several MCEs were observed in the same patient on the same day, only 1 MCE was used, in accordance with the following hierarchy: 1) unstable angina 2) Non-fatal MI 3) Arterial revascularisation 4) Non-fatal CVA 5) CV death.

After a median follow-up of 1.9 years, a significant decrease in the primary endpoint combining non-fatal MI, non-fatal CVA, hospitalisation because of unstable angina, an arterial revascularisation procedure or death from cardiovascular causes was observed with CRESTOR 20 mg/day in comparison with placebo: 142 events versus 251, HR 0.56 [0.46; 0.69], p < 0.001 (7.6 events per 1000 patients versus 13.6 events per 1000 patients, p < 0.001) with an NNT of 95 patients for 2 years of treatment and 31 for 4 years of treatment and a reduction of absolute risk of 5.1 per 1000 patient-years treated.

Arterial revascularisation accounts for 30% of the total number of events observed.
Components of the primary endpoint (not limited to a single MCE per patient):
The following were observed in the CRESTOR group in comparison with placebo:
- 22 events versus 62, HR 0.35 [0.22; 0.58], p < 0.001; or a 65% reduction in the number of non-fatal myocardial infarcts,
- 30 versus 58, HR 0.52 [0.33; 0.80], p = 0.003; or a 48% reduction in the number of non-fatal CVAs,
- 71 versus 131, HR 0.54 [0.41; 0.72], p < 0.001; or a 46% reduction in the number of arterial revascularisations:

No significant difference was observed between the two groups in terms of:
- death from CV causes: 35 events (0.4%) with CRESTOR versus 44 (0.5%) with placebo, NS
- hospitalisation because of unstable angina: 16 events (0.2%) with CRESTOR versus 27 (0.3%) with placebo, NS.

3.2. Adverse effects
In the JUPITER study, tolerance was evaluated in 17,733 patients (8869 patients in the CRESTOR group and 8864 patients in the placebo group). Adverse events were observed in 6969 patients (78.3%) in the CRESTOR group versus 6907 (77.6%) in the placebo group.

The most frequently observed events (> 5%) were:
- urinary tract infection: 772 patients (8.7%) vs 764 patients (8.6%),
- rhinopharyngitis: 679 (7.6%) vs 642 (7.2%),
- back pain: 679 (7.6%) vs 616 (6.9%),
- myalgia: 678 (7.6%) vs 590 (6.6%),
- bronchitis: 643 (7.2%) vs 631 (7.1%),
- hypertension: 624 (7%) vs 695 (7.8%),
- arthritis: 516 (5.8%) vs 495 (5.6%),
- cough: 475 (5.3%) vs 472 (5.3%),
- bone pain: 449 (5%) vs 451 (5.1%).

The specific laboratory adverse events were:
- increased CK: 61 (0.7%) vs 34 (0.5%),
- proteinuria: 149 (1.7%) vs 127 (1.4%).

Finally, specific monitoring of the occurrence of diabetes was defined as one of the secondary endpoints of the JUPITER study. Diabetes was reported in 251 patients in the CRESTOR 20 mg/day group versus 205 patients in the placebo group, HR 1.27, 95% CI [1.05; 1.53], p = 0.015. The LDL-c level was less than 0.55 g/l in these patients. In this study there seems to be a link between the substantial decreases in LDL-c and the increased incidence of diabetes.

As a rough guide, 198/8901 deaths from any cause were observed in the patients in the CRESTOR group and 247/8901 in the patients in the placebo group. To these results it is not possible to add a quantification of the observed effect on account of the risk of potential overestimation of this effect due to premature discontinuation of the trial. Furthermore, the significance of this secondary endpoint is debatable because of the multiplicity of the tests performed.
3.3. Conclusion

In the JUPITER study the efficacy and tolerance of CRESTOR 20 mg/day were evaluated in patients without hypercholesterolaemia (LDL-c level < 1.30 g/l) and high levels of high-sensitivity C-reactive protein (HS-CRP ≥ 2 mg/l).

After a median follow-up of 1.9 years, a significant decrease in the composite primary endpoint combining non-fatal MI, non-fatal CVA, hospitalisation because of unstable angina, an arterial revascularisation procedure or death from cardiovascular causes was observed with CRESTOR 20 mg/day in comparison with placebo: 142 events versus 251, HR 0.56 [0.46; 0.69], p < 0.001 (7.6 events per 1000 patients versus 13.6 events per 1000 patients, p < 0.001) with an NNT of 95 patients for 2 years of treatment and 31 for 4 years of treatment.

Arterial revascularisation accounts for 30% of the total number of events observed.

On the basis of the results of this study, the indication “Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors” was granted by the Marketing Authorisation; this indication is based on a posteriori analysis of the data of a subgroup of patients at high risk.

As regards the components of the primary endpoint (secondary endpoints), the following were observed in the CRESTOR group in comparison with placebo:

- 22 events versus 62, HR 0.35 [0.22; 0.58], p < 0.001; or a 65% reduction in the number of non-fatal myocardial infarcts,
- 30 versus 58, HR 0.52 [0.33; 0.80], p = 0.003; or a 48% reduction in the number of non-fatal CVAs,
- 71 versus 131, HR 0.54 [0.41; 0.72], p < 0.001; or a 46% reduction in the number of arterial revascularisations:

No significant difference was observed between the two groups in terms of:

- death from CV causes: 35 events (0.4%) with CRESTOR versus 44 (0.5%) with placebo, NS
- hospitalisation because of unstable angina: 16 events (0.2%) with CRESTOR versus 27 (0.3%) with placebo, NS.

No data from a direct comparison with the other statins indicated for primary prevention are available.

The most frequently observed adverse events (> 5%) were: urinary tract infection, rhinopharyngitis, back pain, myalgia, bronchitis, hypertension, arthritis, cough, bone pain. In addition, an increased incidence of diabetes was observed in the CRESTOR group in comparison with placebo: HR 1.27, 95% CI [1.05; 1.53], p = 0.015.
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit
Cardiovascular diseases in patients with a high cardiovascular risk can be life-threatening.

Rosuvastatin, according to its Marketing Authorisation description, falls under the category of preventive therapy for cardiovascular events in patients with a high cardiovascular risk in primary prevention (without a history of cardiovascular disease).

Rosuvastatin is a first-line treatment.

For primary prevention, simvastatin, pravastatin, and atorvastatin are alternative treatments.

Public health benefit:
The public-health burden of cardiovascular diseases is a major one. In the subpopulation of patients with a high cardiovascular risk it can be described as substantial in view of the frequency and severity of the cardiovascular events.

Reducing the mortality associated with cardiovascular diseases is a public-health need (law of 9 August 2004 on public health policy).

On the basis of the available data from the JUPITER study, the level of impact of treatment with CRESTOR rosuvastatin at a dose of 20 mg per day on morbidity/mortality in the patients included in the study is substantial, with a decrease in the frequency of cardiovascular events.

However, it is not certain that the results of the JUPITER study can be carried over into practice, in particular because the level of cardiovascular risk of French patients is lower than that of the study patients and because of the heterogeneity of the patients included and the difficulty of identifying patients with a high cardiovascular risk in accordance with Afssaps [French Health Product Safety Agency] recommendations.

Furthermore, it is not possible, on the basis of the duration of the study, to arrive at an adequate answer regarding the tolerance of the treatment, especially the clinical consequences of a substantial reduction of the LDL-c level. Consequently, the impact of the proprietary product CRESTOR in the population of patients with a high cardiovascular risk is moderate.

On the basis of the JUPITER study, an impact on the care system can be expected on account of a reduction of the number of admissions to hospital for arterial revascularisation.

The public-health need is only partially met in view of the existence of other statins and the class effect of statins on all-cause mortality.

Consequently, CRESTOR is expected to have a small public-health benefit in patients with a high cardiovascular risk.

The actual benefit of CRESTOR in this indication is substantial.
4.2. Improvement in actual benefit (IAB)
The efficacy of CRESTOR 20 mg for primary prevention in patients estimated to have a high risk for a first cardiovascular event is based on the data from the JUPITER study. Given that:
- these results are from a high risk patient subgroup defined a posteriori,
- the effect is probably overestimated because of the premature discontinuation of the study,
the transparency Committee is of the view that CRESTOR does not provide an improvement in actual benefit (IAB V) in the management of patients at high risk of having a first cardiovascular event.

4.3. Therapeutic use
In patients with a high cardiovascular risk (estimated either by summation of various risk factors or by using risk models), primary-prevention measures are aimed at preventing or delaying the occurrence of coronary and cardiovascular events.

In these patients, drug therapy should be initiated as soon as possible (Level B) and included as part of global management combining:
- provision of advice on a healthy diet and lifestyle: establishment of an appropriate diet and taking of adequate physical exercise (30 min per day),
- management of associated cardiovascular risk factors: smoking (cessation), overweight (target BMI < 25 kg/m²), diabetes (target HbA1C < 7%) and hypertension (target value < 140/90 mm Hg or < 130/80 mm Hg in patients with diabetes and renal impairment).

In the JUPITER study the efficacy of rosuvastatin 20 mg/day (CRESTOR) was demonstrated on a composite endpoint combining non-fatal MI, non-fatal CVA, hospitalisation because of unstable angina, an arterial revascularisation procedure or death from cardiovascular causes in primary prevention in a subgroup of patients with a high CV risk without hypercholesterolaemia. This study confirmed the importance of global management of cardiovascular risk. The study dosage was 20 mg/day, close to the maximum dose validated by the Marketing Authorisation. The therapeutic benefit of lower dosages was not investigated in these patients.

In this indication patients can be given rosuvastatin, atorvastatin, simvastatin, or pravastatin alike.

4.4. Target population
In this extension of indication in the prevention of major cardiovascular events, the target population of CRESTOR is patients estimated to have a high risk for a first cardiovascular event. This extension is based on the results of the JUPITER study, which recruited men aged 50 years or over and women aged 60 years or over with LDL cholesterol < 1.30 g/l and high-sensitivity CRP (HS-CRP) levels ≥ 2 mg/l, without diabetes and without a history of cardiovascular disease.

In the United States, in the ARIC (Atherosclerosis risk in communities) cohort, 18% of the men and women meeting the JUPITER study age criterion were considered eligible for the study (LDL cholesterol <1.30 g/l and high-sensitivity CRP (HS-CRP) ≥ 2 mg/l, not diabetic and with no history of cardiovascular disease).

Applying this to the French population of men aged 50 years or over and women aged 60 years or over, the population at risk of a first cardiovascular event is estimated to be 1.5 million women and 1.9 million men according to the criteria of the JUPITER study.

5 Women aged 60 years or over in France on 1 January 2010: 8,317,810; men aged 50 years or over in France on 1 January 2010: 10,455,612 (source: http://www.insee.fr)
In the JUPITER study, 25% of the patients could be considered to be at high CV risk (defined, according to the Afssaps recommendations of 2005\textsuperscript{2}, as > 3 risk factors (RF)), i.e. a total or around 850,000 patients (375,000 women and 475,000 men).

The target population of CRESTOR in the extension of indication “prevention of major cardiovascular events in patients estimated to have a high risk for a first cardiovascular event” can thus be estimated at around 850,000 people.

4.5. Transparency Committee recommendations
The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the extension of indication and at the dosage in the Marketing Authorisation.

Packaging: appropriate for the prescription conditions

Reimbursement rate: 65%