Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Rosuvastatin

Proprietary Product Name: Crestor/Visacor

Sponsor: AstraZeneca Pty Ltd

May 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Initial Decision:	20 October 2010
Date of Final Decision:	22 February 2011
Active ingredient(s):	Rosuvastatin
Product Name(s):	Crestor; Visacor[1]
Sponsor's Name and Address:	AstraZeneca Pty Ltd Alma Road North Ryde NSW 2113
Dose form(s):	Film-coated tablets
Strength(s):	5 mg, 10 mg, 20 mg and 40 mg
Container(s):	Blister packs
Pack size(s):	5 mg, 10 mg, 20 mg: packs of 7 and 30; 40 mg: pack of 30
Approved Therapeutic Use following Finalisation of this Submission:	Crestor should be used as an adjunct to diet when the response to diet and exercise is inadequate. Prevention of major cardiovascular events Crestor is indicated for prevention of major cardiovascular events in men ≥ 50 years old or women ≥60 years old with no clinically evident cardiovascular disease but with at least two conventional risk factors for cardiovascular disease (hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease). Crestor is indicated to: · Reduce the risk of nonfatal myocardial infarction · Reduce the risk of nonfatal stroke. · Reduce the risk of coronary artery revascularisation. In patients with hypercholesterolaemia Crestor is indicated for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia). Prior to initiating therapy with Crestor, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

[1] There are two trade names associated with rosuvastatin – Crestor and Visacor. The trade name Crestor will be used for the remainder of this AusPAR.

Route(s) of administration:	Oral
Dosage:	Dosage depends on clinical response. The usual starting dose is 5, 10 or 20 mg once daily. The usual maximum dose is 20 mg once daily.
ARTG Number (s):	119120, 119127, 119128, 119129, 119130, 119131, 119135, 119136

Product Background

Rosuvastatin is a synthetic lipid lowering agent that inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme that converts HMG-CoA to mevalonate, a precursor of cholesterol.

Rosuvastatin has been considered by the Advisory Committee on Prescription Medicines (ACPM) (and its predecessor, ADEC) previously for other indications as follows:

Dec 2002: Initial submission which was recommended for rejection due to inadequate long term safety data, inadequate drug interaction data and renal and myotoxicity.

Feb 2004: Recommended for approval but without the 40 mg tablet and no dyslipidaemia.

Oct 2004: The National Drugs and Poisons Scheduling Committee (NDPSC) sought advice on the pregnancy classification of HMG-CoA reductase inhibitors.

Dec 2004: Recommendation to change the pregnancy classification to Category D.

Mar 2006: Approval of the 40 mg dose but with restrictions.

The current indications are as follows:

Crestor is indicated as an adjunct to diet when the response to diet and exercise is inadequate for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia).

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

This AusPAR describes the evaluation of a submission by AstraZeneca Pty Ltd which seeks to extend the indications for rosuvastatin (Crestor) to reduce the risk of major cardiovascular events in patients at increased risk of cardiovascular disease with risk markers such as age and elevated high sensitivity assay C-reactive protein [CRP](hsCRP) but with "normal" cholesterol levels. The sponsor also applied to slightly modify the current hypercholesterolaemia indication and applying the diet and exercise restriction to both indications.

The proposed indications are:

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

<u>Prevention of Cardiovascular Events</u>

Crestor is indicated to reduce the risk of major cardiovascular events in men aged 50 years and over; and women aged 60 years and over who have at least one other risk marker for increased risk of cardiovascular disease such as elevated hsCRP, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease (see Clinical Trials, Prevention of Cardiovascular Events).

<u>In adult patients with hypercholesterolaemia</u>

Crestor is indicated for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia).

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

Regulatory Status

The product received initial ARTG Registration in 2004.

A similar application to the current Australian submission has been submitted in the USA, Canada and the European Union (EU) with the same data package as submitted to the TGA. The submission was approved in the USA in February 2010, Canada in March 2010 and the EU in March 2010.

The resulting USA approved indication is:

Primary Prevention of Cardiovascular Disease

In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, Crestor is indicated to:

- *reduce the risk of stroke*
- *reduce the risk of myocardial infarction*
- *reduce the risk of arterial revascularization procedures*

The resulting approved indication in Canada is:

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 Trials), Crestor is indicated to:

- *Reduce the risk of nonfatal myocardial infarction*
- *Reduce the risk of nonfatal stroke*
- *Reduce the risk of coronary artery revascularization*

The resulting approved indication in the EU is:

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 section 5.1), as an adjunct to correction of other risk factors.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

Data from three studies were included in the submission in support of efficacy and safety. There was one pivotal study: ***Study D3560L00030 JUPITER***, conducted in 17,802 subjects, 8,901 of whom were exposed to rosuvastatin 20 mg daily (Table 1). There were two supportive studies:

Study D3562C00088 METEOR, conducted in 984 subjects, 702 of whom were exposed to rosuvastatin 40 mg daily (Table 7).

Study D3562C00098 CORONA, conducted in 5011 subjects, 2514 of whom were exposed to rosuvastatin 10 mg daily (Table 10).

In addition there was one Periodic Safety Update Report (PSUR) covering the time period 7 November 2007 to 6 November 2008.

The studies were stated to have been conducted according to Good Clinical Research Practice.

Pharmacokinetics

No new pharmacokinetic data were included in the submission.

Pharmacodynamics

No new pharmacodynamic data were included in the submission.

Efficacy

Pivotal Study

Study D3560L00030 JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) was a multicentre, randomised, double blind, placebo controlled, parallel group trial of rosuvastatin 20 mg for the primary prevention of cardiovascular events in subjects with low levels of low-density lipoprotein cholesterol (LDL-C) and elevated levels of CRP (Table 1). It was conducted in 26 countries in North and South America, Europe and South Africa. In the JUPITER Clinical Study Report, "normal" cholesterol is considered to be a LDL-C <3.36 mmol/L.

Inclusion and exclusion criteria are summarised in Table 1. The study treatments were:

1. Rosuvastatin 20 mg
2. Placebo

The subjects self-administered one tablet orally each day. All subjects received placebo during the four week run-in period. Subjects were randomised to treatment if eligible at the end of the run-in phase.

Table 1: Details of JUPITER Study

Nr. of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation Reference	Criteria for evaluation	Results (efficacy)	Adverse Reactions
89846 subjects were screened, 17802 were randomized : 8901 to rosuvastatin , 8901 to placebo. All randomized subjects were included in the ITT analysis. 8208 (92.2%) subjects in the rosuvastatin group and 8186 (92.0%) in the placebo group completed 11001 (61.8%) males, 6801 (38.1%) females age range 49 to 97 years.	Men aged 50 years and over; women aged 60 years and over Fasting LDL-C value <3.36 mmol/L at Screening Visit 1 hsCRP value ≥2.0 mg/L at Screening Visit 1 Triglycerides (TG) <5.6 mmol/L at Screening Visit 1 Exclusions: Treatment with any HMG-CoA reductase inhibitors or other lipid lowering therapies Prior history of cardiovascular or cerebrovascular events such as MI, unstable angina, prior arterial revascularization, or stroke, or CHD risk equivalent; Current use of postmenopausal oral HRT; Hepatic or renal dysfunction ; Diabetes mellitus	Treatment was for up to 5 years Recruitment was for one year	Rosuvastatin 20 mg One tablet daily All subjects received placebo during the four week run-in period. Subjects were randomised to treatment if eligible at the end of the run-in phase Randomised using an IVRS Placebo	Primary efficacy outcome measure : time to first occurrence of a major cardiovascular event. Secondary efficacy outcome measure: CV death, nonfatal MI, or nonfatal stroke; fatal or nonfatal MI; fatal or nonfatal stroke; Time to first occurrence of the following: total mortality; non-cardiovascular mortality; discontinuation of blinded study medication due to adverse effects; development of diabetes mellitus; development of venous thromboembolic events; bone fractures Safety: adverse events (AEs) and lab values	For the primary efficacy outcome measure, there was a significant reduction in relative risk of 44%: HR (95% CI) 0.56 (0.46 to 0.69) p <0.001. There was a lesser incidence of each of the individual components of the composite endpoint in the rosuvastatin group. The effect was maintained across subgroups and risk strata, except for subjects with lower than median LDL and higher than median hsCRP. Risk of all-cause death was reduced in the rosuvastatin group. In the rosuvastatin group hsCRP, TC, LDL-C and TG decreased and HDL-C increased from baseline, and relative to placebo.	6968 (78.3%) subjects in the rosuvastatin group and 6907 (77.6%) in the placebo group reported at least one TEAE. The most commonly reported AEs in the rosuvastatin group were: urinary tract infection, nasopharyngitis and back pain. AEs leading to non-cardiovascular death occurred in 141 (1.6%) subjects in the rosuvastatin group and 179 (2.0%) in the placebo group. Neoplasia was the most frequent grouping of AEs leading to death. A total of 1,341 (15.1%) subjects in the rosuvastatin group and 1,372 (15.4%) in the placebo group reported at least one treatment emergent SAE.

The primary efficacy outcome measure was the time to first occurrence of a major cardiovascular event (cardiovascular death, stroke, myocardial infarction [MI], unstable angina, or arterial revascularization). The secondary efficacy outcome measures were:

- Cardiovascular (CV) death, nonfatal MI, or nonfatal stroke

- Fatal or nonfatal MI
- Fatal or nonfatal stroke
- Time to first occurrence of the following:
  - all cause mortality
  - non-cardiovascular mortality
  - discontinuation of blinded study medication due to adverse effects
  - development of diabetes mellitus
  - development of venous thromboembolic events (deep vein thrombosis or pulmonary embolism)
  - bone fractures

Covariate effects were examined for the variables: age, sex, age by sex, race, smoking status, body mass index (BMI), hypertension (blood pressure ≥140/90 mmHg or on an antihypertensive medication), geographic region (US or US/Canada versus other countries), high-density lipoprotein cholesterol (HDL-C), LDL-C (continuous; and below versus at or above median), triglycerides (TG), hsCRP (continuous; and below versus at or above median), and LDL-C and hsCRP (categories defined by medians). The safety outcome measures included incidence of adverse events (AEs) and of abnormal laboratory values.

Statistical Analysis Plan for Pivotal Study

Hypothesis tests were performed using time to event analysis using Cox proportional hazards modelling and 95% confidence intervals (CI) for hazard ratios. Kaplan-Meier plots were presented for time-to-event variables.

The sample size calculation was performed for the composite primary endpoint but not for the individual components of the composite primary endpoint or for any secondary endpoint analysis. A primary endpoint event rate was estimated to be between 1.0 and 1.5 per 100 patient-years of follow-up based on data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). In order to detect a 25% reduction from the placebo event rate with 90% power, the study needed to observe 514 events (rounded up to 520 events), based on a two-sided alpha of 0.05, an accrual period of 1 year and the mean follow-up of 3.5 years, 12,000 subjects would have been needed to be randomized. Allowing for drop outs and other exigencies the sample size estimate was raised to 15,000 randomized subjects.

Two interim analyses of the primary endpoint were planned and a group sequential design was used to preserve an overall type 1 error probability of 0.05. Other issues of multiplicity were not addressed in the statistical analysis plan, as presented in the study protocol.

Results for the Pivotal Study

A total of 89,846 subjects were screened, of whom 17,802 were randomized to treatment. Of the subjects that were screened 72,044 (80.2%) were not randomized. For 66,198 (91.9%) of these subjects the reason for failing screening was for failing to meet the inclusion criteria (37,611 [52.2%] with LDL-C concentrations of ≥3.36 mmol/L and 25,993 [36.1%] with hsCRP < 2.0 mg/L). Hence, because fewer than 20% of the screened subjects were enrolled, the study population was highly selected. Other reasons for screening failure were: for 3,487 (4.8%) subjects consent was withdrawn, 602 (0.8%) were excluded for "other reason", 560 (0.8%) were not compliant with the protocol, 439 (0.6%) were lost to follow-up, for 370 (0.5%) there was no information, 283 (0.4%) failed screening at the investigator's discretion, and 105 (0.1%) failed because of a history of an adverse event.

There were 8,901 subjects randomized to rosuvastatin and 8,901 to placebo. All randomized subjects were included in the intention to treat (ITT) analysis. There were 8,208 (92.2%) subjects in the rosuvastatin group that completed the study and 8,186 (92.0%) in the placebo group. Twenty eight (0.3%) subjects in the rosuvastatin group and 22 (0.2%) in the placebo group were lost to follow-up. A total of 665 (7.5%) subjects in the rosuvastatin group and 693 (7.8%) in the placebo group were withdrawn from the study. Study medication was discontinued because of an AE by 584 (6.6%) subjects in the rosuvastatin group and 553 (6.2%) in the placebo group. There were 11,001 (61.8%) males and 6,801 (38.1%) females. The age range was 49 to 97 years. The treatment groups were similar in demographic characteristics and cardiovascular risk factors, baseline physical measures, number of cardiovascular risk factors and metabolic syndrome criteria. Median (range) age was 66 (49 to 94) years in the rosuvastatin group and 66 (50 to 97) years in the placebo group. There were 5475 (61.5%) males and 3426 (38.5%) females in the rosuvastatin group, compared with 5526 (62.1%) males and 3375 (37.9%) females in the placebo group. The rosuvastatin group was 71.4% Caucasian, 12.4% Black and 12.6% Hispanic. The placebo group was 71.1% Caucasian, 12.6% Black and 12.8% Hispanic. A total of 1400 (15.7%) subjects in the rosuvastatin group were smokers, compared with 1420 (16.0%) in the placebo group. A total of 5079 (57.1%) subjects in the rosuvastatin group had hypertension compared with 5129 (57.6%) in the placebo group. The treatment groups were similar in baseline and hsCRP concentrations. Other than ergot alkaloids and fibrates (both of which were used to a greater extent in the placebo group), the use of concomitant medications was similar between the two groups.

For the primary efficacy outcome measure, there was a significant reduction in a major cardiovascular event (MCE) in the rosuvastatin group with a relative risk of 44%: Hazard Ratio (HR) (95% CI) 0.56 (0.46 to 0.69) p <0.001 (Table 2). There were 142 (1.6%) subjects in the rosuvastatin group who experienced an MCE compared with 252 (2.8%) in the placebo group. There was a lesser incidence of all the individual components of the composite endpoint in the rosuvastatin group (Table 2). There was an absolute risk reduction of six MCEs per 1000 patient treatment years. The effect was maintained for up to five years of treatment (Figure 1). There was a significant reduction in relative risk with rosuvastatin for nonfatal stroke, nonfatal MI, and arterial revascularization (Table 3). Note: the numbers of endpoints differ between Tables 3 and 2, because Table 2 presents time to first MCE, which means one of the components, whereas Table 3 presents individual components of the MCE, in which case an individual subject could have experienced more than one of the individual components. The effect was maintained across subgroups (including age, sex, race, BMI, smoking status, and region) except for subjects with both lower than median LDL and higher than median hsCRP. The effect was maintained across risk strata.

Table 2: Number of first events by treatment group for the composite primary endpoint, ITT population - JUPITER Study

	Number of first events	
	Rosuva 20 mg (N=8901)	Placebo (N=8901)
	n	n
First MCE[a]	142	252
Cardiovascular death	29	37
Nonfatal MI	21	61
Non fatal Stroke	30	57
Hospitalized unstable angina	15	27
Arterial revascularization	47	70

	Event rate/1000-patient years			
	Rosuva 20 mg	Placebo	HR (95% CI)	P value
First MCE	7.6	13.6	0.56 (0.46, 0.69)	<0.001

CI Confidence interval; HR Hazard ratio; ITT Intent-to-treat; MCE Major cardiovascular event; MI Myocardial infarction; Rosuva Rosuvastatin.

[a] An MCE is the occurrence of any of the following events: cardiovascular death, stroke, MI, unstable angina or arterial revascularization. Event occurrence counts only 1 MCE for each subject. If subject had more than 1 MCE on the same day, only 1 event is shown , according to the following hierarchy: 1) unstable angina, 2) MI, 3) arterial revascularization, 4) nonfatal stroke, 5) cardiovascular death.

Figure 1: Kaplan-Meier plot for the primary composite endpoint – JUPITER Study

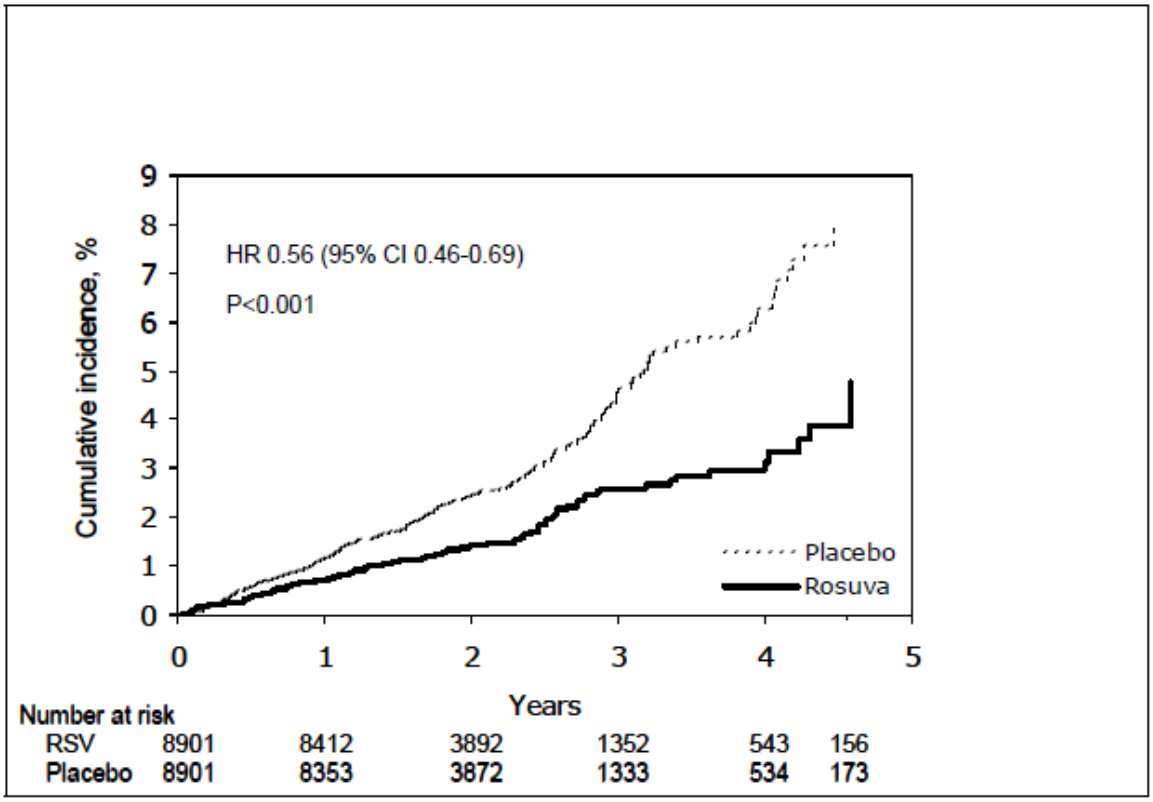


Table 3: Number of first events by treatment group for each individual cardiovascular endpoint, ITT population - JUPITER Study

	Number (%) of subjects with event[a]			
	Rosuva 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)	HR (95% CI)	P value
Cardiovascular death	35 (0.4)	44 (0.5)	0.80 (0.51, 1.24)	0.315
Nonfatal stroke	30 (0.3)	58 (0.7)	0.52 (0.33, 0.80)	0.003
Nonfatal MI	22 (0.2)	62 (0.7)	0.35 (0.22, 0.58)	<0.001
Hospitalized unstable angina	16 (0.2)	27 (0.3)	0.59 (0.32, 1.10)	0.093
Arterial revascularization	71 (0.8)	131 (1.5)	0.54 (0.41, 0.72)	<0.001

CI Confidence interval; HR Hazard ratio; ITT Intent-to-treat; MI Myocardial infarction; Rosuva Rosuvastatin.
[a] Not limited to the first occurrence of an MCE. For example, a subject with a stroke, followed by an MI would be counted twice, once for stroke and once for MI. A subject with serial strokes would only be counted once.

There was a reduced risk of death or MCE with rosuvastatin (Table 4). There was a reduced risk of other composite cardiovascular endpoints with rosuvastatin (Table 5). Risk of all-cause death was reduced in the rosuvastatin group. There were 105 (1.2%) subjects in the rosuvastatin group and 126 (1.4%) in the placebo group that died from non-cardiovascular causes: HR 0.84, p=0.172. More subjects in the rosuvastatin group had investigator-reported diabetes, 251 (2.8%) compared with 205 (2.3%) in the placebo group: HR (95% CI) 1.27 (1.05 to 1.53), p=0.015. Fewer subjects in the rosuvastatin group developed venous thromboembolic events: 26 (0.3%) compared with 46 (0.5%), HR (95% CI) 0.57 (0.35 to 0.91) p=0.018. There was no significant difference between the group in incidence of fractures: 226 (2.5%) subjects in the rosuvastatin group and 214 (2.4%) in the placebo group: HR (95% CI) 1.06 (0.88 to 1.28) p=0.548. In the rosuvastatin group hsCRP, TC, LDL-C and TG decreased from baseline, and relative to placebo, during the study. Baseline, Month 12 and end of study (using Last Observation Carried Forward [LOCF] methodology) mean (standard deviation [SD]) cholesterol, HDL-C, LDL-C, and least squares mean difference (95% CI) in SI units (mmol/L) are presented in Table 6. The reductions in LDL-C and hsCRP were significant when analysed by subgroups (gender, age category, hypertension and smoking status). HDL-C increased in the rosuvastatin group from baseline and relative to placebo.

Table 4: Number of events by treatment group for death or MCE, ITT population – JUPITER Study

	Number of events (% of subjects having an event)						
	Rosuvastatin 20 mg (N=8901)		Placebo (N=8901)				
	n	(%)	n	(%)	HR	95% CI	P-value
MCE or death	265	(3.0)	400	(4.5)	0.66	0.56, 0.77	<0.001

Table 5: Other cardiovascular efficacy endpoints, ITT population – JUPITER Study

	Number of events			
	Rosuva 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)	HR (95% CI)	P value
CV death/MI/stroke	83 (0.9)	158 (1.8)	0.52 (0.40, 0.68)	<0.001
Fatal or nonfatal MI	31 (0.3)	68 (0.8)	0.46 (0.30, 0.70)	<0.001
Fatal or nonfatal stroke	33 (0.4)	64 (0.7)	0.52 (0.34, 0.79)	0.002

CI Confidence interval; CV Cardiovascular; HR Hazard ratio; ITT Intent-to-treat; MI Myocardial infarction; Rosuva Rosuvastatin.

Table 6: Baseline, Month 12 and end of study (LOCF) mean (SD) cholesterol, HDL-C, LDL-C, and least squares mean difference (95% CI) in SI units (mmol/L) – JUPITER Study

	Baseline	After 12 Months	Final Visit (LOCF)
Total Cholesterol			
Rosuvastatin	4.74 (0.639)	3.60 (0.861)	3.72 (0.928)
Placebo	4.74 (0.625)	4.88 (0.776)	4.84 (0.808)
LS Difference (95% CI)		-0.70 (-0.71 to -0.68)	-0.60 (-0.62 to -0.59)
LDL-C			
Rosuvastatin	2.70 (0.489)	1.59 (0.713)	1.70 (0.786)
Placebo	2.70 (0.479)	2.82 (0.647)	2.77 (0.672)
LS Difference (95% CI)		-1.17 (-1.19 to -1.15)	-1.02 (-1.05 to -1.0)
HDL-C			
Rosuvastatin	1.33 (0.397)	1.41 (0.422)	1.43 (0.447)
Placebo	1.33 (0.393)	1.35 (0.403)	1.38 (0.427)
LS Difference (95% CI)		0.12 (0.11 to 0.13)	0.10 (0.09 to 0.12)

Evaluator's comments

Study D3560L00030 JUPITER demonstrates a halving of the risk of MCE in subjects with normal LDL-C and elevated hsCRP value, using a dose of 20 mg daily. The secondary efficacy endpoints supported the findings from the primary efficacy endpoint. The benefit was maintained for up to five years of continuous treatment. The endpoints were clinically relevant and the statistical analysis was appropriate. There was a reduction in MCE of six for every 1000 patient treatment years. This means that treatment of 166 patients for one year would prevent a single patient having a MCE during that year.

The requested indication is determined by the inclusion criteria of the study, that is, specifically subjects with normal LDL-C and elevated hsCRP value. The study population was not selected on the basis of smoking status, hypertension or other cardiovascular risk factors. Hence the subgroup analysis only confirms that the effect is preserved in subjects with normal LDL-C and elevated hsCRP value whether or not the subjects smoked; were hypertensive; were male or female; or had a family history of cardiovascular disease. Hence, the results of the study do not enable the expansion of the indications of rosuvastatin to cardiovascular risk factors other than hsCRP.

Supportive Studies

METEOR

Study D3562C00088 METEOR was a multinational, multicentre, randomized, double-blind, placebo-controlled, parallel group Phase III study, assessing the effects of rosuvastatin 40 mg treatment on the change in the intima media thickness (IMT) of the common carotid artery (CCA), carotid bulb, and internal carotid artery (ICA) (Table 7). It was conducted at 61 centres in 8 countries in the United States and Europe.

Table 7: Details of METEOR Study

Nr. of subjects with age and sex **Duration of Treatment**	**Diagnosis + criteria for inclusion/exclusion**	**Test Product** **Dosage Regimen** **Route of administration** **Formulation** **Reference**	**Criteria for evaluation**	**Results** **(efficacy)**	**Adverse** **Reactions**
5751 subjects were screened,984 were randomised, 702 to rosuvastatin and 282 to placebo age range 45 to 70 years 588 (59.8%) male and 396 (40.2%) female 172 (24.5%) in the rosuvastatin group discontinued, 79 (11.3%) because of AEs 74 (26.2%) in the placebo group discontinued, 22 (7.8%) due to AEs 104 weeks	Men between the ages of ≥45 and ≤70 years or women between the ages of ≥55 and ≤70 years Two or more risk factors and a 10-year Framingham CHD risk <10%: Fasting LDL-C at Visit 1 was ≥3.1 mmol/L and <4.1 mmol/L Patients with age and no other risk factor: Fasting LDL-C at Visit 1 was ≥3.1mmol/L and <4.9 mmol/L TG <5.65 mmol/L at Visit 1 HDL-C levels ≤1.6 mmol/L at Visit 1 Maximum IMT ≥1.2 mm and <3.5 mm at any location in the carotid ultrasound scans conducted at both Visit 2 and Visit 3	Rosuvastatin 40 mg tablets, orally once daily Block randomised by treatment centre Placebo	The primary variable was change from baseline values to end of treatment in maximum carotid intima media thickness (CIMT) over the 12 carotid artery sites. Change in the mean maximum IMT of the near and far walls of the right and left: CCA; carotid bulb; ICA; and CCA Change in LDL-C, TC, HDL-C, TG, non-HDL-C, ApoB, ApoA-I, non-HDL-C/ HDL-C, ApoB/ApoA-I, and CRP	For the primary efficacy outcome measure there was a significant benefit for rosuvastatin: mean difference to placebo (95% CI) was -0.0145 (-0.0196 to -0.0093) mm/year, p<0.0001. For all secondary efficacy outcome measures of IMT, rosuvastatin was superior to placebo. A higher proportion of subjects in the rosuvastatin group had regression of IMT for all 12 carotid sites, the CCA and the carotid bulb, but not for the ICA. Change from baseline in serum lipid parameters was favourable for the rosuvastatin group in comparison with placebo. CRP decreased from baseline in the rosuvastatin group compared with the placebo group. European centres did not have the same benefit for rosuvastatin as the US Subgroup	TEAEs were more common in the rosuvastatin group: 583 (83.3%) subjects compared with 226 (80.4%) in the placebo group. The most commonly reported AEs were: myalgia, nasopharyngitis, arthralgia, influenza and back pain. There was one death in the rosuvastatin group. 63 (9.0%) subjects in the rosuvastatin group and 19 (6.8%) in the placebo group reported SAEs Discontinuation due to AE was more common in the rosuvastatin group: 78 (11.1%) subjects compared with 22 (7.8%) in the placebo group. Elevation in ALT was more common in the rosuvastatin group: 15 (2.2%) subjects compared with two (0.7%) in the placebo group.

The inclusion criteria are summarised in Table 7. The exclusion criteria included:

- Use of pharmacologic lipid-lowering medications (for example, HMG-CoA reductase inhibitors, fibrate derivatives, bile acid binding resins, niacin or its analogues at doses >400 mg) within 12 months
- History of hypersensitivity reactions to other HMG-CoA reductase inhibitors
- Pregnant women, women who were breast-feeding, and women of childbearing potential who were not using chemical or mechanical contraception, or had a positive serum pregnancy test
- Clinical evidence of coronary artery disease (CAD) or any other atherosclerotic disease such as angina, MI, transient ischaemic attack (TIA), symptomatic CAD, cerebrovascular accident (CVA), percutaneous transluminal coronary angioplasty

(PTCA), coronary artery bypass graft (CABG), peripheral arterial disease, abdominal aortic aneurysm (AAA)
- History of malignancy, except in patients who had been disease free for >10 years or whose only malignancy had been basal or squamous cell skin carcinoma
- Women with a history of cervical dysplasia would be excluded unless three consecutive normal cervical smears had subsequently been recorded before entry into the screening period.
- Uncontrolled hypertension defined as either a mean resting diastolic blood pressure (DBP) of ≥100 mm Hg or a resting systolic blood pressure (SBP) of ≥200 mm Hg recorded at any time during the screening period
- History of diabetes mellitus or current diabetes mellitus
- Uncontrolled hypothyroidism defined as a thyroid stimulating hormone (TSH) >1.5 times the upper limit of normal (ULN) at Visit 1 or patients whose thyroid replacement therapy was initiated within the last 3 months
- History of heterozygous or homozygous familial hypercholesterolemia or known hyperlipoproteinemia Types I, III, IV, or V (familial dysbetalipoproteinemia)
- History of alcohol and/or drug abuse within the past 5 years
- Active liver disease or hepatic dysfunction as defined by elevations of ≥1.5 x ULN in alanine aminotransferase (ALT), aspartate aminotransferase (AST) or bilirubin
- Creatine kinase (CK) >3 x ULN
- Serum creatinine >177 mmol/L
- History of a significant medical or psychological condition that, in the opinion of the investigator, would compromise the patient's safety or successful participation in the study

The study treatments were:

1. Rosuvastatin 40 mg tablets,
2. Placebo tablets

Treatments were administered orally once daily.

The primary variable was the change from baseline values to end of treatment in the mean maximum carotid intima media thickness (CIMT) over the 12 carotid artery sites.[2] The secondary efficacy outcome measures were:

- Change in the mean maximum IMT of the near and far walls of the right and left CCA
- Change in the mean maximum IMT of the near and far walls of the right and left carotid bulb
- Change in the mean maximum IMT of the near and far walls of the right and left ICA
- Change in the mean IMT of the near and far walls of the right and left CCA
- Change in LDL-C, TC, HDL-C, TG, non-HDL-C, apolipoprotein B (ApoB), ApoA-I, non-HDL-C/ HDL-C, and ApoB/ApoA-I
- Change in inflammatory marker: CRP

Intimal thickness was measured using ultrasonography. Each patient in the study had an ultrasound scan on seven occasions: twice before randomization; once each at 6, 12, and 18 months; and twice at 24 months after randomization. The safety outcome measures were: vital signs, AEs, clinical laboratory analyses, and electrocardiograms (ECGs).

[2] The 12 carotid artery sites are the near and far walls of the right and left common carotid artery (CCA), the carotid bulb and the internal carotid artery (ICA).

Statistical Analysis Plan for Study D3562C00088: METEOR

Hypothesis tests were performed using a multi-level mixed effects regression model that estimated mean annualized rate of change (mm/year) over the two-year study period for each treatment group.

A total of 840 patients were to be randomized in the ratio 5:2 (rosuvastatin:placebo). It was expected that up to 30% of randomized patients would withdraw from the study before 2 years, leaving as fully evaluable, 415 patients randomized to rosuvastatin and 166 patients randomized to placebo. The sample size was determined using an α of 0.05 for a two-sided hypothesis test, a power of 80%, a decrease in carotid IMT on rosuvastatin of 0.008 mm/year, an increase in the placebo group of 0.012 mm/year, and a SD for both groups of 0.058 mm/year. The treatment effect size was taken from the Asymptomatic Carotid Artery Plaque Study (ACAPS), the Carotid Atherosclerosis Italian Ultrasound Study (CAIUS) and the Atorvastatin Simvastatin Atherosclerosis Progression (ASAP) study.

Results for Study D3562C00088: METEOR

A total of 5751 subjects were screened, of whom 984 were randomised to treatment: 702 to rosuvastatin and 282 to placebo. A total of 172 (24.5%) subjects in the rosuvastatin group discontinued, 79 (11.3%) because of AEs. A total of 74 (26.2%) subjects in the placebo group discontinued, 22 (7.8%) due to AEs. The ITT population comprised those patients who received at least one dose of study medication and had a baseline reading and at least one post-baseline reading for one or more IMT variables. Hence the ITT population included 624 (88.9%) of the randomized subjects in the rosuvastatin group and 252 (89.4%) in the placebo group. The age range of the subjects was 45 to 70 years; 588 (59.8%) were male and 396 (40.2%) were female. The treatment groups were similar in demographic and physical characteristics, baseline CIMT and cardiovascular risk factors. Concomitant medications were taken by 89.2% of the rosuvastatin group and 83.7% of the placebo group. Concomitant medications disallowed by the protocol (including lipid lowering agents) were taken by 67 (10.9%) subjects in the rosuvastatin group and 41 (16.5%) in the placebo group. Tabulations of all concomitant medications were not provided in the submission but concomitant medications would be unlikely to have biased the results.

For all primary and secondary efficacy outcome measures of IMT, rosuvastatin was superior to placebo (Table 8). For the primary efficacy outcome measure the mean difference between rosuvastatin and placebo (95% CI) was minus 0.0145 (-0.0196 to -0.0093) mm/year, $p<0.0001$. For the primary outcome measure, the decrease from baseline in CIMT was not statistically significant (Table 9), but the improvement in comparison with placebo was both clinically and statistically significant. A higher proportion of subjects in the rosuvastatin group had regression of IMT for the mean of all 12 carotid sites, the CCA and the carotid bulb, but not for the ICA. Change from baseline in serum lipid parameters was favourable for the rosuvastatin group in comparison with placebo. CRP decreased from baseline in the rosuvastatin group compared with the placebo group. Subgroup analysis showed that European centres did not have the same benefit for rosuvastatin as the US subgroup. Also there did not seem to be benefit for subjects with higher than average ApoB or TG at baseline. Other than these factors, the subgroup analysis did not suggest any subgroup that would benefit more or less from rosuvastatin.

Table 8: Annualized changes from baseline values to the end of the treatment period (Week 104) in CIMT for the primary and secondary variables (ITT population) – METEOR Study

Annualized change (mm/year)	Rosuva 40 mg (N=624)	Placebo (N=252)	Rousva 40 mg vs placebo (p-value)
Primary variable:			
Maximum CIMT of the 12 carotid artery sites	-0.0014	0.0131	<0.0001
Secondary variables:			
Maximum CIMT of the CCA	-0.0038	0.0084	<0.0001
Maximum CIMT of the carotid bulb	-0.0040	0.0172	<0.0001
Maximum CIMT of the ICA	0.0039	0.0145	0.0228
Mean CIMT of the CCA	0.0004	0.0088	<0.0001

CCA Common carotid artery; CIMT Carotid intima media thickness; ICA Internal carotid artery; ITT Intent-to-Treat; Rosuva Rosuvastatin.

Table 9: Changes from baseline values to the end of the treatment period (Week 104) in maximum CIMT of the 12 carotid artery sites (ITT population) – METEOR Study

Statistical parameter	Rosuvastatin 40 mg (N=624)	Placebo (N=252)
Annualized change (mm/year)	-0.0014	0.0131
Absolute change from time 0 to 2 years (mm)	-0.0028	0.0261
SE of annualized change (mm/year)	0.00140	0.00222
95% CI for annualized change (mm/year)	-0.0041, 0.0014	0.0087, 0.0174

CI Confidence interval; CIMT Carotid intima media thickness; ITT Intent-to-Treat; SE Standard error.

Evaluator's comments

Study D3562C00088 METEOR demonstrates an improvement in CIMT with rosuvastatin 40 mg per day in comparison with placebo. However, METEOR included a different group of patients to JUPITER: LDL-C was higher and elevated hsCRP was not an inclusion criterion. In addition, the dose of rosuvastatin was higher in the METEOR study compared to the JUPITER. The outcome measures were surrogate but were still clinically relevant. The statistical analysis was appropriate.

CORONA

Study D3562C00098 CORONA was a multinational, multicentre, randomised, double blind, placebo controlled, parallel group Phase III study with rosuvastatin in subjects with chronic symptomatic systolic heart failure (Table 10). The study was sponsored by AstraZeneca and conducted at 371 centres in 21 countries in Europe and South Africa.

The study treatments were:

1. Rosuvastatin 10 mg tablets
2. Placebo tablets

Treatments were administered once daily by oral administration. Treatment duration was for up to 3 years. Treatment groups were balanced with respect to age </≥ 75 years, sex, previous MI, diabetes mellitus, hypertension, ejection fraction </≥0.25, New York Heart Association (NYHA) class II/III-IV, beta-blocker use, total cholesterol </≥ 6.0 mmol/L, and prognostic score. Prohibited treatments included statins, gemfibrozil and cyclosporin.

Table 10: Details of CORONA Study

Nr. of subjects with age and sex Duration of Treatment	**Diagnosis + criteria for inclusion/exclusion**	**Test Product Dosage Regimen Route of administration, Formulation Reference**	**Criteria for evaluation**	**Results (efficacy)**	**Adverse Reactions**
9014 subjects were screened, 5459 entered placebo run-in and 5011 patients were randomized: 2514 to rosuvastatin and 2497 to placebo. All randomized patients were analyzed for efficacy and safety. Age range 60 to 102 years, 3831 (76.5%) were male and 1180 (23.5%) were female. Up to 3 years	Age >60 years at date of randomization Chronic symptomatic systolic heart failure of ischemic etiology as judged by the investigator Ejection fraction of: ≤0.40 for a patient in NYHA class III or IV; or ≤0.35 for a patient in NYHA class II within 6 months before enrolment visit 1; or measured between enrolment visit 1 and 2 (not measured earlier than 3 months after an acute myocardial infarction or any invasive intervention such as PTCA or CABG) Optimal therapy for chronic symptomatic systolic heart failure according to the investigator A stable clinical condition during the last two weeks before the randomization visit with no change in symptoms necessitating hospitalization or adjustment of the heart failure medication (eg, ACE inhibitor or beta-blocker dose).	Rosuvastatin 10 mg tablets Once daily oral administration Treatment groups were balanced with respect to age </≥ 75 years, sex, previous MI, diabetes mellitus, hypertension, ejection fraction </≥0.25, NYHA class II/III-IV, beta-blocker use, total cholesterol </≥ 6.0 mmol/L, and prognostic score Placebo tablets	The primary efficacy measure was the time to first event for the combined endpoint of cardiovascular death or nonfatal MI or non-fatal stroke. The secondary efficacy measures were: total mortality; any coronary event; cardiovascular mortality, total number of hospitalizations for cardiovascular causes; time to premature discontinuation of investigational product; change in NYHA classification; Patient-Reported Outcomes questionnaire; change in fasting lipid parameters and hsCRP; newly diagnosed diabetes	Rosuvastatin was not superior to placebo as assessed by the primary efficacy outcome measure. There were 11.4 primary efficacy outcome events per 100 patient years in the rosuvastatin group and 12.3 in the placebo group: HR (95% CI) 0.92 (0.83 to 1.02) p=0.12. There was no difference between the treatment groups for MI and stroke mortality, total mortality, coronary endpoint, cardiovascular death, sudden death, death from worsening heart failure, death from myocardial infarction or newly diagnosed diabetes. There was a lower risk for premature discontinuation in the rosuvastatin group. Serum fasting TC, TG and LDL decreased and HDL increased from baseline, and relative to placebo, in the rosuvastatin group. hsCRP decreased in the rosuvastatin group relative to placebo.	TEAEs were reported by 2155 (85.7%) subjects in the rosuvastatin group and 2162 (86.6%) in the placebo group. The most commonly reported AEs in the rosuvastatin group were: cardiac failure (26.5%), pneumonia (9.2%), atrial fibrillation (7.7%), dizziness (7.8%) and bronchitis (7.3%). Death was reported for 733 (29.2%) subjects in the rosuvastatin group and 774 (31.0%) in the placebo group. 1692 (67.3%) subjects in the rosuvastatin group and 1719 (68.8%) in the placebo group reported SAEs. 204 (8.1%) subjects in the rosuvastatin group and 250 (10.0%) in the placebo group had DAEs. Six patients in the placebo group, had ALT >3xULN on more than one occasion.

The inclusion criteria are summarised in Table 10.

The exclusion criteria included:

- An acute myocardial infarction within 6 months before randomization
- Treatment with any statin or other lipid lowering drug, or a medical condition that in the opinion of the investigator required treatment with a statin or other lipid lowering drug
- History of statin-induced myopathy, or serious hypersensitivity reactions to statins
- Unstable angina pectoris or stroke within 3 months before randomization
- Any of the following concomitant conditions of clinical significance:
    - Uncorrected, primary valvular heart disease
    - Obstructive, hypertrophic cardiomyopathy
    - Malfunctioning artificial heart valve
    - Acute endo- or myocarditis or pericardial disease
    - Systemic disease (for example, uncorrected hyperthyroidism or amyloidosis)
- The following invasive procedures:
    - Planned PTCA, CABG or other angioplasty; planned implantation of implantable cardioverter-defibrillator (ICD) or biventricular pacemaker; or any of these or similar procedures performed within the last 3 months prior to randomization:
    - Previous heart transplant, or heart transplantation planned
    - Previous cardiomyoplasty; or cardiomyoplasty planned
- Unstable decompensated heart failure (for example, pulmonary edema or hypoperfusion) at enrolment or randomisation.
- Acute or chronic liver disease or ALT >2.0 x ULN
- Severe renal disease or serum creatinine above 220 µmol/L
- Chronic muscle disease such as dermatomyositis or polymyositis or unexplained CK above 2.5 x ULN
- Uncontrolled hypothyroidism as indicated by TSH >2 x ULN
- Any other serious disease or condition which might affect life expectancy or make it difficult to successfully manage and follow the patient according to the protocol, such as:
    - Life threatening infectious disease
    - Malignancy
    - Known or suspected alcohol or drug abuse
- Treatment with cyclosporin

The primary efficacy outcome measure was the time to first event for the combined endpoint of cardiovascular death or nonfatal MI or non-fatal stroke. The secondary efficacy outcome measures were:

- Total mortality
- Any coronary event, defined as: sudden death, fatal or non-fatal MI, PTCA, CABG, defibrillation of ventricular fibrillation by ICD, resuscitation from cardiac arrest, or hospitalization for unstable angina
- Cardiovascular mortality with cause specific mortality for sudden death, fatal MI, and death from worsening heart failure
- Total number of hospitalizations for cardiovascular causes, for unstable angina, and for worsening heart failure
- Time to premature discontinuation of investigational product
- Change in NYHA classification between baseline and last available visit
- Patient-Reported Outcomes (PROs) as judged by the McMaster overall treatment evaluation questionnaire (OTE) (in a subset of countries)

- Change in total cholesterol, LDLC, HDL-C, triglycerides, Apo B, Apo A-I, Apo B/Apo A-I ratio from baseline to 3 months after randomization
- Change in hsCRP from baseline to closing visit.
- Time to diagnosis of newly diagnosed diabetes

The safety outcome measures were: AEs, ALT, CK, serum creatinine and TSH.

Statistical Analysis Plan for Study D3562C00098 CORONA

Hypothesis tests were performed for the primary efficacy outcome variable using the Log-rank test plus Cox proportional hazards models (unadjusted). Hypothesis testing for secondary outcome variables used the Log-rank test, Cox proportional hazards models (unadjusted), permutation test, analysis of variance (ANOVA) and the Wilcoxon rank-sum test. The study was designed as a superiority study with no provisions for non-inferiority testing. The ITT population comprised all randomized subjects.

The sample size was determined for the composite primary efficacy endpoint only. For the calculation power was 90%; α was two-sided and 0.05, and these were three adjusted interim analyses before the final analysis; there was an assumption that treatment might have a delay of up to 10 months until a difference in time to event rates was observed between active and placebo; subject accrual would take 16 months and there would be 35 months of continued follow-up (total study time of 51 months). Given these conditions, it was estimated that 4950 subjects were needed to be randomized: 2475 to rosuvastatin and 2475 to placebo.

Results for Study D3562C00098 CORONA

A total of 9014 subjects were screened, 5459 entered placebo run-in and 5011 patients were randomized: 2514 to rosuvastatin and 2497 to placebo. All randomized patients were analyzed for efficacy and safety. The age range was 60 to 102 years; 3831 (76.5%) were male and 1180 (23.5%) were female. The treatment groups were similar in demographic characteristics, physical characteristics, fasting serum lipid parameters, renal function, ischaemic aetiology of cardiac failure, cardiovascular history and heart failure medication at randomisation. More subjects in the placebo group received open treatment with statins during the study. Tabulations of all concomitant medications were not provided in the submission but concomitant medications would be unlikely to have biased the results.

Rosuvastatin was not superior to placebo as assessed by the primary efficacy outcome measure. The primary efficacy outcome measure was recorded for a total of 692 (11.4%) subjects in the rosuvastatin group (11.4 events per 100 patient years) and 732 in the placebo group (12.3 events per 100 patient years of follow-up) HR (95% CI) 0.92 (0.83 to 1.02) p=0.12. There was no difference between the treatment groups for MI and stroke mortality, total mortality, coronary endpoint, cardiovascular death, sudden death, death from worsening heart failure, death from myocardial infarction or newly diagnosed diabetes (Table 11). There was a lower risk for premature discontinuation in the rosuvastatin group (Table 11). Premature discontinuation occurred for 490 (19.5%) subjects in the rosuvastatin group and 546 (21.9%) in the placebo group. Premature discontinuation because of AE occurred in 241 (9.6%) subjects in the rosuvastatin group and 302 (12.1%) in the placebo group. There were significantly fewer hospitalizations in the rosuvastatin group for cardiovascular reasons and for worsening heart failure (Table 12). There was no difference between the groups in change of NYHA classification, p=0.40. Serum fasting cholesterol, triglycerides and LDL decreased and HDL increased from baseline, and relative to placebo, in the rosuvastatin group. There was a significant decrease in hsCRP in the rosuvastatin group relative to placebo. There was no difference between the groups in patient reported outcomes, p=0.64. Subgroup analysis for the

primary efficacy outcome measure indicated benefit for rosuvastatin in the BMI Tertile 2+3, Hypertension Tertile 2+3 and subjects not treated with anticoagulant groups, but these analyses were not adjusted for multiplicity.

Table 11: Efficacy endpoints – METEOR Study

Endpoint	Number of events		HR	95% CI		Log-rank p-value
	Placebo n= 2497	Rosuvastatin n= 2514		Lower	Upper	
Primary endpoint	732	692	0.922	0.831	1.023	0.1237
MI and stroke endpoint	264	227	0.839	0.702	1.002	0.0516
Total mortality	759	728	0.948	0.857	1.050	0.3065
Coronary endpoint	588	554	0.924	0.823	1.038	0.1833
CV death	593	581	0.970	0.865	1.087	0.5976
Sudden death	327	316	0.956	0.819	1.116	0.5707
Death from worsening heart failure	191	193	1.000	0.819	1.221	0.9987
Death from myocardial infarction	9	15	1.652	0.723	3.775	0.2289
Premature discontinuation of IP	546	490	0.876	0.775	0.990	0.0331
Newly diagnosed diabetes	88	100	1.130	0.848	1.505	0.4024

Table 12: Total number of hospitalizations. Comparison of rosuvastatin versus placebo with permutation test – METEOR Study

Hospitalisation	Number of hospitalization		Estimated p-value	99% CI	
	Placebo n= 2497	Rosuvastatin n= 2514		Lower	Upper
Cardiovascular	2564	2193	0.0005	0.0004	0.0005
Unstable angina [a]	90	74	0.3000	0.2988	0.3012
Worsening heart failure	1299	1109	0.0119	0.0116	0.0121

[a] If stated as admission of reason for hospitalization

Evaluator's comments

Study D3562C00098 CORONA did not have sufficient power to detect a difference in 0.9 events per 100 patient years. Hence the study does not provide supportive efficacy data for the indications requested. The study used a lower dose than either JUPITER or METEOR which may have contributed to the negative result. In addition, the subject population was different, in that there was an inclusion requirement of symptomatic heart failure. However, the 10 mg/day dose, although ineffective, does appear to have been well tolerated.

Safety

Safety data from the Pivotal Study

AEs for Study D3560L00030 JUPITER

For ***Study D3560L00030 JUPITER*** a total of 4483 subjects were exposed to rosuvastatin for more than 2 years, of whom 1459 subjects were exposed to rosuvastatin for more than 3 years. The median (range) duration of exposure to rosuvastatin was 657 (0 to 1827)

days. A total of 6968 (78.3%) subjects in the rosuvastatin group and 6907 (77.6%) in the placebo group reported at least one treatment emergent AE (Table 13). The most commonly reported AEs in the rosuvastatin group were urinary tract infection, nasopharyngitis and back pain (Table 14). Back pain and myalgia occurred more frequently in the rosuvastatin group, otherwise the AE profiles of the two groups were similar.

Table 13: Number (%) of subjects who had a treatment-emergent adverse event in any category during the randomized treatment period, ITT population – JUPITER Study

Category of adverse event	Rosuva 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)
Any AE	6968 (78.3)	6907 (77.6)
AE leading to death	141 (1.6)	179 (2.0)
AE leading to discontinuation from the study (DAE)	143 (1.6)	158 (1.8)
Serious AE (SAE)	1341 (15.1)	1372 (15.4)

Table 14: The most common treatment-emergent adverse events (≥1%), summarized by MedDRA preferred term, during the randomized treatment phase, ITT population – JUPITER Study[3]

SYSTEM ORGAN CLASS	MEDDRA PREFERRED TERM	ROSUVA 20 MG N=8,901 N	(%)	PLACEBO N=8,901 N	(%)
	ANY ADVERSE EVENT	6,968	(78.3)	6,907	(77.6)
INFECTIONS AND INFESTATIONS	ANY ADVERSE EVENT	3,873	(43.5)	3,941	(44.3)
	URINARY TRACT INFECTION	772	(8.7)	764	(8.6)
	NASOPHARYNGITIS	679	(7.6)	642	(7.2)
	BRONCHITIS	643	(7.2)	631	(7.1)
	UPPER RESPIRATORY TRACT INFECTION	630	(7.1)	676	(7.6)
	INFLUENZA	357	(4.0)	324	(3.6)
	SINUSITIS	356	(4.0)	332	(3.7)
	LOWER RESPIRATORY TRACT INFECTION	254	(2.9)	244	(2.7)
INFECTIONS AND INFESTATIONS (CONT.)	PNEUMONIA	199	(2.2)	242	(2.7)
	PHARYNGITIS	195	(2.2)	198	(2.2)
	GASTROENTERITIS	165	(1.9)	148	(1.7)
	CYSTITIS	141	(1.6)	170	(1.9)
	HERPES ZOSTER	141	(1.6)	125	(1.4)
	CELLULITIS	125	(1.4)	135	(1.5)
	RHINITIS	125	(1.4)	138	(1.6)
	VIRAL INFECTION	87	(1.0)	87	(1.0)
	RESPIRATORY TRACT INFECTION	78	(0.9)	88	(1.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ANY ADVERSE EVENT	3,293	(37.0)	3,037	(34.1)
	BACK PAIN	679	(7.6)	616	(6.9)
	MYALGIA	678	(7.6)	590	(6.6)
	ARTHRITIS	516	(5.8)	495	(5.6)
	BONE PAIN	449	(5.0)	451	(5.1)
	ARTHRALGIA	341	(3.8)	287	(3.2)
	MUSCLE SPASMS	318	(3.6)	282	(3.2)
	MUSCULOSKELETAL PAIN	281	(3.2)	297	(3.3)
	PAIN IN EXTREMITY	191	(2.1)	183	(2.1)
	OSTEOARTHRITIS	156	(1.8)	124	(1.4)
	BURSITIS	134	(1.5)	116	(1.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (CONT.)	TENDONITIS	121	(1.4)	123	(1.4)
	NECK PAIN	102	(1.1)	87	(1.0)
	OSTEOPOROSIS	91	(1.0)	70	(0.8)
GASTROINTESTINAL DISORDERS	ANY ADVERSE EVENT	2,231	(25.1)	2,209	(24.8)
	DIARRHOEA	417	(4.7)	406	(4.6)
	CONSTIPATION	294	(3.3)	263	(3.0)
	ABDOMINAL PAIN	224	(2.5)	227	(2.6)
	NAUSEA	218	(2.4)	202	(2.3)
	DYSPEPSIA	212	(2.4)	226	(2.5)
	GASTROOESOPHAGEAL REFLUX DISEASE	190	(2.1)	226	(2.5)
	GASTRITIS	137	(1.5)	153	(1.7)
	VOMITING	129	(1.4)	125	(1.4)
	HAEMORRHOIDS	118	(1.3)	118	(1.3)
	ABDOMINAL PAIN UPPER	86	(1.0)	88	(1.0)

[3] MedDRA = Medical Dictionary for Regulatory Activities

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ANY ADVERSE EVENT	1,445	(16.2)	1,429	(16.1)
	COUGH	475	(5.3)	472	(5.3)
	DYSPNOEA	162	(1.8)	189	(2.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS (CONT.)	CHRONIC OBSTRUCTIVE PULMONARY DISEASE	129	(1.4)	140	(1.6)
	ASTHMA	117	(1.3)	122	(1.4)
	PHARYNGOLARYNGEAL PAIN	104	(1.2)	140	(1.6)
	EPISTAXIS	85	(1.0)	74	(0.8)
NERVOUS SYSTEM DISORDERS	ANY ADVERSE EVENT	1,424	(16.0)	1,492	(16.8)
	HEADACHE	338	(3.8)	356	(4.0)
	DIZZINESS	308	(3.5)	352	(4.0)
	SCIATICA	121	(1.4)	125	(1.4)
	PARAESTHESIA	88	(1.0)	102	(1.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ANY ADVERSE EVENT	1,342	(15.1)	1,255	(14.1)
	CONTUSION	151	(1.7)	127	(1.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (CONT.)	MUSCLE STRAIN	96	(1.1)	127	(1.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ANY ADVERSE EVENT	1,238	(13.9)	1,228	(13.8)
	OEDEMA PERIPHERAL	329	(3.7)	263	(3.0)
	FATIGUE	325	(3.7)	311	(3.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS (CONT.)	NON-CARDIAC CHEST PAIN	196	(2.2)	209	(2.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ANY ADVERSE EVENT	1,106	(12.4)	1,145	(12.9)
	RASH	219	(2.5)	222	(2.5)
	ECZEMA	102	(1.1)	111	(1.2)
	PRURITUS	85	(1.0)	94	(1.1)
VASCULAR DISORDERS	ANY ADVERSE EVENT	937	(10.5)	1,095	(12.3)
	HYPERTENSION	624	(7.0)	695	(7.8)
INVESTIGATIONS	ANY ADVERSE EVENT	865	(9.7)	810	(9.1)
	ALANINE AMINOTRANSFERASE INCREASED	122	(1.4)	91	(1.0)
	BLOOD GLUCOSE INCREASED	90	(1.0)	64	(0.7)
RENAL AND URINARY DISORDERS	ANY ADVERSE EVENT	812	(9.1)	817	(9.2)
	HAEMATURIA	216	(2.4)	181	(2.0)
	PROTEINURIA	127	(1.4)	113	(1.3)
METABOLISM AND NUTRITION DISORDERS	ANY ADVERSE EVENT	684	(7.7)	752	(8.4)
	DIABETES MELLITUS	267	(3.0)	222	(2.5)
	GOUT	106	(1.2)	137	(1.5)
EYE DISORDERS	ANY ADVERSE EVENT	631	(7.1)	665	(7.5)
	CATARACT	180	(2.0)	196	(2.2)
	CONJUNCTIVITIS	106	(1.2)	122	(1.4)
PSYCHIATRIC DISORDERS	ANY ADVERSE EVENT	625	(7.0)	646	(7.3)
	INSOMNIA	226	(2.5)	208	(2.3)
	DEPRESSION	184	(2.1)	214	(2.4)
	ANXIETY	128	(1.4)	157	(1.8)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	ANY ADVERSE EVENT	608	(6.8)	676	(7.6)
	BASAL CELL CARCINOMA	92	(1.0)	78	(0.9)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	ANY ADVERSE EVENT	551	(6.2)	602	(6.8)
	BENIGN PROSTATIC HYPERPLASIA	141	(1.6)	158	(1.8)
	ERECTILE DYSFUNCTION	111	(1.2)	134	(1.5)
CARDIAC DISORDERS	ANY ADVERSE EVENT	543	(6.1)	636	(7.1)
	ATRIAL FIBRILLATION	145	(1.6)	171	(1.9)
	PALPITATIONS	88	(1.0)	84	(0.9)
EAR AND LABYRINTH DISORDERS	ANY ADVERSE EVENT	438	(4.9)	452	(5.1)
	VERTIGO	136	(1.5)	150	(1.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANY ADVERSE EVENT	295	(3.3)	292	(3.3)
	ANAEMIA	192	(2.2)	183	(2.1)
HEPATOBILIARY DISORDERS	ANY ADVERSE EVENT	189	(2.1)	187	(2.1)
	CHOLELITHIASIS	89	(1.0)	83	(0.9)

Deaths, SAEs and Discontinuation Adverse Events (DAEs) for Study D3560L00030 JUPITER

AEs leading to non-cardiovascular death occurred in 141 (1.6%) subjects in the rosuvastatin group and 179 (2.0%) in the placebo group. During the randomized phase cardiovascular deaths were not included in the tally of AEs leading to death, since they were reported as primary endpoint events. Neoplasia was the most frequent grouping of AEs leading to death. A total of 1,341 (15.1%) subjects in the rosuvastatin group and

1,372 (15.4%) in the placebo group reported at least one treatment emergent serious adverse event (SAE). No single SAE preferred term was reported by more than 1% of subjects in either group. The System Organ Class (SOC) most commonly reported with treatment emergent SAEs was *Neoplasms Benign, Malignant, and Unspecified (includes cysts and polyps)*. There were 286 (3.2%) subjects in the rosuvastatin group and 306 (3.4%) in the placebo group with neoplasm reported as a SAE, with no clear preponderance of neoplasm subtype in the rosuvastatin group. Musculoskeletal, gastrointestinal and psychiatric disorders reported as SAEs were more common in the rosuvastatin group. Discontinuation due to AE (DAEs) occurred in 143 (1.6%) subjects in the rosuvastatin group and 158 (1.8%) in the placebo group. No single AE preferred term leading to discontinuation was reported by more than 1% of subjects in either group.

AEs of special interest for Study D3560L00030 JUPITER

Hepatic AEs were slightly more common in the rosuvastatin group, primarily due to more subjects having elevations in ALT (127 [1.4%] versus 93 [1.0%]). Muscle related AEs occurred in 1421 (16.0%) subjects in the rosuvastatin group and 1375 (15.4%) in the placebo group. Rhabdomyolysis was reported for one subject in the rosuvastatin group. Renal related AEs were reported in 535 (6.0%) subjects in the rosuvastatin group and 480 (5.4%) in the placebo group. The greater incidence of renal AEs in the rosuvastatin group is primarily influenced by haematuria: 241 (2.7%) subjects compared with 203 (2.3%) in the placebo group; and proteinuria: 149 (1.7%) subjects compared with 127 (1.4%) in the placebo group.

Investigator-reported diabetes mellitus occurred more frequently in the rosuvastatin group, 251 (2.8%) subjects compared with placebo, 205 (2.3%). Fasting blood glucose concentrations were similar for the two groups, but there was a greater increase in mean glycosylated haemoglobin (HbA1c) from baseline in the rosuvastatin group. Although this increase was statistically significant it is unlikely to be clinically significant.

Confusional state was reported more commonly in the rosuvastatin group (17 [0.2%] versus four [0.0%] subjects). Cognition-related AEs, including dementia, cognitive disorder, confusional state, and personality change, were reported in 34 (0.4%) subjects in the rosuvastatin group and 27 (0.3%) in the placebo group.

Laboratory AEs for Study D3560L00030 JUPITER

ALT >3 x ULN was reported in 124 (1.45%) subjects in the rosuvastatin group and 87 (1.0%) in the placebo group. CK >10 x ULN was reported in two subjects in the rosuvastatin group and one in the placebo group. Creatinine >100% above baseline was reported in ten subjects in the rosuvastatin group and six in the placebo group. There were no significant differences between the groups in haematology parameters. There were no significant differences between the treatment groups in urinalysis findings.

Safety data from Supportive Studies

METEOR

AEs for Study D3562C00088: METEOR

For Study D3562C00088: METEOR, 409 subjects were exposed to rosuvastatin for more than 2 years. The mean (range) duration of exposure to rosuvastatin was 622 (2 to 792) days. Treatment emergent AEs were slightly more common in the rosuvastatin group: 583 (83.3%) subjects compared with 226 (80.4%) in the placebo group (Table 15). However, on perusal of individual AEs there is no obvious explanation for the increase. The most commonly reported AEs were myalgia (12.7% subjects in the rosuvastatin group; 12.1%

in the placebo group), nasopharyngitis (11.6%; 10.7%); arthralgia (10.1%; 7.1%); influenza (9.4%; 10.3%) and back pain (8.4%; 10.3%).

Table 15: Number (%) of patients who had an adverse event in any category (Randomized safety population) – METEOR Study

	Rosuvastatin 40 mg (N=700)		Placebo (N=281)	
Category of adverse event	**N (%)**		**N (%)**	
Any adverse event	583	83.3	226	80.4
AEs leading to death	1	0.1	0	
AEs leading to study discontinuation	78	11.1	22	7.8
Serious AEs	64	9.1	19	6.8
Treatment-related AEs	140	20.0	48	17.1
Treatment-related AEs leading to death	0		0	
Treatment-related AEs leading to study discontinuation	49	7.0	9	3.2
Treatment-related serious AEs	1	0.1	4	1.4

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
AEs Adverse events.

Deaths, SAEs and DAEs for Study D3562C00088: METEOR

There was one death during the study. The subject was in the rosuvastatin group and died from dementia (stated to be Creutzfeldt-Jacob disease) 207 days after starting treatment, and 60 days after the last dose. More SAEs were reported in the rosuvastatin group (63 [9.0%] subjects compared with 19 [6.8%] in the placebo group). Ironically, there was a higher rate of cardiac disorders reported as SAEs in the rosuvastatin group (8 [1.1%] subjects compared with none in the placebo group). DAEs was also more common in the rosuvastatin group (78 [11.1%] subjects compared with 22 [7.8%] in the placebo group). Gastrointestinal AEs, elevated liver enzymes, myalgia and headache accounted for the excess in DAEs in the rosuvastatin group.

Laboratory AEs for Study D3562C00088: METEOR

Elevation in ALT was more common in the rosuvastatin group (15 [2.2%] subjects compared with two [0.7%] in the placebo group). One subject in the placebo group had cholecystitis with a clinically significant elevation of ALT. Significant elevations in CK (>5 x ULN) were more common in the rosuvastatin group (eight [1.2%] subjects compared with two [0.7%] in the placebo group). One subject in the rosuvastatin group had exercise induced muscle pain with elevation in CK >10 x ULN. No subject had a significant elevation in serum creatinine. There were no clinically significant changes in haematology parameters, vital signs or ECGs.

CORONA

AEs for Study D3562C00098 CORONA

For Study D3562C00098 CORONA, 2209 subjects were exposed to rosuvastatin for 1 year, of whom 1932 were exposed for 2 years and 856 for 3 years. Treatment emergent AEs were reported by 2155 (85.7%) subjects in the rosuvastatin group and 2162 (86.6%) in the placebo group (Table 16). There were no individual AEs that were clearly more

common in the rosuvastatin group. The most commonly reported AEs in the rosuvastatin group were: cardiac failure (26.5%), pneumonia (9.2%), atrial fibrillation (7.7%), dizziness (7.8%) and bronchitis (7.3%). There was no excess of muscle related AEs in the rosuvastatin group. Renal related AEs were reported in 241 (9.6%) subjects in the rosuvastatin group and 236 (9.5%) in the placebo group. Hepatic related AEs were slightly more common in the rosuvastatin group because of a higher frequency of elevations in ALT (14 [0.6%] in the rosuvastatin group compared with 4 [0.2%] in the placebo group).

Table 16: Number (%) of patients who had at least one AE in any category, with AE start date after randomization – CORONA Study

AE category	Number (%) of patients	
	Placebo n= 2497	Rosuvastatin n= 2514
Any AE	2162 (86.6)	2155 (85.7)
Any SAE	1719 (68.8)	1692 (67.3)
Any AE leading to death	774 (31.0)	733 (29.2)
Any AE leading to permanent discontinuation of IP	250 (10.0)	204 (8.1)
Any AE leading to temporary discontinuation of IP	364 (14.6)	348 (13.8)

Deaths, SAEs and DAEs for Study D3562C00098 CORONA

Death was reported for 733 (29.2%) subjects in the rosuvastatin group and 774 (31.0%) in the placebo group. There were no clear differences between the treatments groups in the causes of death and cardiac failure was the most common cause of death in both groups. A total of 1692 (67.3%) subjects in the rosuvastatin group and 1719 (68.8%) in the placebo group were reported with SAEs. There was no difference between the treatment groups in the pattern of SAEs. A total of 204 (8.1%) subjects in the rosuvastatin group and 250 (10.0%) in the placebo group were reported with an AE leading to permanent discontinuation of study treatment. Other than hepatobiliary disorders and skin disorders there was no clear preponderance of any AE leading to discontinuation in the rosuvastatin group.

Laboratory AEs for Study D3562C00098 CORONA

One subject in each treatment group had a CK reported as being >10 x ULN. Six patients in the placebo group, and four in the rosuvastatin group had ALT >3 x ULN on more than one occasion. More subjects in the rosuvastatin group had ALT concentrations above the reference range at each on treatment visit. Serum concentrations of coenzyme Q10 decreased by 40% in the rosuvastatin group during the study. There was no difference between the treatment groups in changes in estimated glomerular filtration rate ($eGFR_{MDRD}$) or serum creatinine.

Evaluator's comments

Although **Study D3560L00030 JUPITER** demonstrates that rosuvastatin is overall well tolerated, there was a slightly higher rate of hepatic AEs, renal AEs and confusional state reported in the rosuvastatin group.

Study D3562C00088 METEOR had a slightly higher rate of AEs reported in the rosuvastatin group. There was a higher rate of discontinuation due to AEs. Significant elevation in ALT occurred in 2.2% subjects treated with rosuvastatin. Myalgia and elevated CK were more common in the rosuvastatin group. These higher rates of hepatic and muscle related AEs may have been due to the 40 mg per day dose.

For **Study D3562C00098 CORONA**, although rosuvastatin had a similar AE profile to placebo, there was a higher rate of elevated ALT in the rosuvastatin group.

Post-marketing data

A PSUR was provided covering the time period 7 November 2007 to 6 November 2008.

A medical review of amyotrophic lateral sclerosis, micturition disorders, myasthenia gravis, peripheral neuropathy, severe cutaneous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, tendon rupture/rotator cuff syndrome and thrombocytopenia did not demonstrate reasonable evidence of a causal relationship between rosuvastatin and the reported events. A medical review of memory loss, other muscle events (excluding rhabdomyolysis), pancreatitis, and proteinuria, all listed events in the Crestor Core Company Datasheet (CCDS), did not identify any new safety issues.[4]

The cumulative global spontaneous reporting rate for rhabdomyolysis was <0.01%. In pharmacoepidemiological studies, rosuvastatin had a slightly higher rate of rhabdomyolysis than other marketed strains of statins: 0.82 (95% CI: 0.26 to 2.59) compared to 0.14 (95% CI: 0.05 to 0.37) per 10000 patient-years. The reporting rate for rhabdomyolysis increased with dose, and was highest at the 40 mg dose level.

Evaluator's comments

The PSUR contributed useful information about the risks for rhabdomyolysis. No additional safety issues were identified by the PSUR.

The sponsor noted that the product information (see Appendix) which results from the evaluation of all the raw data remains the best means for communicating to prescribers the findings from PSURs.

Clinical Summary and Conclusions

The data presented in the current submission supported treatment of men aged 50 years and over; and women aged 60 years and over, with normal LDL-C and elevated hsCRP, with rosuvastatin 20 mg daily. **JUPITER** demonstrates a halving of the risk of MCE in subjects with normal LDL-C and elevated hsCRP value, using a dose of 20 mg daily. The secondary efficacy endpoints supported the findings from the primary efficacy endpoint. The benefit was maintained for up to five years of continuous treatment. The endpoints were clinically relevant and the statistical analysis was appropriate. There was a reduction in MCE of six for every 1000 patient treatment years. This means that treatment of 166 patients for one year would prevent one of those patients having a MCE during that year.

CRP is an acute phase reactant and is used as a marker for inflammation. CRP is in common use for this purpose both in primary and secondary care. High sensitivity CRP (hsCRP) is a measure of CRP at lower levels, and measures CRP down to 0.04 mg/L. CRP is usually less than 10 mg/L in normal individuals in the absence of inflammation. CRP at concentrations above 3.0 mg/L has been reported to have a relative risk (95% CI) for incident coronary heart disease of 1.58 (1.37 to 1.83) compared to levels below 1.0 mg/L.[5] However, although hsCRP is available through pathology providers in Australia, it is not routinely performed and is not currently recommended as part of cardiovascular risk assessment by the National Vascular Disease Prevention Alliance. Currently, there is no guidance as to how hsCRP should be applied. The approval of the present application might lead to widespread application of hsCRP as a screening test without regard to current guidelines.

[4] A Company Core Data Sheet (CCDS) is a company-internal global reference labelling document used to direct the content of local (affiliate) labelling.

[5] Buckley D, Fu R, Freeman M, Rogers K, Helfland M. C-Reactive Protein as a Risk Factor for Coronary Heart Disease: A Systematic Review and Meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med 2009; 151: 483-495.

METEOR demonstrates an improvement in CIMT with rosuvastatin 40 mg per day in comparison with placebo. However, METEOR included a different group of patients to JUPITER: LDL-C was higher and elevated hsCRP was not an inclusion criterion. In addition, the dose of rosuvastatin was higher in the METEOR study compared to the JUPITER. The statistical analysis was appropriate. The outcome measures were surrogate, but were still clinically relevant. However the outcome measure is not the same as MCE. Hence the study is supportive, but not pivotal.

CORONA did not have sufficient power to detect a difference in 0.9 events per 100 patient years. Hence the study does not provide supportive efficacy data for the indications requested. The study used a lower dose than either JUPITER or METEOR, which may have contributed to the negative result. In addition, the subject population was different, in that there was an inclusion requirement of symptomatic heart failure. However, the 10 mg/day dose although ineffective, does appear to have been well tolerated.

With regard to the safety data, safety for the requested change in indication has only been demonstrated for 20 mg dose and not for the 40 mg dose. Although **JUPITER** demonstrates that rosuvastatin is overall well tolerated, there was a slightly higher rate of hepatic AEs, renal AEs and confusional state reported in the rosuvastatin group.

METEOR had a slightly higher rate of AEs reported in the rosuvastatin group. There was a higher rate of discontinuation due to AEs. Significant elevation in ALT occurred in 2.2% subjects treated with rosuvastatin. Myalgia and elevated CK were more common in the rosuvastatin group. These higher rates of hepatic and muscle related AEs may have been due to the 40 mg per day dose.

For **CORONA**, although rosuvastatin had a similar AE profile to placebo, there was a higher rate of elevated ALT in the rosuvastatin group.

The PSUR covering the time period 7 November 2007 to 6 November 2008 indicated that serious adverse reactions with rosuvastatin were rare. No previously unreported associations of AEs with rosuvastatin were reported. However, the report indicates that the reporting rate for muscle related AEs increases with dose and is highest at the 40 mg/day dose level.

The rewording of the currently approved indications is not acceptable because not all of the indications sought are supported by the data presented in the submission. With regard to the indications: age, hypertension, low HDL-C, smoking or a family history of premature heart disease were not indications for inclusion in ***JUPITER.*** Hence these treatment indications are not supported by the data in the present submission. Although an effect may be maintained in these subgroups, it is quite a different issue as to whether they should be used as indications for treatment. The requested indication is determined by the inclusion criteria of the study, that is, specifically subjects with normal LDL-C and elevated hsCRP value. The study population was not selected on the basis of smoking status, hypertension or other cardiovascular risk factors. Hence the subgroup analysis only confirms that the effect is preserved in men aged 50 years and over; or women aged 60 years and over, and with normal LDL-C and elevated hsCRP value whether or not subjects smoked; were hypertensive; were male or female; or had a family history of cardiovascular disease. Hence, the results of the study do not enable the expansion of the indications of rosuvastatin to cardiovascular risk factors other than hsCRP. Subjects who had normal hsCRP values and/or were aged less than 50 years, but who smoked, were hypertensive or had a family history of cardiovascular disease were <u>not</u> included in the study.

Deficiencies in the Submission

There were no data demonstrating a decrease in the rate of MCE on the basis of age, hypertension, low HDL-C, smoking or a family history of premature heart disease in subjects who were aged less than 50 years and/or who had a normal hsCRP. Subgroup analysis was performed on the data from the JUPITER study indicating that treatment effect was preserved in subjects with elevated hsCRP when analysed by the subgroups of: age, hypertension, low HDL-C, smoking or a family history of premature heart disease. However, this does not equate with efficacy for the indications of: age group, hypertension, low HDL-C, smoking or a family history of premature heart disease; since patients with these risk factors were not part of the inclusion criteria.

Recommendations

Crestor should be approved for the following amended indications:

Crestor should be used as an adjunct to diet when the response to diet and exercise is inadequate

Prevention of Cardiovascular Events

Crestor 20 mg daily is indicated to reduce the risk of major cardiovascular events in men aged 50 years and over; and women aged 60 years and over, at increased risk of cardiovascular disease due to the presence of elevated hsCRP level (See Clinical Trials, Prevention of Cardiovascular Events).

In adult patients with hypercholesterolaemia

Crestor is indicated for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia)

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

LDL-C does not need to be stated in the indications as hypercholesterolaemia is already an indication for treatment, and a low LDL-C is therefore not a requirement for treatment on the basis of elevated hsCRP. Patients with normal or elevated LDL-C would all be indicated for treatment in the presence of elevated hsCRP. Although the subgroup analysis indicated that there may be lesser efficacy in the subgroup of patients with the combination of lower than median LDL-C and higher than median hsCRP, the subgroup analysis does not carry sufficient weight to justify amending the indications.

The Advisory Committee on Prescription Medicines (ACPM) should also consider the effect of the decision upon the potential widespread application of hsCRP as a screening test. Approval of the application might lead to widespread use of hsCRP as a screening tool for cardiovascular risk in contradiction to current cardiovascular risk assessment guidelines.

V. Pharmacovigilance Findings

Risk Management Plan

As required by the TGA, the sponsor submitted a Risk Management Plan (RMP) which identified the following safety concerns (Table 17):

Table 17: Safety concerns for Crestor

Safety concern	
Important identified risks	**Skeletal muscle effects:** rhabdomyolysis, myopathy, myositis, myalgia, Creatine kinase increases, myoglobinaemia, and myoglobinuria **Hepatic effects**: increased transaminases, hepatitis, jaundice **Pancreatitis** **Memory Loss** **Urinary events**: proteinuria **Asian population**: increased plasma exposure **Stevens-Johnson syndrome/ Toxic epidermal necrolysis** **Drug interactions** :drug-drug interactions including: gemfibrozil, ciclosporin, warfarin, other coumarin derivatives, and lopinavir/ritonavir

Safety concern	
Important potential risks	**Renal effects:** renal failure (including acute and chronic renal failure) and renal impairment **Hepatic failure**: includes hepatic necrosis and fulminant hepatitis **Tendon rupture and Rotator cuff syndrome** **Micturition disorders** **Thrombocytopenia** **Myasthenia gravis** **Depression** **Peripheral neuropathy** **Sleep disturbances** **Amyotrophic lateral sclerosis** **Drug interactions**: drug-drug interaction with ezetimibe and fibrates (other than gemfibrozil)
Special patient populations	**Severe hepatic impairment** **Elderly subjects** **Severe renal impairment** **Pregnancy and lactation** **Paediatric subjects**

The sponsor proposed enhanced pharmacovigilance activities for the safety concerns of skeletal muscle adverse events, renal impairment and hepatic impairment.[6] Routine risk minimisation activities were proposed for the following: pancreatitis, memory loss, drug interactions, proteinuria, use in an Asian population, Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), hepatic failure, tendon rupture and rotator cuff syndrome, use in individuals who are pregnant and lactating and use in special populations (paediatric, severe renal impairment, severe hepatic impairment and elderly).[7] An assessment of the requirement to provide a Risk Minimisation Plan concluded that additional risk minimisation activities were required for the safety concerns of skeletal muscle adverse events, renal impairment and hepatic impairment. Risk minimisation activities were not proposed for the following potential risks: thrombocytopenia, micturition disorders, myasthenia gravis, depression, peripheral neuropathy, sleep disturbances and amyotrophic lateral sclerosis (ALS). The justification for not including these potential risks in the PI/Consumer Medicines Information (CMI) is that there is insufficient evidence to establish causality. The proposed additional risk minimisation activities included a number of different education and promotional activities with the objective of maintaining compliance with the prescribing and safety information in the PI.

Following a review by the TGA's Office of Medicines Safety Monitoring (OMSM) (now the Office of Product Review [OPR]), the RMP was considered acceptable. There were five issues noted in the assessment report of the RMP .

1. With regard to the potential interaction of rosuvastatin with ezetimibe and fibrates not in the PI, the sponsor argued that this issue was adequately covered in the PI. The OMSM accepted the argument.
2. The OMSM noted that the sponsor agreed to a change all instances in the PI of coumarin anticoagulants to vitamin K antagonists.
3. The sponsor clarified why some potential risks were included as adverse events in the PI (routine risk minimisation) and some were not. The OMSM accepted the sponsor's explanation which was based on the level of evidence of a causal association.
4. The classification of SJS/TEN as an identified risk was imposed on the European RMP by the EU. The sponsor proposed to include it as a potential risk in the Australian RMP and this was accepted by the OMSM.
5. The OMSM noted that the reporting of the AURORA and PLANET studies would be included in the next version of the RMP.

[6] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[7] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no new quality data submitted.

Nonclinical

There were no new nonclinical data submitted.

Clinical

Evaluator's recommendation

The clinical data relies on one pivotal study (JUPITER) in 17,802 patients of whom 8901 received 20 mg daily of rosuvastatin for an average of 700 days. Two supportive studies were also submitted (METEOR, CORONA). The clinical evaluator recommended approval for a modified indication in the evaluation report as follows:

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

Prevention of Cardiovascular Events

Crestor 20 mg daily is indicated to reduce the risk of major cardiovascular events in men aged 50 years and over; and women aged 60 years and over, at increased risk of cardiovascular disease due to the presence of elevated hsCRP level (See Clinical Trials, Prevention of Cardiovascular Events).

In adult patients with hypercholesterolaemia

Crestor is indicated for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia).

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

The issues noted by the evaluator in this submission included:

- A lack of data demonstrating a decrease in the rate of Major Cardiovascular Events (MCE) on the basis of age, hypertension, low HDL-C, smoking or a family history of premature heart disease in subjects who were less than 50 years old or who had a normal hsCRP.
- Although treatment effect of rosuvastatin was preserved in subjects with elevated hsCRP and a cardiovascular risk factor, this did not equate with efficacy in these subgroups alone for the indication as these groups were not specific inclusion criteria.
- Subjects with normal hsCRP were not included in the study.
- The use of hsCRP testing as a screening tool.

Efficacy

JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin): This pivotal study was a multicentre, randomised double blind, placebo controlled, parallel group study of 20 mg daily of rosuvastatin vs placebo for the

primary prevention of major cardiovascular events in 17,802 patients for up to 5 years with "normal" cholesterol, elevated hsCRP levels and no prior history of cardiovascular or cerebrovascular events.

The primary efficacy endpoint of time to first occurrence of a major cardiovascular event (CV death, stroke, MI, unstable angina or arterial revascularisation) was statistically significantly reduced on rosuvastatin with a relative risk reduction of 44% (HR 0.56, 95%CI 0.46, 0.69) and an absolute risk reduction of 1.2%. There were 142 events (1.6%) on rosuvastatin vs 252 events (2.8%) on placebo and the effect was maintained for up to 5 years (although a significant loss of patients). The individual components of the primary endpoint were all less on rosuvastatin than placebo but only significantly for nonfatal stroke, nonfatal myocardial infarction and arterial revascularisation and not significantly for cardiovascular death or hospitalisation for unstable angina. The risk reduction for the primary endpoint was also maintained across predefined subgroups of age, sex, race, body mass index, smoking status, hypertension, HDL-C, LDL-C, triglyceride and hsCRP levels. The risk reduction was also seen across the risk stratification categories based on the Framingham criteria and the Systematic Coronary Risk Evaluation (SCORE). Secondary efficacy endpoints were supportive with reductions in all cause mortality (2.2 vs 2.8%), CV death/MI/stroke (0.9 vs 1.8%), fatal or nonfatal MI (0.3 vs 0.8%) and fatal or nonfatal stroke (0.4 vs 0.7%), however diabetes mellitus was higher on rosuvastatin (2.8 vs 2.3%). During the study, hsCRP, total cholesterol, LDL-C and TG decreased on rosuvastatin and HDL-C increased on rosuvastatin from baseline and compared to placebo. At 12 months, comparing rosuvastatin with placebo, hsCRP was 2.20 vs 3.50 mg/L, LDL-C was 1.59 mmol/L vs 2.82 mmol/L and HDL-C was 1.41 vs 1.34 mmol/L. The reductions in LDL-C and hsCRP were maintained across subgroups of sex, age, hypertension and smoking status. At 12 months, hsCRP decreased 47% on rosuvastatin and decreased 20% on placebo compared to baseline.

METEOR: This was a multicentre, randomised, double blind, placebo controlled, parallel group study in 984 patients on 40 mg rosuvastatin daily vs placebo to assess the change in intima media thickness of the common carotid artery, carotid bulb and internal carotid artery. The primary efficacy endpoint which was the change in carotid intima media thickness demonstrated an improvement in CIMT with rosuvastatin. This study has been previously evaluated by the TGA and is included in the PI. This trial included a different groups of patients compared to JUPITER, used a surrogate endpoint, did not have elevated hsCRP as an inclusion criterion and used a higher dose of rosuvastatin than in JUPITER.

CORONA: This was a multicentre, randomised, double blind, placebo controlled, parallel group study of 10 mg rosuvastatin daily vs placebo in 5011 patients with chronic symptomatic systolic heart failure. The primary efficacy endpoint which was time to first event for the combined endpoint of cardiovascular death or non-fatal myocardial infarction or non-fatal stroke was not significantly different between rosuvastatin and placebo. This study used a different population to JUPITER, used a lower dose of rosuvastatin, had an inclusion criterion of heart failure and did not establish efficacy in this setting.

Safety

JUPITER: The median exposure to rosuvastatin was 657 days, with 4483 exposed for 2 years and 1459 exposed for more than 3 years. Treatment emergent adverse events were reported by 78% of subjects with similar rates to placebo with the most common being urinary tract infection, nasopharyngitis, back pain and myalgia with the latter two being more common on rosuvastatin (back pain 7.6 vs 6.9% and myalgia 7.6 vs 6.6%). Mortality was less on rosuvastatin, including total (2.2 vs 2.8%), cardiovascular (0.4 vs 0.5%) and non-cardiovascular (1.6 vs 2.0%) of which neoplasia was the most common cause. Serious

adverse events were similar to placebo (15.1 vs 15.4%) with the most common being neoplasia (3.2 vs 3.4%) of no clear type. Discontinuations due to adverse events were less common on rosuvastatin than placebo (1.6 vs 1.8%). Hepatic adverse events were slightly higher on rosuvastatin (2.4 vs 2.1%) which was driven by ALT increases (1.4 vs 1.0%). ALT>3 x ULN was 1.45% on rosuvastatin vs 1% on placebo. Muscle related adverse events were slightly higher on rosuvastatin (16 vs 15.4%) and renal adverse events were also slightly higher (6 vs 5.4%), driven mainly by haematuria (2.7 vs 2.3%) and proteinuria (1.7 vs 1.4%). One case of rhabdomyolysis was reported on rosuvastatin. CK>10 x ULN was seen in 2 rosuvastatin patients vs one placebo patient. Creatinine >100% above baseline was seen in 10 vs 6 patients. Diabetes mellitus was higher on rosuvastatin (2.8 vs 2.3%) with similar fasting blood glucose but greater increases in HbA1c on rosuvastatin (+0.30 vs +0.22) from baseline to final visit.

METEOR showed slightly higher adverse events on rosuvastatin compared to placebo (for example, myalgia (12.7 vs 12.1%), nasopharyngitis, arthralgia, influenza and back pain). One death was reported on rosuvastatin. Serious adverse events were higher (9 vs 6.8%, including cardiac (1.1 vs 0%)) and discontinuations due to adverse events (11.1 vs 7.8%, mainly GI, liver enzymes, myalgia and headache). ALT elevations were higher (2.2 vs 0.7%), CK>5 x ULN (1.2 vs 0.7%). **CORONA** showed similar adverse event profiles to placebo, including muscle and renal events but ALT elevations were greater (0.6 vs 0.2%). Deaths (29.2 vs 31%) showed cardiac failure as the most common cause. A PSUR reported rhabdomyolysis of <0.01% but higher on rosuvastatin than other statins, which increased with dose.

Risk Management Plan (RMP)

The Office of Medicines Safety Monitoring (OMSM) found the RMP submitted by the sponsor acceptable, including the sponsor's responses to the report. The following RMP activities were noted for rosuvastatin:

- Routine risk minimisation activities: pancreatitis, memory loss, drug interactions, proteinuria, use in an Asian population, SJS/TEN, hepatic failure, tendon rupture and rotator cuff syndrome, use in individuals who are pregnant and lactating and use in special populations (paediatric, severe renal impairment, severe hepatic impairment and elderly).
- Enhanced pharmacovigilance activities and additional risk minimisation activities: skeletal muscle adverse events, renal impairment and hepatic impairment.
- Risk minimisation activities were not proposed for: thrombocytopenia, micturition disorders, myasthenia gravis, depression, peripheral neuropathy, sleep disturbances and ALS. The justification for not including these in the PI/CMI was accepted; however there are a number of educational and promotional activities proposed to maintain compliance with the information in the PI.

There were five issues noted in the report which were responded to by the sponsor and accepted by OMSM: the potential interaction being rosuvastatin with ezetimibe and fibrates not in the PI (already covered in the PI), monitoring of INR for patients on Vitamin K antagonists (PI change needed), inclusion of some adverse events (clarified), classifying SJS/TEN as an important potential risk and the reporting of the AURORA and PLANET studies (in the next version).

Initial Risk-Benefit Analysis

Delegate Considerations

Efficacy

The JUPITER study demonstrated the efficacy of a 20 mg daily dose of rosuvastatin in reducing the relative risk of a major cardiovascular event by 44% in patients with elevated hsCRP, "normal" cholesterol and age ≥50 years for males or ≥60 years for females. This benefit was seen to 5 years, but the study was stopped early at a median follow-up of 1.9 years due to the demonstrated efficacy, therefore there were minimal patients in later years. JUPITER patients had no prior history of cardiovascular or cerebrovascular events, however all patients had age as a risk factor and 76% of them had at least one other risk factor (smoking, hypertension, low HDL or family history of CHD). The benefit was seen within the individual components of the primary endpoint with 3 of the 5 components showing a significant reduction (nonfatal stroke, nonfatal myocardial infarction and arterial revascularisation) and within the subgroups of age, sex, race, body mass index, smoking status, hypertension, HDL-C, LDL-C, triglyceride, hsCRP levels and risk stratification categories based on the Framingham criteria and SCORE. Secondary endpoints were supportive, including all cause mortality which was less on rosuvastatin. During the study, LDL-C and hsCRP both decreased on rosuvastatin and these reductions were maintained across risk factor subgroups. The supportive studies were not directly relevant.

Safety

Rosuvastatin was well tolerated in the JUPITER trial, with similar rates of adverse events, serious adverse events and discontinuations due to adverse events as placebo. Hepatic adverse events, muscle related adverse events and renal adverse events were slightly higher on rosuvastatin and diabetes mellitus was reported as higher on rosuvastatin (similar fasting blood glucose but greater increases in HbA1c on rosuvastatin), the mechanism being unclear. Given the median follow-up was 1.9 years, the longer term safety is unclear in this population, but 1459 were exposed for more than 3 years. An acceptable RMP has been provided, including the responses to it by the sponsor. The RMP of 12 November 2009, including the responses of 30 November 2009, will be a condition of registration.

Data Deficiencies

The early termination of the study at a median follow-up of 1.9 years leaves some doubt as to the longer term efficacy and safety of rosuvastatin in this relatively healthy population, including the effects of further lowering of cholesterol. The absolute risk reduction is lower than expected compared to patients with cardiovascular disease and there are no data on patients with both low LDL-C and low hsCRP (a likely large study) or men <50 years or women <60 years old. The population studied was highly selected as seen by the large number of patients who were screened out. The mechanism of action is also unclear. It is unclear if hsCRP is an index of inflammation and rosuvastatin is having an anti-inflammatory effect or lipid modifying effect or if hsCRP is an incidental finding and that further lowering of cholesterol is better. The trial did not compare subjects with elevated and normal hsCRP, nor compare elevated hsCRP with other cardiovascular risk factors as an indicator of efficacy. Further research is needed in this area.

New Indication

There are no data to demonstrate a benefit in patients with traditional cardiovascular risk factors independently of age and elevated hsCRP (as requested in the indication), therefore the proposed indication as worded is too broad and needs revision. All patients

had to have age and elevated hsCRP as entry criteria and then could or could not have other cardiovascular risk factors. The JUPITER study did not include traditional cardiovascular risk factors as entry criteria and benefit was not independently seen in each of these other risk factors by themselves. The data have only demonstrated a benefit if a subject has elevated hsCRP and age as factors, regardless of the status of the other risk factors of smoking status, hypertension, low HDL-C or family history of cardiovascular disease. Nevertheless, 76% of subjects did have at least one other cardiovascular risk factor (hypertension in 58%, low HDL-C in 23%, smoking in 16% and family history of CHD in 12%) besides age and elevated hsCRP in the study, that is, only 24% of subjects had only age and elevated hsCRP as risk factors. A post-hoc analysis of subjects reported in the US PI with hsCRP≥2 mg/L and no other traditional risk factors (smoking, hypertension, low HDL-C) other than age, showed that after adjustment for high HDL-C, there was no significant benefit with rosuvastatin treatment. Therefore it would be reasonable to require that the indication reflect that patients should have age, hsCRP and at least one other cardiovascular risk factor (smoking, hypertension, low HDL-C or family history of cardiovascular disease) included as criteria for treatment. The population was without clinically evident CHD but this could be covered in the Clinical Trials section of the PI. Although only 3 of 5 components of the primary composite endpoint showed significant benefit, this could also be covered in the Clinical Trials section of the PI with a cross-reference from the Indications. The evaluator has recommended that the indication only refer to the 20 mg dose of rosuvastatin as this was the only dose used in the JUPITER trial. This information could be placed in the Dosage and Administration section of the PI.

In response to the clinical evaluation report, the sponsor has claimed that hsCRP ≥2 mg/L is not essential to identify the appropriate patient population for treatment. This was based on a post-hoc analysis of data using a second hsCRP level which was taken at Visit 2 at pre-randomisation. When this second level was averaged with the first hsCRP level taken (which was the eligibility criterion), then 3516 patients had a "baseline" hsCRP level of <2 mg/L. When this subgroup was analysed, they had a 55% reduction in the primary endpoint (HR 0.45). This led the sponsor to revise the indication to that at the start of this document, which is claimed to be consistent with current guidelines and clinical practice. This raises some questions on whether hsCRP is a relevant risk marker or whether it may be an incidental bystander if patients with a hsCRP level of <2 mg/L still derive a benefit. Nevertheless, the indication still claims independent benefit in patients with any of those risk factors besides age, which has not been demonstrated, and this is all based on a post-hoc subgroup analysis which is not based on the eligibility criterion of the study for hsCRP and would require further study to confirm benefit.

Current Indication

The sponsor has reworded the current hypercholesterolaemia indication by applying the current wording of using it as an adjunct to diet when the response to diet and exercise is inadequate to both the current and new indication and has also added "adult" to the current indication. The former is acceptable but the latter would specifically restrict hypercholesterolaemia to adults.

Availability of hsCRP Testing

hsCRP is a measure of CRP at low levels and can measure down to 0.04 mg/L. A normal CRP is usually <10 mg/L in the absence of inflammation. The evaluator has noted that CRP levels >3 mg/L have been reported to be associated with an increased risk of coronary heart disease compared to levels <1 mg/L. hsCRP testing is available in Australia but not routinely performed nor recommended in routine cardiovascular risk assessment. Therefore this submission could lead to increased hsCRP testing.

Summary

This submission has demonstrated the efficacy and safety of a 20 mg daily dose of rosuvastatin in reducing the relative risk of major cardiovascular events in patients with elevated hsCRP, "normal" cholesterol, age ≥50 years for males or ≥60 years for females and with at least one additional cardiovascular risk factor. An acceptable RMP has been provided but the indication requires some revision to reflect the data submitted.

The Delegate proposed to approve the submission to extend the indications for Crestor, to reduce the risk of major cardiovascular events in patients at increased risk of cardiovascular disease due to the presence of risk factors, based on the safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above.

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

Prevention of Cardiovascular Events

Crestor is indicated to reduce the risk of major cardiovascular events in men ≥ 50 years old or women ≥ 60 years old who are at increased risk of cardiovascular disease due to the presence of hsCRP level ≥ 2 mg/L and at least one additional cardiovascular risk factor (hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease), see Clinical Trials, Prevention of Cardiovascular Events.

In patients with hypercholesterolaemia

Crestor is indicated for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia).

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

The sponsor should address the following issues in their Pre-ACPM response:

- The sponsor's view on the possible mechanism of action for rosuvastatin in reducing major cardiovascular events in patients with "normal" cholesterol levels and elevated hsCRP.
- The availability of hsCRP testing in Australia.
- If the intention is to specifically restrict the hypercholesterolaemia indication to "adults".
- A summary of the post-hoc analysis reported in the US with patients with hsCRP ≥2 mg/L and no other traditional risk factors (smoking, hypertension, low HDL-C) other than age, which showed that after adjustment for high HDL-C, there was no significant benefit with rosuvastatin.

The Delegate also posed a number of questions to the ACPM.

- Is elevated hsCRP accepted as a risk marker for cardiovascular disease?
- Is hsCRP testing widely available in Australia?
- Should the indication require age, elevated hsCRP levels and at least one other cardiovascular risk factor (smoking status, hypertension, low HDL-C or family history of cardiovascular disease)?
- Should the indication specify a lack of clinically evident coronary heart disease?

- Given that only 3 of the 5 components of the primary endpoint in JUPITER were significant, should the indication only refer to these endpoints?
- Should the indication or dosage section be specific as to the dosage of 20 mg daily or allow the current wider dose interval of 5-40 mg daily?

Sponsor Response

In its pre-ACPM response, the sponsor addressed the questions which the Delegate directed at the sponsor. With respect to the mechanism of action, the sponsor's position was that CV event reduction with rosuvastatin can be ascribed to LDL-C reduction. Statins are highly effective cholesterol-lowering agents that have been proven to reduce CV events in numerous clinical studies. The Cholesterol Treatment Trialists' meta-analysis of over 90000 statin study subjects concluded that statin therapy can safely reduce the incidence of major CV events largely irrespective of the initial lipid profile or other presenting characteristics such as age, sex, or the presence or absence of diabetes or prevalent CHD.[8] A figure in the supplement to the NEJM JUPITER publication (Jupiter publication supplement 2008) demonstrates the relationship between extent of LDL-C reduction and CV event reduction for the JUPITER study in the context of prior statin trials.[9]

The principal investigator for the JUPITER study has also suggested that hsCRP-lowering by rosuvastatin also plays a role (Ridker et al 2009); the sponsor takes no position on that mechanism as the JUPITER trial was not designed to address that hypothesis.[10]

The availability of hsCRP testing is addressed below and on reconsideration, the sponsor agreed to remove the word "adult" from the hypercholesterolaemia indication.

In post-hoc analysis, rosuvastatin did not reduce CV events in JUPITER subjects with 0 ATP III (Adult Treatment Panel III) risk factors; rosuvastatin statistically significantly reduced CV events in those with one or more risk factors. The ATP III risk factors are age (≥45 years for men, ≥55 for women), smoking, family history of premature CHD, hypertension, HDL-C <40 mg/dL (NCEP Program 2001).[11] The guidance is to subtract one risk factor if HDL-C ≥60 mg/dL (~1.5 mmol/L). Since all JUPITER subjects met the age criterion, the subgroup not benefiting from rosuvastatin consisted of individuals with HDLC ≥ 60mg/dL (~1.5 mmol/L) and no other risk factor (smoking, family history, hypertension). This subgroup constituted 8% of the total cohort.

The sponsor also addressed the general issue of the indication (which addressed the third point directed to the ACPM) and the other questions directed to the ACPM. The sixth point which concerns the proposed PI is not included in this AusPAR discussion.

The sponsor's preferred indication was:

<u>*Prevention of Cardiovascular Events*</u>
Crestor is indicated to reduce the risk of major cardiovascular events in men aged 50 years and over; and women aged 60 years and over who have at least one other risk marker for

[8] Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol lowering treatment: prospective meta-analysis of data from 90 056 subjects in 14 randomized trials of statins. Lancet 2005; 366:1267-78.

[9] Supplement to: Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195-207.

[10] Ridker PM et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 2009; 373: 1175–82.

[11] Third Report of the National Cholesterol Education Program Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults published by the (US) National Institutes of Health, National Heart, Lung and Blood Institute, 2001.

increased risk of cardiovascular disease such as elevated hsCRP, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease (See Clinical Trials, Prevention of Cardiovascular Events).

Its reasoning is based on a post-hoc analysis of the JUPITER study which indicated that an elevated hsCRP level is not necessary to identify patients in whom rosuvastatin treatment prevented cardiovascular (CV) events. Also questioned was the clinical applicability of having an absolute requirement for elevated hsCRP in the indication and the importance of the practitioner's global assessment of the patient's CV risk.

The rationale provided by the Delegate for the Delegate's proposed indication seems in part to be based on the statement in the US PI regarding a post-hoc analysis of JUPITER subjects with elevated hsCRP and age as the only risk factors. The US PI statement is:

In a post-hoc subgroup analysis of JUPITER subjects (n=1405; rosuvastatin=725, placebo=680) with a hsCRP ≥2 mg/L and no other traditional risk factors (smoking, BP ≥140/90 or taking antihypertensives, low HDL-C) other than age, after adjustment for high HDL-C, there was no significant treatment benefit with rosuvastatin treatment.

In the post-hoc subgroup analysis, since all JUPITER subjects met the age and elevated hsCRP criterion, the subgroup not benefiting from rosuvastatin consisted of individuals with HDL-C ≥ 60 mg/dL (~1.5 mmol/L) and no other risk factor (smoking, family history, hypertension). This subgroup constituted only 8% of the total cohort. Whilst the sponsor acknowledged this finding, it did not consider that it warrants the requirement of a third CV risk factor in the indication, given that most patients with two risk factors should benefit from rosuvastatin treatment.

However, in acknowledgement of this finding, and in compliance with the Delegate's request for PI changes, the sponsor proposed to include the US PI post-hoc analysis in the Clinical Trials section of the PI. As the sponsor's proposed indication refers to the Clinical Trials section, the group of patients not gaining benefit from rosuvastatin treatment is clearly identified.

In response to the questions directed to the ACPM, the sponsor noted that an international panel of experts that was convened by the United States Centers for Disease Control (CDC) and the American Heart Association (AHA) in 2002 reviewed data relevant to the association of hsCRP levels and CV risk. This CDC/AHA panel of experts recommended that risk assessments based on hsCRP levels be modelled in a manner similar to the approach used to characterize risk based on blood lipid levels.[12] The panel's recommendations, which were published after initiation of the JUPITER study, included a classification of hsCRP into 3 levels: "low risk hsCRP" (<1 mg/L), "average risk hsCRP" (1 to 3 mg/L), and "high risk hsCRP (>3 mg/L).

hsCRP is also accepted as a risk marker for CV disease in (1) the (US) National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines (NACB LMG Committee 2009), (2) the 2009 Canadian Cardiovascular Society/Canadian Guidelines for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease in the Adult – 2009 recommendations (Canadian CV Guidelines 2009) and (3) the 2009 Royal College of Pathologists of Australasia Manual (RCPA Manual 2009).[13,14,15]

[12] Pearson et al. Markers of inflammation and cardiovascular disease application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107: 599-511.

[13] National Academy of Clinical Biochemistry Laboratory Medicine Practice guidelines: emerging biomarkers for primary prevention of cardiovascular disease. Clin Chem 2009; 55: 378-84.

There are three different assay methods for measuring CRP: (1) standard method, (2) ultrasensitivity (usCRP) method and (3) high sensitivity (hsCRP) method. The three CRP tests differ in sensitivity in the lower ranges. The typical sensitivity for standard CRP, usCRP and hsCRP is ~3 mg/L, 0.2 - 0.4 mg/L and 0.1 mg/L respectively. Therefore, the usCRP method is also sufficiently sensitive to measure CRP levels below the 2 mg/L level.

Findings from a recent survey of clinical laboratories around Australia showed that CRP is currently measured using the usCRP method. The hsCRP method is in limited use and is more expensive. The survey indicated that the usCRP test is widely available through key diagnostic service providers.

The sponsor did not agree that the indication should specify clinically evident coronary heart disease (CHD). In the Cholesterol Treatment Trialists' meta-analysis (CTT Collaborators 2005), CV event reduction with statin treatment was independent of baseline characteristics, including the presence or absence of CHD. Thus, although JUPITER enrolled only subjects without prevalent CV disease due to ethical concerns with randomizing CV disease patients to placebo, clinical evidence indicates that patients with CV disease would have derived similar benefit to that seen in the JUPITER cohort.

The sponsor also noted that the indication refers to the Clinical Trials section which clearly indicates that subjects had no clinically evident (originally "established") CV disease.

The prespecified primary endpoint was the composite of major CV event (CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina or coronary revascularization). JUPITER was designed similarly to other large morbidity and mortality trials in that the composite endpoint was not designed to achieve statistically significant benefit for the individual components. Thus, the scientifically appropriate indication, based on prespecified study design, is for prevention of major CV events.

The sponsor also noted that the indication refers to the Clinical Trials section which clearly indicates components of the primary endpoints met.

Advisory Committee Consideration

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the submission for the revised indication proposed by the sponsor:

Prevention of Cardiovascular Events

Crestor is indicated to reduce the risk of major cardiovascular events in men aged 50 years and over; and women aged 60 years and over who have at least one other risk marker for increased risk of cardiovascular disease such as elevated hsCRP, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease (See Clinical Trials, Prevention of Cardiovascular Events).

In making this recommendation, the ACPM advised that the risk benefit profile is less clear in the clinical context which proposes the long term prophylactic use, as opposed to a treatment for a condition, in an otherwise healthy population. The effects of long term intensive LDL cholesterol lowering in apparently healthy people is uncertain and may present risks that could not be assessed, as the pivotal clinical trial was terminated early and has not generated adequate long term safety evidence.

[14] 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations. Can J Cardiol 2009; 25: 567-579.

[15] Royal College of Pathologists of Australasia Manual 2009.

The ACPM also considered the option to require a combination of cardiovascular risk factors such as age, elevated *hs*CRP level and one other factor. However, again the Committee did not consider that the benefit in the context of long term use of a relatively high dose of this potent statin to be balanced with an appropriate safety profile. In addition, the ACPM expressed concern that *hs*CRP testing is currently not widely available in Australia.

Further Risk Benefit Analysis

Questions from the TGA

Following the ACPM meeting, the TGA met with the sponsor and their colleagues to discuss the submission. The sponsor was requested to provide any further information to address a number of matters of concern (see next section) with their submission.

The sponsor provided a response that addressed all the questions and also provided an updated Risk Management Plan (RMP). The RMP was reviewed by the Office of Medicines Safety Monitoring and the other questions are discussed below.

Response from the Sponsor

The sponsor's responses to the questions are summarised below (*in Italics*) along with the Delegate's comments.

Q1: More information was requested on the availability of CRP testing, including hsCRP and usCRP testing in Australia, including the number of pathology places offering the testing across the country.

The sponsor provided a table indicating an increasing relative risk of future cardiovascular events with increasing CRP levels however when this is adjusted for conventional coronary heart disease risk factors, the increased risk is less clear.

There are three different assays for CRP testing in Australia, high sensitivity (hsCRP), ultra sensitivity (usCRP) and standard CRP. Both the high sensitivity and ultra sensitivity CRP test can measure CRP levels below 2 mg/L which is the cut-off proposed for the indication. CRP testing is widely available in Australia, although the hsCRP testing availability is less clear.

Comment: It would be appropriate for the indication to remove the "hs" requirement from the CRP testing given that the usCRP assay will also detect levels down to 2 mg/L.

Q2: The reasons for terminating the trial early (median exposure of 1.9 years), how this decision was made, if there were predefined stopping rules, the potential for committing a Type I error from multiple checking and the potential consequences of terminating this trial early on the efficacy and safety of rosuvastatin for this population.

The JUPITER trial had two pre-specified interim analyses when 37.5% and 75% of the planned 520 primary endpoints were reached. The protocol also specified trial termination if the stopping rule was met and agreed by the independent data monitoring board and steering committee. At the first interim analysis, the stopping boundary had been passed but it was decided to continue for another 6 months at which point there were nearly 5 standard deviations difference in the primary endpoint and the trial was then terminated early. The protocol was designed prospectively for multiple checking of results so as to preserve an overall Type 1 error and the final p-value for the study was highly significant thus minimising potential for bias. The trial was terminated at a median 2 years, although 1439 patients had at least 3 years exposure and 613 had at least 4 years exposure with some having 5 years of exposure. The Dutch regulatory agency (MEB) noted that the decision to terminate the trial early was a fair decision and although the median follow up has been

limited, there are data from other trials, for example, METEOR (2 years) with rosuvastatin and other statin trials to support it.

Comment: The stopping rules appear reasonable, given the extra 6 months of checking and pre-specified interim analyses that preserved the overall Type I error. Although the median exposure was only 2 years, there were some patients studied for longer along with other supporting trials (see below).

Q3: The lack of long term safety data for a population of otherwise healthy people with no clinically evident cardiovascular disease and "normal" cholesterol.

The sponsor identified long term exposure in different populations using rosuvastatin or other statins to address the lack of long term data with rosuvastatin in this population:

Patients without prevalent CHD: The West of Scotland Coronary Prevention Study (WOSCOPS) has studied pravastatin for 5 years plus 10 years follow up (baseline LDL 5 mmol/L) which showed no long term harm from cancer or mortality. The Japanese MEGA study has studied pravastatin for 9 years which showed no increased risk of death or cancer.

Patients without prevalent CHD and normal cholesterol: The Heart Protection Study subgroup using simvastatin for 5 years (baseline LDL 3.2 mmol/L), the ASCOT study using atorvastatin for 5.5 years (baseline LDL 3.4 mmol/L) and the CARDS study for 3.9 years (baseline LDL 3 mmol/L) did not appear to demonstrate significant differences in safety outcomes based on the limited information provided.

Long term safety of rosuvastatin: Rosuvastatin has had long term follow up in the AURORA trial (end stage renal disease patients for 3.8 years, baseline LDL 2.6 mmol/L) and in the CORONA trial (heart failure patients for 2.7 years, baseline LDL 3.55 mmol/L) with similar safety profiles to placebo. The JUPITER trial had 1439 patients followed for 3 years and 613 for 4 years with similar safety profiles to placebo except for higher muscle disorders and diabetes mellitus on rosuvastatin.

Comment: Long term data using rosuvastatin at very low LDL levels are limited to the JUPITER trial's 3 year and 4 year cohort of patients. However there are supporting data from other statins such as HPS, ASCOT and CARDS used in patients with low LDL which provide some reassurance but these did not reach the low levels of LDL as seen in the JUPITER trial. However the AURORA study with rosuvastatin did reach a similar level of LDL reduction (1.5 mmol/L compared to 1.4 mmol/L in JUPITER). The sponsor proposes to add low LDL to the RMP and notes that rosuvastatin has been approved since 2002 in Netherlands with approval now in >100 countries with an estimated 19 million patients exposed. This too is reassuring but there nevertheless remains a lack of robust long term safety data with rosuvastatin using 20 mg daily in the primary prevention of major cardiovascular events.

Q4: The long term safety consequences of intensive LDL cholesterol lowering in a population with "normal" cholesterol levels and potential for new risks to develop in this population.

Specific concerns raised with very low LDL include cancer, neuropsychiatric events and intracerebral haemorrhage. A meta-analysis of 14 statin trials by the Cholesterol Treatment Trialists Collaborators 2005 with a mean follow up of 5 years did not demonstrate increased risks of death or cancer including with increasing treatment duration. Neuropsychiatric events were assessed in the PROSPER trial (pravastatin for 3 years, LDL on treatment to 2.5 mmol/L) and HPS trial (simvastatin for 5 years, LDL on treatment to 2.1 mmol/L) which showed no significant difference to placebo. Intracerebral haemorrhage was a concern in the SPARCL study (atorvastatin 80 mg) but a comparison of 5 rosuvastatin trials showed similar results compared to placebo. Safety profiles were also said to be similar to placebo

from the CARDS study (on treatment LDL of 1.7 mmol/L with atorvastatin) and HPS (on treatment LDL of 1.8 mmol/L with simvastatin).

With rosuvastatin, the METEOR trial of 2 years (on treatment LDL of 2.0 mmol/L), ASTEROID for 2 years (on treatment LDL of 1.6 mmol/L), CORONA trial of 5 years (on treatment LDL of 2 mmol/L) and AURORA trial (on treatment LDL of 1.5 mmol/L) had safety profiles as expected. In JUPITER, a pre-specified safety analysis of patients with LDL above or below 1.3 mmol/L showed similar safety profiles.

Comment: These data provide some reassurance, except for the finding of diabetes mellitus (see below), however the long term safety data of 20 mg rosuvastatin in patients with very low LDL remain limited. The sponsor acknowledges this in the RMP but only proposes routine surveillance activities to address it. The RMP evaluator did not recommend any further changes in this regard. The PI has however been updated to include a precaution on the lack of data on long term exposure in patients with a low LDL. Further trials should be conducted on the long term safety of intensive LDL lowering.

Q5: The less clear risk/benefit balance in the clinical context of long term prophylactic use, as opposed to a treatment for a condition (that is, hypercholesterolaemia), in an otherwise healthy population.

The sponsor stated that CHD is the leading cause of death in Australia and that statins have been proven to reduce cardiovascular events in numerous trials, but despite this, half of all future cardiovascular events will occur in patients with "normal cholesterol" level who are not recommended for cholesterol lowering treatment. The JUPITER trial has shown a significant reduction in cardiovascular events in this latter population. A post-hoc analysis of the AFACPS/TEXCAPS study indicated that in patients with low LDL, having an elevated CRP doubled your CHD risk. In comparing the results of JUPITER with the Framingham data (which excluded CRP), the JUPITER patients were at double the risk of CHD events compared to traditional risk factors. According to the sponsor, this doubling of risk in patients with elevated CRP is similar to the risk from smoking, diabetes mellitus or increased cholesterol. Therefore the sponsor believed that this increased risk from an elevated CRP implies JUPITER patients were not an "otherwise healthy population" and that the JUPITER population should not be viewed in the same light. The sponsor has summarised the benefits and risks in Table 18.

Table 18: Summary of clinical risks and benefits in the JUPITER study

Potential Benefits	Potential Risks
40 fewer patients with a non-fatal myocardial infarction	0.1% increase in Hb_{A1c}; 48 more cases of reported diabetes
28 fewer patients with a non-fatal stroke	
11 fewer patients with unstable angina	
60 fewer patients with arterial revascularization	
49 fewer patients who died	
Treatment of ~8900 patients x 1.9 years	

Comment: The benefits and known risks have been previously discussed, but the concern here relates to the unknown risks from long term treatment in this type of population. It was noted that the population could be seen as being at increased risk of a CHD event based on traditional risk factors, but the extrapolation for the CRP elevation is not

conclusive, also given its post-hoc analysis derivation which is hypothesis generating. An additional study with longer exposure using rosuvastatin in this type of population would help to interpret the risk benefit balance, which is much clearer in a hypercholesterolaemia population based on the multitude of studies and years of treatment experience.

Q6: Why a relatively high dose of this potent statin was chosen for this trial and why no lower doses were investigated.

The 20 mg dose was chosen as it was anticipated it would achieve a 50% reduction in LDL whilst maintaining a favourable safety profile. Lower doses were not used because the intent was to obtain at least a 50% reduction in LDL. The sponsor noted that this is consistent with other statin trials such as WOSCOPS (40 mg pravastatin) and HPS (40 mg simvastatin). Overseas this has been handled differently by other regulatory agencies for their PIs: USA (10-20 mg is the usual starting dose), Canada and Europe (both state 20 mg is the dose used in the JUPITER trial). For Australia, the sponsor proposes a 20 mg dose but with advice that individualising the dose should be considered.

Comment: The following PI statement appears a reasonable approach, however it would have been preferred to have data on a lower dose, for example 10 mg.

> **Prevention of cardiovascular events**
>
> A dose of 20 mg once daily has been found to reduce the risk of major cardiovascular events (see Clinical Trials – Prevention of Cardiovascular Events).

Q7: The regulatory status of the submission overseas including the EU, the indications approved for this submission and copies of any advice provided by advisory committees from the FDA, Health Canada or EMA on this submission.

The submission has been approved in USA, Canada and Europe with different indications based somewhat around the ASCOT trial for atorvastatin (Table 19). The sponsor notes some similarities between the trial populations (that is, large trials, both stopped prematurely, without a history of symptomatic coronary heart disease and presence of CV risk factors). The ASCOT trial also had patients with total cholesterol ≤6.5 mmol/L and an indication similar to JUPITER:

Table 19: Summary of ASCOT and JUPITER studies and corresponding approved indications in Canada, the EU and US

	ASCOT	JUPITER
Australian indication	LIPITOR is indicated in hypertensive patients with multiple risk factors for coronary heart disease (CHD) which may include diabetes, history of stroke or other cerebrovascular disease, peripheral vascular disease or existing asymptomatic CHD (see CLINICAL TRIALS, Prevention of Cardiovascular Disease) to reduce the risk of non-fatal myocardial infarction and non-fatal stroke.	***Proposed indication***: Prevention of cardiovascular events Crestor is indicated to reduce the risk of major CV events in men ≥ 50 years old or women ≥ 60 years old with no clinically evident cardiovascular disease who are at increased risk of cardiovascular disease due to the presence of CRP level ≥ 2 mg/L and at least one additional cardiovascular disease risk factor (hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease), see Clinical Trials, Prevention of Cardiovascular Events.

Issues of concern to other regulatory agencies included: avoiding treatment in very low risk patients by adding the requirement for at least one other risk factor other than CRP and age (USA), requiring the indication to include only those components for the primary endpoint that reached independent statistical significance (USA and Canada), differences in glucose metabolism to be a class effect (USA), CRP not to be a validated biomarker (Canada),

precedent from the ASCOT trial (EU) and adding a precaution on diabetes mellitus (USA, Canada and EU).

(Section I of this AusPAR has been updated to reflect the current regulatory status).

Comment: It was noted that this submission has been approved in the major regulatory agencies overseas and that the ASCOT trial has informed the decision making process. The issues raised overseas have been addressed in the PI for Australia. Concern remains over the validation of CRP as an acceptable biomarker for cardiovascular disease risk and whether it should be included in the indication wording.

Q8: The external validity of the JUPITER trial to the Australian population, given the large number of inclusion/exclusion criteria (which was evident from the large number of patients who were screened out during the selection phase) and whether any changes are being proposed to the PI as a result, for example, Clinical Trials or Indications.

The sponsor has provided a rationale for the JUPITER study design which centres on an enriched cohort for cardiovascular risk, ethical conduct for the study, compliance with current safety labelling and practical considerations. Given that patients in the proposed indication were not expected to routinely see a doctor for cardiovascular reasons then a wider public outreach was needed for recruitment which led to the large number of people being screened out. The led to the 80% exclusion of patients with half due to an elevated LDL and a third due to too low CRP. The JUPITER population was 71% Caucasian, 13% Black and 13% Hispanic which is dissimilar to the Australian population but a subgroup analysis did not indicate that race determined effect. Aboriginal Australians were not included however an independent study of 954 indigenous Australians showed 60% of men and 80% of women had a CRP >3 mg/L.

Comment: The JUPITER population is a highly selected population and the sponsor has modified the indication as a result to include at least one traditional risk factor. The Clinical Trials section describes the population but should also include the average population age. Although the population distribution is dissimilar to Australia, trials accepted in the past have had dissimilar populations and there was no racial interaction for the primary endpoint. Therefore the external validity of the trial appears acceptable.

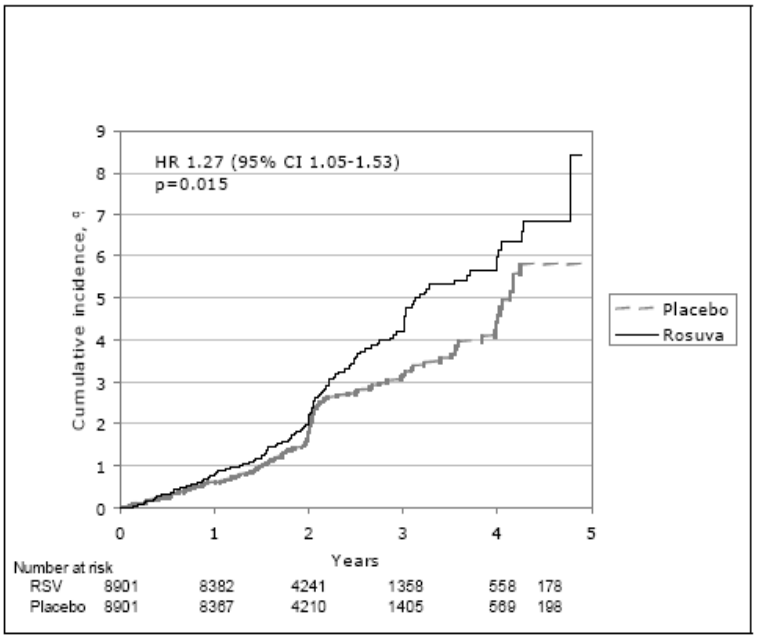
Q9: The reports of confusional state and diabetes noted in the JUPITER trial and any analyses on these adverse effects.

Neurological and psychiatric adverse events had a similar distribution between rosuvastatin and placebo, except for confusional state which was higher on rosuvastatin than placebo (0.2% (n=18) vs 0.04% (n=4)). The sponsor believes this to be a chance finding given that an explanation for the change in mental state was documented in 17 of the 18 cases, 4 had not received rosuvastatin for 6 months prior to the event and 10 patients resumed rosuvastatin without recurrence of their confusion. The FDA Advisory Committee considered that a connection to the drug was not likely.

Comment: Although this may be a chance finding, the sponsor should examine this issue in the first PSUR for this indication if this submission is approved. The explanation appears reasonable at this stage. It was noted that the PI includes memory loss as an adverse event.

JUPITER was designed to test if rosuvastatin reduced the incidence of diabetes mellitus however it found that it was significantly increased at 2.8% on rosuvastatin associated diabetes mellitus vs 2.3% on placebo (HR 1.27: 95%CI 1.05-1.53). Of these patients, the increase was seen in those with or without impaired fasting glucose at baseline but only significantly so for those with impaired fasting glucose at baseline. The risk appeared from the second year onwards (Figure 2).

Figure 2: JUPITER – Kaplan Meier plot of time to investigator-reported diabetes mellitus (ITT population)



Risk factors for diabetes were present in 97% of rosuvastatin vs 95% of placebo groups. A post-hoc analysis indicated no difference in diabetes medication use and changes in mean fasting glucose levels were similar between both groups. Increases in glucose from baseline to ≥7 mmol/L were non-significantly higher on rosuvastatin (7.8 vs 7.2%) but changes in HbA1c were significantly higher from baseline of 0.30% vs 0.22%. An increase in HbA1c to ≥7% was seen in 3.2% rosuvastatin vs 2.3% placebo. There were no reports of diabetic ketoacidosis, hypoglycaemic non-ketotic coma or other complications of severe hyperglycaemia. The primary efficacy endpoint (major CV events) was still significantly reduced in the pre-specified subgroup of patients who had impaired fasting glucose at baseline. An analysis by the sponsor of three other rosuvastatin trials (AURORA, CORONA and METEOR) did not show an increased risk. A pooled analysis of all rosuvastatin controlled and uncontrolled trials from non-diabetic patients showed no dose response effect for diabetes adverse effects.

Comment: The data indicate an increased risk of diabetes mellitus and an increase in HbA1c with rosuvastatin. This was seen in those with normal or impaired fasting glucose at baseline and although it was only significant for those with impaired fasting glucose at baseline, the number of patients with normal fasting glucose at baseline was too small to be sure. The absolute difference between rosuvastatin and placebo for the increases in reports of diabetes and increases in HbA1c remain small though and no severe consequences were reported in this large trial. The beneficial effect of a reduction in major cardiovascular events was still significant for those with impaired fasting glucose at baseline. Although the sponsor has not identified other rosuvastatin trials with similar findings, the large size of this trial and consistent effect after 2 years exposure does raise some concern. The sponsor has updated the PI with a precaution on diabetes mellitus and information on adverse effects. The RMP has also been updated with identified and

potential risks of diabetes mellitus (see page 48). These measures seem appropriate at this stage but further study is needed.

Q10: The possibility of malignancy from long term rosuvastatin use, given the SEAS trial noted an increased risk involving another statin, and the uncertainty this presents for an otherwise healthy population, along with any proposals to address this, for example in the Crestor Risk Management Plan.

The sponsor provided a summary of cancer incidence for numerous statin trials and noted that despite an earlier trial with pravastatin (PROSPER) showing an increased incidence (8.5 vs 6.8% placebo), subsequent trials and meta-analyses did not demonstrate a clear increased risk. A publication by Alsheikh-Ali et al 2007 indicated an inverse relationship between achieved LDL level with statin treatment and the rate of newly diagnosed cancer, however this was an exploratory finding.[16] The same study, which did not include rosuvastatin, found there was no significant relationship between percent LDL lowering and rates of cancer, nor between absolute LDL lowering and rates of cancer. A subsequent study by the same author (Alsheikh-Ali et al 2008) to examine this finding found an inverse relationship between on-treatment LDL and incident cancer but that statins despite causing large reductions in LDL, were not associated with an increase in cancer.[17]

The SEAS study, which was not included in the above analysis, studied ezetimibe-simvastatin combination vs placebo in aortic stenosis patients in which the LDL was lowered to 1.4mmol/L and found a significantly increased risk of cancer (11.1% vs 7.5%, p=0.01). The authors concluded this may have been due to chance but further study was needed.

In JUPITER, cancer was not increased on rosuvastatin (3.4 vs 3.5%) and significantly fewer cancer deaths were reported on rosuvastatin. In the HPS study (simvastatin, n>10000, 5 years), there was no increase in cancer seen. The Cholesterol Treatment Trialists' Collaboration study also did not show an increase in cancer with statins. Other rosuvastatin trials did not indicate an increased risk and post-marketing data have not demonstrated a safety signal. The sponsor will monitor this through routine surveillance activities and has not included it in the RMP at this time. The RMP evaluator has noted no clear pattern of malignancies and that a signal is not substantiated at this time.

Comment: The sponsor should continue to monitor this situation. The data do not appear to indicate a risk at present, given also the lack of a signal from JUPITER, but longer term exposure would be needed to confirm an effect on cancer incidence.

Q11: Any risk minimising activities, including further amendments to the Product Information or use of the product, which could address the concerns raised by ACPM.

The sponsor proposed amendments to their indication to address the committee's concerns by adding "at least one other cardiovascular risk factor" in line with the Delegate's previously proposed action. By requiring patients at greater risk in the indication, this is claimed to improve the risk benefit profile. Having two risk factors (age plus one other traditional cardiovascular risk factor) shows a significant reduction in CV events with 1.4% on rosuvastatin vs 2.9% on placebo (HR 0.50, 95%CI 0.35, 0.70) (Table 20). This compares favourably with the increase risk for diabetes mellitus. The indication also removes the "hs" from CRP and adds patients with "with no clinically evident cardiovascular disease" as per the study population. The sponsor also added precautions on diabetes, endocrine effects and use in patients with low LDL. The Adverse Effects section is being updated with depression,

[16] Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RH. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer. J Am Coll Cardiol 2007; 50: 409-418.

[17] Alsheikh-Ali AA, Trikalinos TA, Kent DM, Karas RH. Statins, low-density lipoprotein cholesterol, and risk of cancer. JACC 2008; 52: 1141-7.

sleep disorders and diabetes. The RMP has been updated with diabetes and low LDL and the next PSUR will examine diabetes risk.

Table 20: JUPITER – Primary endpoint by number of risk factors

	Rosuvastatin (N=8901)			Placebo (N=8901)			
# risk factors[a]	N	# events (%)	Rate	N	# events (%)	Rate	HR (95% CI)
0[b]	725	13 (1.8)	8.5	680	8 (1.2)	5.5	1.54 (0.64-3.70)
1	2679	35 (1.3)	6.3	2640	58 (2.2)	10.5	0.60 (0.40-0.92)
2	3451	50 (1.4)	7.0	3487	101 (2.9)	14.1	0.50 (0.35-0.70)
3	1661	35 (2.1)	10.0	1730	64 (3.7)	18.0	0.56 (0.37-0.84)
4	358	7 (2.0)	9.1	344	16 (4.7)	22.2	0.41 (0.17-0.99)
5	27	2	35.1	20	5	122.3	0.29 (0.06-1.50)

[a] Risk factors in this analysis were counted as recommended by the National Cholesterol Education Program Adult Treatment Panel III1: age (>45 men, >55 women), HDL-C<40 mg/dL (1.0 mmol/L), hypertension, smoking, and family history premature CHD (CHD in male 1st degree relative <55y, female1st degree relative <65y). One risk factor was subtracted if HDL-C>60 mg/dL (1.6 mmol/L).

[b] Subjects with 0 risk factors (8% of the cohort, N = 1405), had age as a risk factor and high HDL-C, which subtracted 1 risk factor.

Comment: The sponsor's proposed changes to the PI appear reasonable and the deletion of "hs" from the CRP also appears acceptable as both usCRP and hsCRP can detect a CRP ≥2 mg/L. Although the sponsor has weighed the primary endpoint with the risk of diabetes, it only considers one risk rather than all risks associated with rosuvastatin treatment.

Q12: Any PSUR reports from the use of rosuvastatin overseas for this indication and whether they address the concerns raised above.

No PSURs were available that specifically include this indication yet with the first expected after 6 Nov 2010. The sponsor has commented that when this is available it will be submitted to TGA but is unlikely to contain specific information related to this indication. Confusional state will be monitored and reported in the next PSUR and cancer will be monitored through routine surveillance.

Comment: The TGA will review the PSURs that follow from this indication if approved.

Q13: If any further clinical trials have been completed but not submitted to the TGA or if there are any further trials currently ongoing with rosuvastatin in this indication. Please identify these studies and if they could address the concerns raised above.

The sponsor has identified three other studies. GISSI-HF used fish oils and rosuvastatin in heart failure patients which did not show a benefit compared to placebo. Two ongoing studies include: SATURN of atorvastatin 80 mg vs rosuvastatin 40 mg on coronary atheroma using intravascular ultrasound and HOPE-3 which is a 11,000 patient trial using a rosuvastatin 10 mg arm on major cardiovascular events for 3 years with results expected 2014.

Risk Management Plan

The sponsor submitted an updated RMP (28 May 2010) which was found to be acceptable by the Office of Product Review (which has replaced the OMSM) in the TGA. The sponsor addressed all outstanding matters from the previous Delegate's Request for ACPM Advice on the RMP and has also included diabetes mellitus as an identified risk when the fasting glucose is ≥5.6 mmol/L and as a potential risk when the fasting glucose is <5.6 mmol/L. The RMP has also been updated to include patients with very low LDL-C as a special

patient population although no specific risk minimising activities are proposed for this group.

Delegate Considerations

The sponsor submitted a comprehensive response to the 13 matters raised by TGA and ACPM on rosuvastatin, including PI amendments and an updated acceptable Risk Management Plan. Since the submission was considered by ACPM in April 2010 when this submission was only approved in the USA, this indication (in different forms) has also been approved in Europe and Canada and the sponsor has amended the indication to be similar to that previously proposed by the Delegate and approved in the USA. The sponsor has also pointed out that atorvastatin (Lipitor) is approved in Australia for a cardiovascular disease prevention indication in patients with total cholesterol ≤6.5 mmol/L based on the ASCOT study which has similarities to the JUPITER trial. The indication has attempted to exclude those patients who would be at very low risk of a CHD event by excluding them based on requiring a certain number of risk factors (that is, age, at least one traditional CV risk factor and elevated CRP). The main concern remains the lack of long term exposure data with rosuvastatin at this dose in this type of population with respect to safety given its use is intended for primary prevention. However the sponsor has tried to address this with supportive evidence from other trials using rosuvastatin and other statins and by the example set by the ASCOT trial using atorvastatin. The JUPITER trial also had some patients being treated for longer with 1439 patients followed for 3 years and 613 for 4 years with similar safety profiles to placebo except for muscle disorders and diabetes mellitus being higher on rosuvastatin. Overall, the submission appears approvable based on the further information and PI changes proposed by the sponsor. The advice of ACPM was requested with respect to the following two questions:

Has the sponsor presented sufficient information to address the concerns of the Committee to enable approval?

Should a CRP level be included in the indication as in the USA, but which was not included in Canada or Europe?

The submission to extend the indications for rosuvastatin for the prevention of cardiovascular events, appears approvable based on the safety and efficacy of the product being satisfactorily established for the indication below:

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

Prevention of Cardiovascular Events

Crestor is indicated to reduce the risk of major CV events in men ≥ 50 years old or women ≥60 years old with no clinically evident cardiovascular disease who are at increased risk of cardiovascular disease due to the presence of CRP level ≥2mg/L and at least one additional cardiovascular disease risk factor (hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease) see Clinical Trials, Prevention of Cardiovascular Events.

In patients with hypercholesterolaemia

Crestor is indicated for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia).

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

Advisory Committee Consideration

The ACPM, having considered additional information presented, reaffirmed its recommendation for rejection of the submission.

In making this recommendation the ACPM considered the additional information and advised that the data do not adequately demonstrate a sufficient positive long term safety profile to balance the uncertain efficacy benefit profile long term for the target population.

The ACPM reaffirmed its previous advice in that the risk benefit profile remains uncertain in the clinical context which proposes the long term prophylactic use, as opposed to a treatment for a disease, in a healthy population. The effects of long term intensive LDL cholesterol lowering in apparently healthy people remains uncertain and may present safety risks that could not be assessed, as the pivotal clinical trial was terminated early, failed to clarify key end points such as cardiac mortality prevention and has not generated adequate long term safety evidence.

The ACPM also reconsidered the option to require a combination of cardiovascular risk factors such as age, elevated *hs*CRP level and one other factor however, but again did not consider the benefit in the context of long term use of a relatively high dose of this potent statin to be balanced with appropriate safety evidence. In addition, the ACPM expressed concern that there were no reliable direct data comparing sub populations with and without *hs*CRP testing and that this test is not currently widely available in Australia.

The ACPM also was of the view that it would be useful for prescribers if the updated PI included the absence of benefit in patients with cardiac failure (CORONA study) and those on haemodialysis (AURORA).

Initial Outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of Crestor containing rosuvastatin, indicated for:

Prevention of Cardiovascular Events

Crestor is indicated to reduce the risk of major CV events in men ≥ 50 years old or women ≥60 years old with no clinically evident cardiovascular disease who are at increased risk of cardiovascular disease due to the presence of CRP level ≥2 mg/L and at least one additional cardiovascular disease risk factor (hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease) see Clinical Trials, Prevention of Cardiovascular Events.

Final Outcome

Following the initial decision described above, the sponsor appealed under Section 60 of the Therapeutic Goods Act whereby a review of the initial decision was conducted by the Minister.

Procedural fairness

The Delegate of the Minister noted that following the sponsor's responses to a comprehensive set of questions designed to address the concerns of the ACPM arising from the Delegate's first request for advice in April 2010, the Delegate resubmitted the application with the recommendation that the application "appears approvable on the safety and efficacy of the product being satisfactorily established for the indication……". The Delegate of the Minister was persuaded by the sponsor's assertion that, without the prior knowledge of AstraZeneca, reference to and the appearance of reliance on information in a number of articles recorded in the Minutes of the ACPM of its meeting on 1 October 2010 may have contributed to the decision to reject the application and this could be viewed as compromising procedural fairness.

The Delegate of the Minister commented briefly on the reasons for rejection of the application by the TGA and the sponsor's responses.

The provision of data relating to long term safety

The Delegate of the Minister noted that for the target population administration of this product could theoretically extend for a number of decades. Long term, in considering the safety of a product, has no strict definition in regulatory guidelines or legislation. The pivotal trial which provided the data to support the application was planned to continue for five years but terminated prematurely at a median of 1.9 years of follow-up. However, the early termination is stated to be in accordance with rules in place before the study began and, based on statistically significant findings at this point, complied with the recommendations of the Declaration of Helsinki on Ethical Principles for Medical Research on Human Subjects.

The study complies with the TGA-adopted EU guidelines which recommends a minimum of 12 months and preferably longer, notably when the intended use is lifelong.[18,19] The latter document acknowledges that no pre-marketing study is likely to provide a complete picture of long-term adverse reactions, and manufacturers are urged to undertake post-marketing monitoring.

Efficacy

The Delegate of the Minister noted that the JUPITER study demonstrated the efficacy of a 20 mg daily dose of rosuvastatin in that it reduced the relative risk of a major cardiovascular event by 44% in patients with elevated hsCRP, "normal" cholesterol and age ≥50 years for males or ≥60 years for females. This benefit was seen to 5 years but there were minimal patients in later years as the study was stopped early at a median follow-up of 1.9 years due to the demonstrated efficacy.

The sponsor provided additional information that is supportive of the efficacy and safety of intensive LDL lowering.[20] Against a background that lowering of LDL cholesterol with standard statin regimens reduces the risk of occlusive vascular events in a wide range of individuals, the authors concluded that further reductions in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularisation, and of ischaemic stroke, with each 1·0 mmol/L reduction reducing the annual rate of these major vascular events by just over a fifth. There was no evidence of any threshold within the cholesterol range studied; suggesting that reduction of LDL cholesterol by 2–3 mmol/L would reduce risk by about 40–50%.

The Cochrane review is more cautious in its conclusion.[21] Although reductions in all-cause mortality, composite endpoints and revascularisations were found with no excess of adverse events, there was evidence of selective reporting of outcomes, failure to report adverse events and inclusion of people with cardiovascular disease. Only limited evidence showed that primary prevention with statins may be cost effective and improve patient

[18] EMEA, Committee for Medicinal Products for Human Use (CHMP), 29 July 2004. Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders, CPMP/EWP/3020/03.

[19] pp. 127-132 of Rules Governing Medicinal Products in the European Union 1998 (3C) – 3CC6A, February 1987. Clinical Investigation of Medicinal Products for Long-Term Use. http://www.tga.gov.au/docs/pdf/euguide/vol3c/3cc6aen.pdf

[20] Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010; 376: 1670–81.

[21] Taylor F et al; Statins for the primary prevention of cardiovascular disease (Review) Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD004816.

quality of life. The final recommendation was that caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.

The Delegate of the Minister agreed that efficacy and safety of the 20 mg Crestor dose should rely primarily on data generated in the JUPITER study. These data indicate a small but significant reduced relative risk of a major cardiovascular events and a small increase in diabetes mellitus through an unknown mechanism but the latter was considered by the clinical evaluator, the Delegate and, in the reports submitted with the appeal submission, in the opinion of two expert clinicians to be clinically insignificant. Even so the sponsor has agreed to update the PI with a precaution on diabetes mellitus and information on adverse events in response to observed but not clinically or statistically significant higher incidences of hepatic disorders, muscular disorders, renal disorders and confusional state in subjects receiving Crestor compared to those receiving placebo. However, The Delegate of the Minister agreed with the statement by one of the experts that *"ongoing longer-term follow-up with pharmacovigilance data needs to be undertaken to complement the safety data for the JUPITER study"*

Rationale for the 20 mg dose chosen for this trial and no lower doses investigated

The Delegate of the Minister indicated that the notion that a lower dose may have similar efficacy and an improved safety profile in the target population was, in his view, speculative. However, other than the rationale to choose a mid range dose for Crestor, the Delegate of the Minister discounted the sponsor's comparison with simvastatin. The indications for the use of simvastatin rest with those in the Heart Protection Study (HPS) which the Delegate of the Minister extracted from the TGA approved PI.

This was a large, multicenter, randomised, placebo-controlled, double-blind study with a mean duration of 5.3 years conducted in 20, 536 patients (10,269 on LIPEX 40 mg and 10,267 on placebo). Patients were 40-80 years of age and at high risk of developing a major coronary event based on ***3 main categories*** *of past medical history: Coronary disease (definite or probable clinical diagnosis of MI, unstable angina, stable angina, PTCA or CABG); occlusive disease of non-coronary arteries (clinical, angiographic or ultrasound diagnosis of carotid artery stenosis (eg TIA or non-disabling stroke not thought to be haemorrhagic), carotid endarterectomy, leg artery stenosis (eg intermittent claudication) or surgery); or diabetes mellitus (clinical diagnosis of insulin dependent or maturity-onset diabetes).*

While the TGA-approved PI provides specific direction for the use of simvastatin, the TGA consumer information indicates that:

Simvastatin may be used in these people, regardless of their cholesterol level to:

∗ help prolong life by reducing the risk of a heart attack

∗ reduce the risk of stroke,

This does suggest a more liberal interpretation for criteria of use of statins and encourage expectations in the community which the extended indication for Crestor would, in part, meet.

C-reactive protein (CRP) as a relevant risk marker of cardiovascular disease

The Delegate of the Minister noted that the difference in the approved indication for simvastatin and for the target population for Crestor is the extension to persons at increased risk of cardiovascular events without clinical evidence of cardiovascular disease. To further define this group the sponsor recommends the exclusion of subjects with a low C-reactive protein (CRP). Concern remains over the validity of CRP as an acceptable biomarker for cardiovascular disease risk and whether it should be included in the

indication wording. Data were provided that support the association of an elevated CRP as a marker of increased risk from thrombotic cardiovascular events when considered in conjunction with other cardiovascular risk factors. Although the interpretation of the role of the association of an elevated CRP as a marker for increased risk for cardiovascular disease remains controversial, there are sufficient data to suggest that assessment of CRP in an individual may be useful for further stratification to a higher or lower risk category. The level of CRP may assist in the evaluation of persons being considered as candidates for the extended indication for Crestor for persons with a number of globally accepted conventional risk factors. It, therefore, would be reasonable to include reference to the use of CRP in the PI as a recommendation in the assessment of candidates being considered for the extended indication for the use of Crestor.

The primary concern of the ACPM and the controversy over the validity of JUPITER

The Delegate of the Minister noted that the primary concern of the ACPM is recorded in the minutes of the meeting on 1 October 2010 as: *that the risk profile was less clear in a clinical context which proposed the long term prophylactic use of Crestor in an otherwise healthy population as opposed to a treatment of a condition.* The Committee recommended rejection on that basis.

The articles, summarised below, considered by the Committee appear to have been influential in determining this view. The primary messages in these articles were:

Hlatky, in an editorial accompanying the publication of the JUPITER trial in 2008, proffers that JUPITER provides yet more evidence about the effectiveness of statin therapy in reducing cardiovascular risk, even among persons who would not currently be considered for pharmacotherapy.[22,23] Guidelines, he predicted, for primary prevention will surely be reassessed on the basis of the JUPITER results but the appropriate size of the orbit of statin therapy depends on the balance between the benefits of treatment and its long-term safety and cost. Three articles in the Archives of Internal Medicine, published in June 2010, seek to address the issue raised in the latter sentence.

Ray et al. concluded, based on aggregate data on 65 229 men and women from 11 studies, yielding approximately 244 000 person-years of follow-up and 2793 deaths, that statin therapy for an average period of 3.7 years had no benefit on all-cause mortality in a high-risk primary prevention population.[24] Current prevention guidelines endorse statin therapy for subjects at high global risk of incident CVD as a means to reduce fatal and nonfatal vascular events. Due consideration is needed in applying statin therapy in lower-risk primary prevention populations. de Lorgeril et al. focused on the JUPITER controversy and concluded that the results of the trial do not support the use of statin treatment for primary prevention of cardiovascular diseases and raise troubling questions concerning the role of commercial sponsors.[25]

Green, in the editorial in the same issue in which he assesses the controversy, notes that the stakes in the debate into which these two articles enter are high.[26] Most patients who

[22] Hlatky MA. Expanding the orbit of Primary Prevention - Moving beyond JUPITER". N Engl J Med 2008; 359; 2280-82.

[23] Ridker PM, Danielson E, Fonseca FAH et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359; 2195-2207.

[24] Ray KK, Seshasai SR, Erqou S, Sever P, Jukema JW, Ford I, Sattar N. Statins and all-cause mortality in high risk primary prevention: a meta-analysis of 11 randomised controlled trials involving 65,229 participants. Arch Intern Med 2010; 170; 1024-31.

[25] de Lorgeril M, Salen P, Abramson J et al. Cholesterol lowering, cardiovascular diseases, and the Rosuvastatin - JUPITER controversy: a critical appraisal. Arch Intern Med 2010; 170; 1032-36.

[26] Green L. Cholesterol lowering therapy for primary prevention: still much we don't know. Arch Intern Med 2010; 170; 1007-08.

have major coronary events do not have previously known disease, so primary prevention could deliver large outcome benefits.

In addition, he notes that very large numbers of patients, who had comorbidities and were taking other medication were excluded from or under represented in the trials, would take medications for far longer periods than they did in the trials, so serious adverse effects that were not detected in the trials could manifest over time. He also makes the statement that three-quarters of the patients who take statins are taking them for primary prevention, so enormous expenditures (from payors' perspectives) or revenues (from industry's perspective) are at stake.

He admits the uncertainty concerning outcomes is also high. The trials, he notes, are short, only 5 to 7 years, in comparison to clinical use that will go on for decades. He makes an observation that advocates for lipid lowering for primary prevention assert that cumulative benefit will accrue over a longer time, while sceptics postulate that low-hanging fruit is picked early and little incremental benefit accrues later. No data settle the increasing returns versus the diminishing-returns extrapolations; both are extrapolations based on differing beliefs about pathophysiology. Ray and colleagues' meta-analysis, he reports, makes it clear that in the short term, for true primary prevention, the benefit, if any, is very small. In the long term, although sincere advocates on both sides will try to convince us otherwise, he admits that we do not know what the outcomes will be. He recommends good research to find out and, as he notes, de Lorgeril and colleagues have pointed out that research must be free of incentives to find any particular desired answer.

The Delegate of the Minister further noted that JUPITER was a prospective trial conducted according to established guidelines and regulatory requirements. It is the pivotal study that supports the submission for the extension of indications for the use of Crestor. The findings are recorded above under the heading of efficacy. The findings have been assessed to be valid by the clinical evaluator, the Delegate and this view is supported in two reports authored by company sponsored medical experts.

Recently published articles were also considered by the ACPM that evaluated both the JUPITER trial and made conclusions based on the meta-analysis of a number of trials conducted to assess the value of statins as pharmaceutical prophylaxis in persons without clinical evidence of cardiovascular disease identified at high risk of cardiac events. The interpretation of data analysed retrospectively, while identifying deficiencies in trial design, implementation and unless the primary trial is fundamentally flawed tend to arrive at more subjective conclusions than those derived from data obtained in the primary trial. These articles, while valuable in providing a note of caution to indicate that more data is required should not, in the view of the Delegate of the Minister, discount the conclusions toward a favourable benefit to adverse event ratio presented in JUPITER. Further trials are required to confirm or discount this conclusion.

Regulatory status in other countries

The Delegate of the Minister noted that it was clear that countries with comparable regulatory requirements have made a decision with respect to this dilemma and have, on submission of the same data package, approved the use of Crestor for the extended indication during 2010, that is: the USA, EU, Canada, and New Zealand.

Conclusion

The Delegate of the Minister noted that as a preventive strategy, confirmation that the administration of pharmaceuticals which have a risk benefit ratio for favourable outcomes versus adverse outcomes over many years, possibly decades, to a healthy target population requires very long term prospective trials free of commercial incentives. Trials with these characteristics to resolve the uncertainties emerging with respect to the proposed long term prophylactic use of Crestor in an otherwise healthy population as opposed to a treatment of a condition are unlikely, it seems, to provide a conclusive evidence to confirm or refute this hypothesis in the near future.

Post market surveillance with an appropriate level of reported clinical vigilance to assess the outcomes of the use of the product in a target population with risk factors, but without clinical evidence of disease, where the product is known to be effective in the treatment of persons with clinically evident disease and the adverse event profile of the product, over the short term, is acceptably low is an alternative approach. This approach relies on treating clinicians undertaking the primary role in assessing the risk factors for potential candidates. Central to this role will be the medical practitioner's requirement to inform identified candidates seeking pharmaceutical prophylactic prevention for cardiovascular disease that there is uncertainty relating to favourable outcomes and the potential for adverse events. At the same time candidates should be advised to make modifications to reduce the impact of identified life style risk factors for cardiovascular disease. If the candidate proceeds with the prophylactic pharmaceutical intervention, importantly, there will be the requirement for the continued monitoring and recording of the outcomes and adverse events.

As the generation of new data to answer this uncertainty, in the short term, is not likely to be forthcoming, it was the view of the Delegate of the Minister that it is difficult to justify a delay of an opportunity of an intervention, based on known risk factors with a product with known efficacy and safety profile in the treatment of persons with clinical evidence of cardiovascular disease until after a clinical event has occurred, that possibly has the potential to reduce mortality from cardiovascular disease. If future pharmacovigilance or data generated in ongoing or future trials provide an indication for an unfavourable benefit to adverse outcome event ratio consideration then should be given to withdrawing approval for the extended indications.

Results of consideration of the initial decision

The Delegate of the Minister decided to revoke that decision and make a decision in substitute for the initial decision. The decision was:

Crestor/Visacor (rosuvastatin) may be registered in Australia for extension of indications:

Prevention of major cardiovascular events in men ≥ 50 years old or women ≥ 60 years old with no clinically evident cardiovascular disease but with at least two conventional risk factors for cardiovascular disease (hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease).

Crestor is indicated to:

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

and the Product Information (PI) to include:

- *A recommendation for the testing for C-Reactive Protein (CRP) as an accessory marker to assist in the stratification between high and low risk categories of patients.*

- *A reference to the current controversy relating to the prophylactic use of Crestor in persons without evidence of cardiovascular disease.*

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

CRESTOR®

rosuvastatin calcium

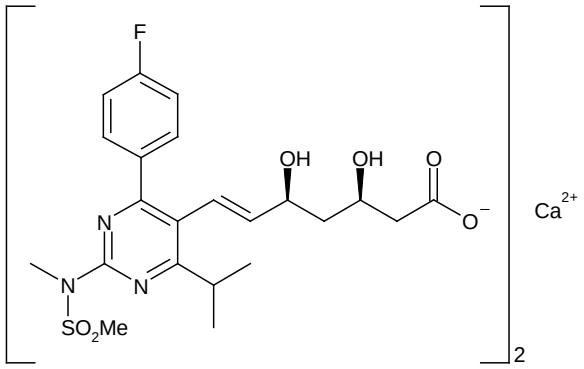
PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient in CRESTOR® is rosuvastatin, as rosuvastatin calcium. The chemical name is bis [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino]pyrimidin-5-yl] (3R, 5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt.

CRESTOR, rosuvastatin calcium, is a HMG-CoA reductase inhibitor for the treatment of dyslipidaemia.

The chemical structure of rosuvastatin calcium is:



CAS Number: 147098-20-2

Molecular formula: $(C_{22}H_{27}FN_3O_6S)_2Ca$

Molecular weight: 1001.14

DESCRIPTION

Rosuvastatin calcium is an amorphous solid, which is slightly soluble in water (7.8 mg/mL at 37°C) and has a pKa of 4.6. Rosuvastatin calcium is the (3*R*,5*S*,6*E*) enantiomer.

CRESTOR film-coated tablets contain 5 mg, 10 mg, 20 mg and 40 mg of rosuvastatin (as calcium). The tablets also contain the following inactive ingredients: crospovidone, lactose, microcrystalline cellulose, calcium phosphate, magnesium stearate, glycerol triacetate, hypromellose and titanium dioxide. The 5 mg tablets also contain iron oxide yellow CI77492 whereas the 10 mg, 20 mg and 40 mg tablets contain iron oxide red CI77491.

PHARMACOLOGY

Rosuvastatin is a fully synthetic 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 functions, 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 and TG, and 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 the lowering of nonHDL-C (ie all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.

Pharmacokinetics

Absorption

Peak plasma levels occur 5 hours after dosing. Absorption increases linearly over the dose range. Absolute bioavailability is 20%. The half-life is 19 hours and does not increase with increasing dose. There is minimal accumulation on repeated once daily dosing.

Distribution

Volume of distribution of rosuvastatin at steady state is approximately 134 litres. Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin.

Metabolism

Rosuvastatin is not extensively metabolised; approximately 10% of a radiolabelled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin.

Excretion

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.

Clinical Efficacy

A therapeutic response (reduction in LDL-C) to rosuvastatin 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.

Special Populations

Race: A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

Hypercholesterolaemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidaemia (Fredrickson Type IIa and IIb)

CRESTOR reduces total-C, LDL-C, ApoB, nonHDL-C, and TG, and increases HDL-C, in patients with hypercholesterolaemia and mixed dyslipidaemia.

The clinical trial program showed that CRESTOR is effective in a wide variety of patient populations regardless of race, age or sex, and in special populations such as diabetics or patients with familial hypercholesterolaemia.

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 1). 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

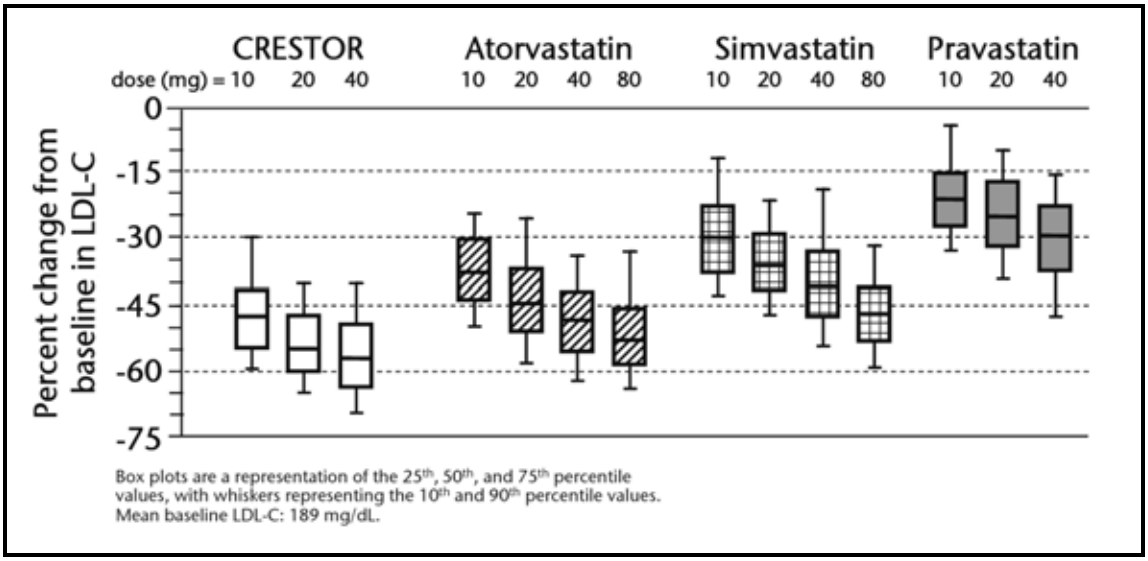


Table 1. LSMean[§] % change in LDL-C from baseline to Week 6 for each statin treatment group. N=number of patients at each dose of each statin.

	Treatment Daily Dose							
Treatment	**10 mg**		**20 mg**		**40 mg**		**80 mg**	
	N	**Mean (95%CI)**	**N**	**Mean (95%CI)**	**N**	**Mean (95%CI)**	**N**	**Mean (95%CI)**
Rosuvastatin	156	-46[ψ] (-48, -44)	160	-52[β] (-54, -50)	157	-55[ω] (-57, -53)	-	-
Atorvastatin	158	-37 (-39, -35)	154	-43 (-45, -41)	156	-48 (-50, -46)	165	-51 (-53, -49)
Pravastatin	160	-20 (-22, -18)	164	-24 (-26, -22)	161	-30 (-32, -28)	-	-
Simvastatin	165	-28 (-30, -26)	162	-35 (-37, -33)	158	-39 (-41, -37)	163	-46 (-48, -44)

[ψ]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)

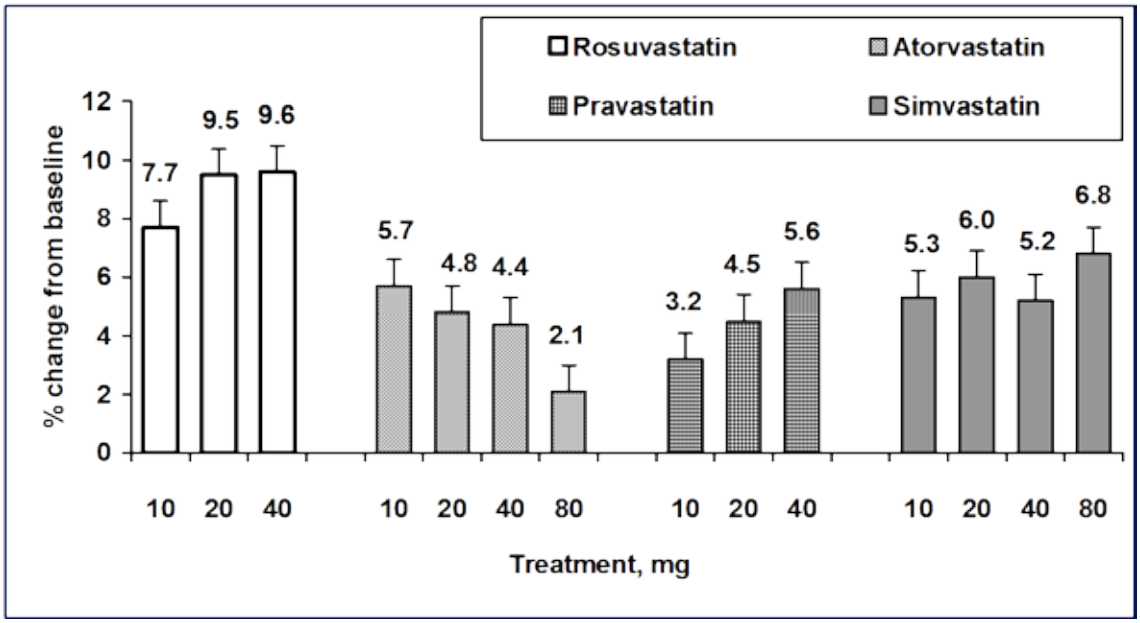
[β]Rosuvastatin 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg, and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. (p<0.002)

[ω]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



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 2.

Table 2. LSMean % change in HDL-C from baseline to Week 6 for each statin treatment group. N=number of patients at each dose of each statin.

	Treatment Daily Dose							
Treatment	**10 mg**		**20 mg**		**40 mg**		**80 mg**	
	N	**Mean (95%CI)**	**N**	**Mean (95%CI)**	**N**	**Mean (95%CI)**	**N**	**Mean (95%CI)**
Rosuvastatin	156	8 (6, 9)	160	9 (8, 11)	157	10 (8, 11)	-	-
Atorvastatin	158	6 (4, 7)	154	5 (3, 7)	156	4 (3, 6)	165	2 (0, 4)
Pravastatin	160	3 (2, 5)	164	4 (3, 6)	161	6 (4, 7)	-	-
Simvastatin	165	5 (4, 7)	162	6 (4, 8)	158	5 (4, 6)	163	7 (5, 8)

Table 3 below summarises the pooled lipid variable data for rosuvastatin 5 and 10 mg from 5 Phase III efficacy trials (Trials 24-28).

Table 3. Pooled lipid variable data for rosuvastatin at 12 weeks from Trials 24-28. The data is presented as both the mean % and mean absolute change (mg/dL) from baseline with 95% CI for each lipid variable. N=number of patients at each dose of CRESTOR.

Dose	Rosuvastatin 5 mg		Rosuvastatin 10 mg	
	N=630		N=615	
	% change (95% CI)	Absolute change mg/dL (95% CI)	% change (95% CI)	Absolute change mg/dL (95% CI)
LDL-C	-41 (-42, -40)	-78 (-80, -76)	-47 (-48, -46)	-88 (-90, -86)
TC	-29 (-30, -29)	-81 (-83, -79)	-33 (-34, -32)	-91 (-93, -88)
HDL-C	8 (7, 9)	4 (3, 4)	9 (8, 10)	4 (4, 5)
TG	-16 (-18, -14)	-33 (-37, -29)	-20 (-21, -18)	-37 (-41, -34)
NonHDL-C	-38 (-39, -37)	-85 (-87, -82)	-43 (-44, -42)	-95 (-98, -93)
ApoB	-33 (-33, -32)	-59 (-61, -57)	-37 (-38, -36)	-66 (-68, -64)
ApoA-I	6 (5, 7)	8 (6, 9)	7 (6, 8)	9 (7, 10)

Heterozygous Familial Hypercholesterolaemia

In a study of patients with heterozygous familial hypercholesterolaemia, 435 subjects were given CRESTOR 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%.

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 4).

Table 4. Dose-Response in Patients With Primary Hypertriglyceridaemia Over 6 Weeks Dosing Median (Min, Max) Percent Change From Baseline

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

Homozygous Familial Hypercholesterolaemia

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 reduction of less than 15%, 3 had no response or an increase in LDL-C.

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 5 summarises the results for the mean percentage change from baseline at 8 weeks in lipid and lipoprotein variables.

Table 5: 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.

Variable	Mean % change[Ψ] RSV 40 mg N=432	Mean % change[Ψ] ATV 80 mg N=439	Difference in ls mean % changes	95%CI[§]	p value[ω]
LDL-C	-55.89	-52.18	-3.71	-5.61 to –1.82	<0.001
HDL-C	9.58	4.35	5.23	3.04 to 7.43	<0.001
TC	-40.40	-39.27	-1.13	-2.63 to 0.36	0.138[b]
NonHDL-C	-50.75	-48.27	-2.48	-4.25 to –0.72	0.006
ApoB	-44.64	-42.29	-2.35	-4.17 to –0.52	0.012
ApoA-I	4.20	-0.47	4.67	2.71 to 6.63	<0.001
TG	-22.21	-27.02	4.81	1.10 to 8.53	0.011[a]

[Ψ]Mean % change from baseline

[§]95% confidence interval for the difference between the least squares means

[ω]p<0.05 was statistically significant

[a]statistically significant in favour of atorvastatin

[b]ns = not significant

RSV = rosuvastatin; ATV = atorvastatin; ls = least squares

Ultrasonographic study in carotid 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, which is measured using B-mode ultrasonography) were randomised to 40 mg rosuvastatin once daily or placebo for 2 years, using a 5:2 randomisation split (rosuvastatin:placebo).

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.

There was an absence of disease progression in 52.1% of patients in the rosuvastatin group compared to 37.7% of patients in the placebo group (p=0.0002). A multi-level fixed effects regression model was used for the statistical analysis and the cited results were calculated using the ITT population.

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 40 mg. The 40 mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk (see DOSAGE AND ADMINISTRATION).

Prevention of 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 clinically evident cardiovascular disease, LDL-C levels <3.3 mmol/L (130 mg/dL) and hs-CRP levels ≥2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.6% over 10 years based on the Framingham risk criteria and included a high percentage of patients with additional risk factors such as hypertension (58%), low HDL-C levels (23%), cigarette smoking (16%) or a family history of premature CHD (12%). Study participants had a median baseline LDL-C of 2.8 mmol/L (108 mg/dL) and hsCRP of 4.3 mg/L. The average age of study participants was 66 years. Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years. The JUPITER study was stopped early by the Data Safety Monitoring Board due to meeting predefined stopping rules for efficacy in rosuvastatin-treated subjects.

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

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

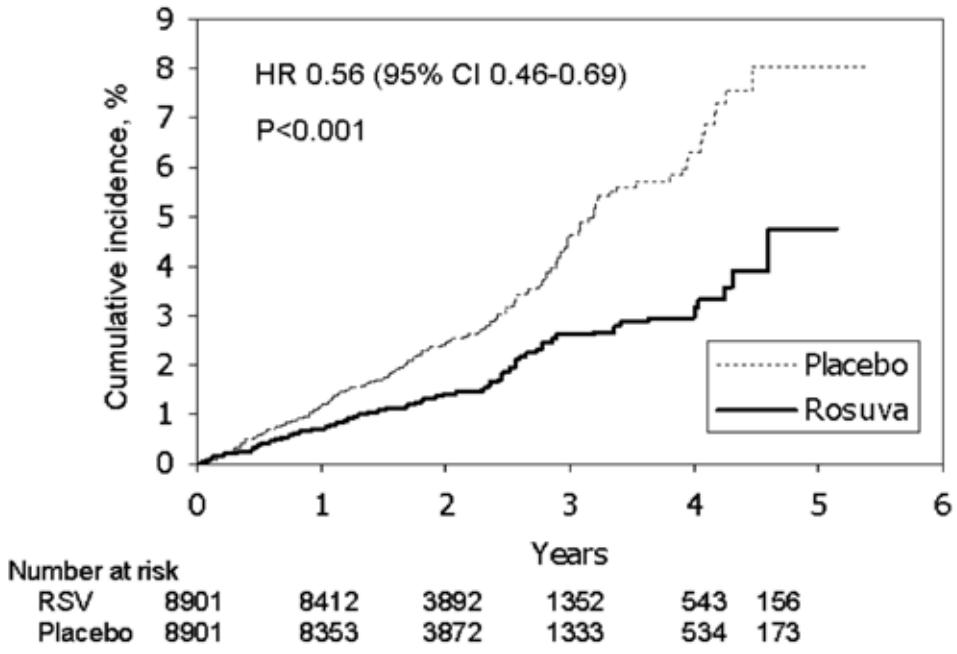
Table 6: Summary of Risk Reductions from JUPITER trial

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

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

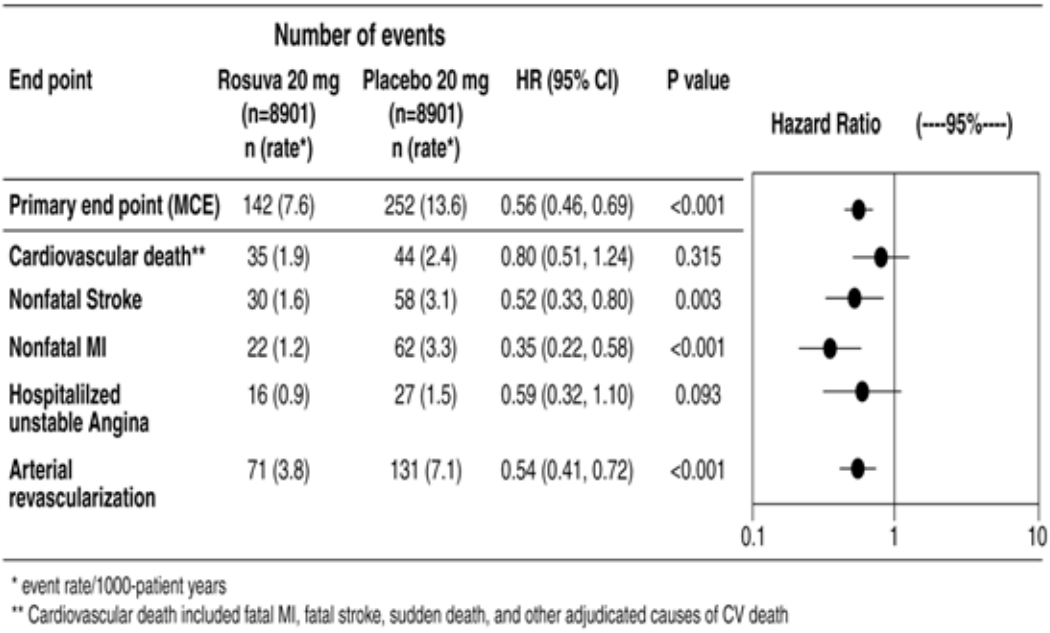
There were no statistically significant reductions in the rate of noncardiovascular death or the incidence of bone fractures in the rosuvastatin treated group compared to placebo.

Figure3. Time to occurrence of major cardiovascular events in JUPITER



The individual components of the primary end point are presented in Figure 4. Rosuvastatin significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the rosuvastatin and placebo groups for death due to cardiovascular causes or hospitalizations for unstable angina.

Figure 4. Major CV events by treatment group in JUPITER



* event rate/1000-patient years

** Cardiovascular death included fatal MI, fatal stroke, sudden death, and other adjudicated causes of CV death

In a post-hoc subgroup analysis of JUPITER subjects (n=1405; rosuvastatin = 725, placebo = 680) with a hsCRP ≥2 mg/L and no other traditional risk factors (smoking, BP ≥140/90 or taking antihypertensives, low HDL-C) other than age, after adjustment for high HDL-C, there was no significant treatment benefit with rosuvastatin treatment.

At one year, rosuvastatin increased HDL-C (1.41 vs 1.34 mmol/L) and reduced LDL-C (1.59 mmol/L vs. 2.82 mmol/L), hsCRP (2.20 vs. 3.50 mg/L), total cholesterol and serum triglyceride levels (p<0.001 for all versus placebo).

In separate studies of patients with established heart failure (CORONA study) and those with end-stage renal disease (AURORA study), rosuvastatin did not reduce cardiovascular events.

INDICATIONS

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

Prevention of Cardiovascular Events

CRESTOR is indicated for prevention of major cardiovascular events in men ≥50 years old and women ≥60 years old with no clinically evident cardiovascular disease but with at least two conventional risk factors for cardiovascular disease (hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease). CRESTOR is indicated to:

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

In patients with hypercholesterolaemia

CRESTOR is indicated for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia).

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

CONTRAINDICATIONS

Known hypersensitivity to any of the ingredients.

Patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN).

During pregnancy, in nursing mothers and in women of childbearing potential, unless they are taking adequate contraceptive precautions.

CRESTOR 40mg 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.

PRECAUTIONS

Liver effects

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.

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.

Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see Special Patient Populations, DOSAGE and ADMINISTRATION). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin (see CONTRAINDICATIONS).

In a pooled analysis of placebo-controlled trials, increases in serum transaminases to >3 times the upper limit of normal occurred in 1.1% of patients taking rosuvastatin versus 0.5% of patients treated with placebo.

Myopathy/Rhabdomyolysis

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in rosuvastatin treated patients (see ADVERSE REACTIONS). Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosuvastatin at doses up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In postmarketing experience, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose

patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥65 years), hypothyroidism, and renal insufficiency. The incidence of myopathy increased at doses of rosuvastatin above the recommended dosage range.

Consequently:

1. Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism.

2. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

3. The 40 mg dose of rosuvastatin is reserved only for those patients who are not adequately controlled at the 20 mg dose, considering their level of LDL-C and overall CV risk profile.

4. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies, protease inhibitors, or cyclosporin (see INTERACTIONS). **The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with rosuvastatin and gemfibrozil should generally be avoided (see DOSAGE AND ADMINISTRATION and INTERACTIONS).**

5. The risk of myopathy during treatment with rosuvastatin may be increased in circumstances that increase rosuvastatin drug levels (see PHARMACOLOGY: Special populations, and PRECAUTIONS: Renal insufficiency).

6. Rosuvastatin therapy should also 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).

In rosuvastatin trials there was no evidence of increased skeletal muscle effects when rosuvastatin 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 cyclosporin, nicotinic acid, azole antifungals, macrolide antibiotics and fibric acid derivatives including gemfibrozil (see ADVERSE REACTIONS, INTERACTIONS and DOSAGE AND ADMINISTRATION).

Endocrine effects

Increases in HbA1c and fasting serum glucose levels have been reported with rosuvastatin. Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if rosuvastatin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

Caution in prevention of cardiovascular events

The long term safety and efficacy of rosuvastatin treatment in patients commencing treatment with LDL-C < 3.4 mmol/L who have been assessed to be at risk of cardiovascular events have not been established. There is also uncertainty associated with the safety of long term intensive reduction of LDL-C to very low levels. Data are currently available for up to 2 years for the 20 mg dose only (see Clinical Trials – Prevention of cardiovascular events). The risk benefit balance for longer term use of rosuvastatin in this population has therefore not been established. The benefits of longer term treatment should be weighed against safety and tolerability risks (see ADVERSE EFFECTS). Clinically significant benefit in using CRESTOR in patients without clinically evident cardiovascular disease and who are assessed as having a low risk of cardiovascular events (men ≥50 and women≥60 years of age with hsCRP>2mg/L, but no other cardiovascular disease risk factor) has not been established.

Use of CRP testing in prevention of cardiovascular effects

Recent studies indicate that elevated levels of C Reactive Protein (≥2 mg/L) may be a marker for increased risk of cardiovascular disease. However, elevated CRP is not a widely established marker of cardiovascular disease and concerns remain over its validity to predict cardiovascular disease risk. The JUPITER trial was conducted in a population with elevated CRP levels however there is no comparative data of rosuvastatin in patients with normal CRP levels or in patients with elevated CRP levels compared to other traditional cardiovascular risk factors. In conjunction with cardiovascular risk assessment, testing for CRP levels may be useful to assist in determining those individuals at higher risk of cardiovascular events. In the JUPITER trial, the hsCRP test was used but this specific test is not widely available. The usCRP test is also suitable for identifying patients with elevated CRP levels and is widely available.

Diabetes Mellitus

Increases in HbA1c and serum glucose levels have been observed in patients treated with rosuvastatin. An increased frequency of diabetes mellitus has been reported with rosuvastatin in patients with risk factors for diabetes mellitus (see ADVERSE EFFECTS).

Special patient populations

Renal insufficiency

Pharmacokinetic evaluation in subjects with varying degrees of renal impairment, determined that 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 (see DOSAGE AND ADMINISTRATION).

Hepatic dysfunction

Pharmacokinetic evaluation in subjects with varying degrees of hepatic impairment determined that there was no evidence of increased exposure to rosuvastatin other than in 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 (see DOSAGE AND ADMINISTRATION).

Race

The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients (see PHARMACOKINETICS and DOSAGE AND ADMINISTRATION).

Age and Sex

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

Use in pregnancy

Category D is defined as drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Cholesterol and other products of cholesterol biosynthesis are essential components for foetal development, including synthesis of steroids and cell membranes. Since HMG-CoA reductase inhibitors decrease cholesterol synthesis, rosuvastatin is contraindicated during pregnancy. The risk of foetal injury outweighs the benefits of HMG-CoA reductase inhibitor therapy during pregnancy.

In two series of 178 and 143 cases where pregnant women took a HMG-CoA reductase inhibitor (statin) during the first trimester of pregnancy serious foetal abnormalities occurred in several cases. These included limb and neurological defects, spontaneous abortions and foetal deaths. The exact risk of injury to the foetus occurring after a pregnant woman is exposed to a HMG-CoA reductase inhibitor has not been determined. The current data do not indicate that the risk of foetal injury in women exposed to HMG-CoA reductase inhibitors

is high. If a pregnant woman is exposed to a HMG-CoA reductase inhibitor she should be informed of the possibility of foetal injury and discuss the implications with her pregnancy specialist.

Use in Lactation

The safety of rosuvastatin while breast-feeding has not been established. It is not known if rosuvastatin is excreted into human milk, but a study in rats showed that unchanged drug and metabolites are excreted in milk at concentrations up to 3 times greater than those in maternal plasma. Therefore rosuvastatin is contraindicated in breastfeeding women.

The results of animal and *in vitro* studies of rosuvastatin are summarised below.

Carcinogenicity

Oral administration of rosuvastatin for 2 years to rats and mice increased the development of benign uterine stromal polyps in both species and malignant uterine sarcomas and adenosarcomas in rats. Systemic concentrations of rosuvastatin (AUC) at the no-effect dose for benign and malignant uterine tumours in either species were lower than or similar to those expected in humans taking 40 mg/day rosuvastatin.

Genotoxicity

Rosuvastatin showed no evidence for mutagenic activity (*in vitro* assays of reverse mutation in bacterial cells and forward mutation in mammalian cells) or clastogenic activity (*in vitro* assay in mammalian cells and *in vivo* in the mouse micronucleus test).

There have been no adequate studies investigating the potential carcinogenic or genotoxic activity of the main human metabolite of rosuvastatin, N-desmethyl rosuvastatin.

Effects on fertility

In 1 of 3 monkeys treated with rosuvastatin PO at 30 mg/kg/day for 6 months degenerative changes in the testicular epithelium were seen. The no-effect dose of 10 mg/kg/day was associated with rosuvastatin plasma concentrations (AUC) similar to those expected in humans taking 40 mg rosuvastatin daily.

Rosuvastatin had no effect on male or female fertility when administered to rats at PO doses of 50 mg/kg/day (systemic rosuvastatin concentrations (AUC) 4.8-6.6 times those expected in humans). The main human metabolite of rosuvastatin, N-desmethyl rosuvastatin, has not been assessed for activity in rat fertility studies.

Animal Studies

Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC comparisons). Cataracts were seen in dogs treated for 12 weeks by

oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC comparisons).

Effects on ability to drive and operate machinery

Pharmacological testing revealed no evidence of a sedative effect of rosuvastatin. From the safety profile, rosuvastatin is not expected to adversely affect the ability to drive or operate machinery.

Interactions with other medicines

Warfarin and Other Vitamin K antagonists

Co-administration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). In patients taking vitamin K antagonists and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR has been documented, INR can be monitored at the intervals usually recommended for patients on vitamin K antagonists. If the dose of rosuvastatin is changed, the same procedure should be repeated. Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants.

Cyclosporin

Co-administration of rosuvastatin with cyclosporin resulted in no significant changes in cyclosporin plasma concentration. However, rosuvastatin steady state $AUC_{(0-t)}$ increased up to 7-fold over that seen in healthy volunteers administered the same dose. These increases are considered to be clinically significant and require special consideration in the dosing of rosuvastatin (See DOSAGE AND ADMINISTRATION).

Digoxin

Co-administration of digoxin with rosuvastatin resulted in no change to digoxin plasma concentrations.

Fenofibrate

Co-administration of fenofibrate with rosuvastatin resulted in no significant changes in plasma concentrations of rosuvastatin or fenofibrate.

Gemfibrozil

Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and $AUC_{(0-t)}$. This increase is considered to be clinically significant (see DOSAGE AND ADMINISTRATION).

Protease Inhibitors

Increased systemic exposure to rosuvastatin has been observed in subjects receiving CRESTOR with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by the use of CRESTOR in HIV patients receiving protease inhibitors and the

potential for increased rosuvastatin plasma concentrations when initiating and up-titrating CRESTOR doses in patients treated with protease inhibitors.

Antacids

Simultaneous administration of rosuvastatin and 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 rosuvastatin. The clinical relevance of this interaction has not been studied.

Cytochrome P450 enzymes

In vitro and *in vivo* data indicate that rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. This has been confirmed in studies with known cytochrome P450 3A4 inhibitors (ketoconazole, erythromycin, itraconazole).

Ketoconazole: Co-administration of ketoconazole (200 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in no change in plasma concentrations of rosuvastatin.

Erythromycin: Co-administration of erythromycin (500 mg four times daily for 7 days) with rosuvastatin (80 mg) decreased AUC and C_{max} of rosuvastatin by 20% and 31%, respectively. These reductions are not considered clinically significant.

Itraconazole: Itraconazole (200 mg twice daily for 5 days) resulted in a 39% and 28% increase in AUC of rosuvastatin after 10 mg and 80 mg dosing, respectively. These increases are not considered clinically significant.

Fluconazole: Co-administration of fluconazole (200 mg twice daily for 11 days) with rosuvastatin (80 mg) resulted in a 14% increase in AUC of rosuvastatin. This increase is not considered clinically significant.

Oral contraceptives

Co-administration of oral contraceptives (ethinyl estradiol and norgestrel) with rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively. This increase is not considered clinically significant.

Other medications

In clinical studies, rosuvastatin was co-administered with anti-hypertensive agents and anti-diabetic agents. These studies did not produce any evidence of clinically significant adverse interactions.

ADVERSE EFFECTS

Rosuvastatin is generally well tolerated. The adverse events seen with rosuvastatin are generally mild and transient. In controlled clinical trials less

than 4% of rosuvastatin treated patients were withdrawn due to adverse events. This withdrawal rate was comparable to that reported in patients receiving placebo.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Central Nervous System

Common:	dizziness

Gastrointestinal

Common:	constipation, nausea, abdominal pain
Rare:	pancreatitis

Musculoskeletal

Common:	myalgia, asthenia
Rare:	myopathy (including myositis) and rhabdomyolysis

Skin

Uncommon:	pruritus, rash, urticaria
Rare:	hypersensitivity reactions including angioedema

Miscellaneous

Common:	headache

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.

Laboratory effects

As with other HMG-CoA reductase inhibitors, a dose-related increase in liver transaminases, CK, glucose, glutamyl transpeptidase, alkaline phosphatase and bilirubin and thyroid function abnormalities have been observed in a small number of patients taking rosuvastatin. Increases in HbA1c have also been observed in patients treated with rosuvastatin. Proteinuria and microscopic haematuria has been detected by dipstick testing in the clinical trial program in a small number of patients taking rosuvastatin and other HMG-CoA reductase inhibitors at their recommended doses. The proteinuria was mostly tubular in

origin and was more frequent in patients on rosuvastatin 40 mg. It was generally transient and not associated with worsening renal function. Although the clinical significance is unknown, dose reduction should be considered in patients on rosuvastatin 40 mg with unexplained persistent proteinuria and/or haematuria.

Other effects

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

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

In the JUPITER study the safety profile for subjects taking rosuvastatin 20 mg was generally similar to that of subjects taking placebo. There were 6.6% of rosuvastatin and 6.2% of placebo subjects who discontinued study medication 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). In JUPITER, there was a significantly higher frequency of diabetes mellitus reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in rosuvastatin-treated patients compared to placebo-treated patients. The number of patients with a HbA1c >6.5% at the end of the trial was significantly higher in rosuvastatin-treated versus placebo-treated patients.

In JUPITER, increased hepatic transaminases were observed in 1.9% of rosuvastatin and 1.5% of placebo subjects and renal events were reported in 6.0% of rosuvastatin and 5.4% of placebo subjects. Confusion was reported in 0.2% of rosuvastatin and 0.1% of placebo subjects.

Adverse reactions in JUPITER reported in ≥ 2% of patients and at a rate greater than or equal to placebo were myalgia (7.6% rosuvastatin, 6.6% placebo), arthralgia (3.8% rosuvastatin, 3.2% placebo), constipation (3.3% rosuvastatin, 3.0% placebo) nausea (2.4% rosuvastatin, placebo, 2.3%) and haematuria (2.4% rosuvastatin, placebo 2.0%).

In the METEOR study, involving 981 participants treated with rosuvastatin 40 mg (n=700) or placebo (n=281) with a mean treatment duration of 1.7 years, 5.6% of subjects treated with rosuvastatin versus 2.8% of placebo-treated subjects discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: myalgia, hepatic enzyme increased, headache, and nausea.

Adverse reactions in METEOR reported in ≥ 2% of patients and at a rate greater than placebo were myalgia (12.7% rosuvastatin, 12.1% placebo), arthralgia (10.1% rosuvastatin, 7.1% placebo), headache (6.4% rosuvastatin, 5.3% placebo), dizziness (4.0% rosuvastatin, 2.8% placebo), increased CPK

(2.6% rosuvastatin, 0.7% placebo), abdominal pain (2.4% rosuvastatin, 1.8 placebo) and ALT>3x ULN (2.2% rosuvastatin, 0.7% placebo).

Post marketing Experience

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

Musculoskeletal disorders

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.

Hepatobiliary disorders

Rare	increased hepatic transaminases
Very rare	jaundice, hepatitis
Frequency unknown	hepatic failure

Nervous system disorder

Very rare	memory loss

Psychiatric disorders

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

DOSAGE AND ADMINISTRATION

Prior to initiating CRESTOR, the patient should be placed on a standard cholesterol-lowering diet. The dose should be individualised according to the goal of therapy and patient response and should take into account the potential risk for adverse reactions (see ADVERSE EFFECTS).

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

Hypercholesterolaemia

The recommended starting dose is 5 mg or 10 mg once per day both in statin naïve patients and in those switched from another HMG-CoA reductase inhibitor. The choice of starting dose should take into account the individual patient's cholesterol level and future cardiovascular risk.

A dose adjustment can be made after 4 weeks of therapy where necessary. The usual maximum dose of rosuvastatin is 20 mg once per day.

A dose of 40 mg once per day should only be considered in patients who are still at high cardiovascular risk after their response to a dose of 20 mg

once per day is assessed. This may particularly apply to patients with familial hypercholesterolaemia. 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.

Specialist supervision should be considered when the dose is titrated to 40 mg.

Prevention of cardiovascular events

A dose of 20 mg once daily has been found to reduce the risk of major cardiovascular events (see Clinical Trials – Prevention of Cardiovascular Events).

Dosage in Asian patients

Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolaemia is not adequately controlled at doses of 5, 10 or 20 mg once daily (see PHARMACOKINETICS and PRECAUTIONS).

Dosage in patients taking other drugs

Cyclosporin

In patients taking cyclosporin, CRESTOR dosage should be limited to 5 mg once daily (see INTERACTIONS).

Gemfibrozil

Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant CRESTOR and gemfibrozil (see INTERACTIONS). If CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily.

Use in children

The safety and efficacy of rosuvastatin in children has not been established. Use of this agent for the treatment of homozygous familial hypercholesterolaemia in this age group is not recommended.

Geriatrics

The usual dose range applies.

Hepatic insufficiency

The usual dose range applies for patients with mild to moderate hepatic impairment.

Patients with severe hepatic impairment should start therapy with CRESTOR 5 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 PRECAUTIONS and CONTRAINDICATIONS).

Renal insufficiency

The usual dose range applies in patients with mild to moderate renal impairment.

For patients with severe renal impairment (CL_{cr}<30 mL/min/1.73m^2) not on dialysis the dose of CRESTOR should be started at 5 mg once daily and not exceed 10 mg once daily (see PRECAUTIONS).

OVERDOSAGE

There is no specific treatment for overdose. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised. Haemodialysis is unlikely to be of benefit. Contact the Poisons Information Centre for advice on management.

PRESENTATION AND STORAGE CONDITIONS

CRESTOR 5 mg are yellow, round, film-coated, biconvex tablets impressed with "ZD4522 5" on one side. Packed in blister packs of 7 and 30 tablets.

CRESTOR 10 mg are pink, round, film-coated, biconvex tablets impressed with "ZD4522 10" on one side. Packed in blister packs of 7 and 30 tablets.

CRESTOR 20 mg are pink, round , film-coated, biconvex tablets impressed with "ZD4522 20" on one side. Packed in blister packs of 7 and 30 tablets.

CRESTOR 40 mg are pink, oval, film-coated, biconvex tablets, impressed with "ZD4522" on one side and "40" on the other side. Packed in blister packs of 30 tablets.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4).

DATE OF APPROVAL

Date of TGA approval: 31 March 2011

CRESTOR is a trade mark of the AstraZeneca group of companies

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au

Reference/Publication #