AWMSG Secretariat Assessment Report – Advice no. 1311
Rosuvastatin (Crestor®) for the prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

This assessment report is based on evidence submitted by AstraZeneca UK on 31 March 2011.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Rosuvastatin (Crestor®) for the prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors (extended licence)[1].
Restrictions to submission	The company has restricted their submission to high risk patients intolerant or contra-indicated to simvastatin[2].
Dosing	The recommended dose for this indication is 20 mg once daily. Refer to the Summary of Product Characteristics for information regarding up-titration of dose to 20 mg[1]. Rosuvastatin is an oral formulation and may be given at any time of the day, with or without food. Patients should be placed on a cholesterol-lowering diet prior to initiating treatment[1]. Rosuvastatin is not recommended for use in children under ten years old.
Marketing authorisation date	29 April 2010[2].
UK Launch date	Rosuvastatin was originally launched on the 21 March 2003 for the treatment of hypercholesterolaemia.[1]

2.0 DECISION CONTEXT

2.1 Background

Cardiovascular disease (CVD) is the single most common cause of death in Wales (33.6% of all deaths in 2009), and underlies major events such as myocardial infarction, stroke, angina, transient ischaemic attack (TIA), and peripheral arterial disease[3]. The prevalence and risk of CVD is associated with age, gender (male bias), cholesterol levels, smoking, high blood pressure, diabetes and obesity[4]. Patients with a higher risk for a first major event are those with a Framingham 10-year CVD risk of ≥ 20%[5] or a European SCORE risk ≥ 5%[6] (see Glossary).

It is recommended that simvastatin (or a drug with similar efficacy and acquisition cost) is routinely offered for the primary prevention of CVD in high risk patients[7]. The applicant

company estimates that 232,451 patients in Wales aged 40–74 years are at high-risk of a first cardiovascular (CV) event in 2011, of which 134,017 are currently treated with simvastatin[2]. Company estimates for 2011 suggest that 2,680 of these patients (2%) are intolerant to simvastatin and therefore would be eligible for rosuvastatin treatment[2,8].

Statins inhibit the rate-controlling enzyme of cholesterol production, HMG-CoA reductase, thereby reducing cholesterol levels and enhancing low-density lipoprotein (LDL) removal. Simvastatin metabolism is mediated primarily by CYP3A4/5[9], whereas metabolism is a minor clearance route for rosuvastatin[10]; statin interactions and intolerance may be associated with these underlying differences in metabolic pathways.

2.2 Comparators

The Welsh Medicines Partnership (WMP) originally requested the following comparators:

- Simvastatin
- Atorvastatin (Lipitor®)

However, following the restriction of the submission to patients intolerant of simvastatin, and in line with the All Wales Medicines Strategy Group (AWMSG) statin guidelines (under review), the company, in agreement with WMP, used pravastatin as the comparator.

2.3 Guidance and related advice

- National Institute for Health and Clinical Excellence (NICE). Statins for the prevention of cardiovascular events. Technology appraisal 94. January 2006[4].
- Scottish Intercollegiate Guidelines Network (SIGN). Risk estimation and the prevention of cardiovascular disease. Guideline 97. February 2007.[11]
- National Collaborating Centre for Primary Care and Royal College of General Practitioners. Clinical guidelines and evidence review for lipid modification: cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease. May 2008[12].
- AWMSG template for the use of statins (see section 6.3).

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

3.1 Clinical effectiveness evidence

3.1.1 Post-hoc analysis of the JUPITER trial

The company submission includes data from Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER); a placebo-controlled, randomised, double-blind, multi-centre, phase III trial[13]. The study population (n = 17,802) was randomised 1:1 and had a maximal follow-up of 60 months; it included men ≥ 50 years and women ≥ 60 years with low density lipoprotein (LDL) levels < 3.4 mM, high-sensitivity C-reactive protein (hsCRP) levels ≥ 2 mg/L, and no history of CVD. Of all potentially eligible subjects, only those that demonstrated acceptable levels of compliance (defined as taking at least 80% of all dosed placebo tablets) during a four-week run-in phase were enrolled.

The objective of JUPITER was to study the long-term effect of rosuvastatin 20 mg on major CV events. The extended licence is supported by a post-hoc analysis of JUPITER which was restricted to a high risk CVD cohort (Framingham 10-year CVD risk of ≥ 20% or a European SCORE risk ≥ 5%)[14], with median LDL levels of 2.8 mM (range: 2.5–3.1

mM)[13,14]. Of the total trial population (n = 17,802), 9% were considered at high risk using the Framingham algorithm, 52% using an extrapolated SCORE system, and 35% using a capped SCORE system[14]. As the original SCORE system is only calibrated for 45–64 year old patients and 57.5% of patients in the JUPITER trial were > 65 years, an extended SCORE model was extrapolated in order to assess the entire JUPITER population. The capped SCORE model assigns the risk of a 64-year old to all subjects older than 65 years.

The post-hoc analysis focused on the incidence of the primary composite endpoint (CV death, stroke, myocardial infarction (MI), unstable angina or arterial revascularisation), MI/stroke/CV mortality and total mortality in the high risk cohort. Analyses were performed on an intention-to-treat basis after a median follow-up of 1.8 years (maximum 5 years). For all reported CV/mortality endpoints, rates of occurrence were lower in rosuvastatin-treated patients than in those treated with placebo, but the difference between treatment groups was not statistically significant in all cases (Table 1).

Table 1. Hazard ratios (rosuvastatin versus placebo; hazard ratios < 1 favour rosuvastatin) for JUPITER endpoints in a post-hoc analysis of high-risk patients.

Endpoint: primary composite			
Model	**Hazard ratio**	**95% CI ***	**p-value**
Framingham risk > 20%	0.70	0.43–1.14	0.155
SCORE ≥ 5% (extrapolated)	0.61	0.48–0.78	<0.0001
SCORE ≥ 5% (capped)	0.56	0.42–0.74	<0.0001
Endpoint: MI/stroke/CV death			
Model	**Hazard ratio**	**95% CI**	**p-value**
Framingham risk > 20%	0.50	0.27–0.93	0.028
SCORE ≥ 5% (extrapolated)	0.57	0.43–0.78	<0.001
SCORE ≥ 5% (capped)	0.47	0.32–0.68	<0.0001
Endpoint: total mortality			
Model	**Hazard ratio**	**95% CI**	**p-value**
Framingham risk > 20%	0.73	0.46–1.17	0.193
SCORE ≥ 5% (extrapolated)	0.82	0.66–1.02	0.076
SCORE ≥ 5% (capped)	0.74	0.57–0.96	0.022
* CI: confidence interval			

3.1.2 Indirect comparison of rosuvastatin with pravastatin

In the absence of head-to-head trial data for rosuvastatin (20 mg/day) and pravastatin (40 mg/day), the company presented an adjusted indirect comparison (based on the Bucher method[15]) using placebo-controlled trials for each treatment[2]. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) was selected as the most appropriate study for comparison with the high-risk JUPITER primary prevention sub-group (n = 9,347), however only 56% (n = 3,250) of the PROSPER population were primary prevention patients. Only data from the PROSPER primary prevention subgroup were used in the adjusted indirect comparison. This sub-group was classified as high-risk using indices of smoking, hypertension and diabetes[16] and had comparable baseline characteristics to the JUPITER high-risk sub-group[17]. However, it should be noted that 66% of PROSPER subjects had an LDL level ≥ 3.41 mM[16]; by contrast the maximum LDL level for inclusion in JUPITER was 3.4 mM, and high risk subjects had median LDL levels of 2.8 mM[13,14]. The number of treatment outcomes reported for the PROSPER sub-group

was not as extensive as it was for the full patient population. Therefore, outcome approximations consisting of composite endpoints were used to provide comparability between the two trials (full details in company submission)[2]. Sensitivity analysis was also conducted, using a different approach where specific endpoints from the JUPITER trial were compared to equivalent modified outcomes from PROSPER. Results from the indirect comparison suggest that rosuvastatin treatment reduces the risk of CV events in comparison to pravastatin (Table 2).

Table 2. Adjusted indirect comparison of rosuvastatin and pravastatin. Relative risks (RR, values < 1 favours rosuvastatin) and 95% CI for the treatment of major CV events.

	Primary analysis		*Sensitivity analysis*	
	RR	**95% CI**	**RR**	**95% CI**
Unstable angina	0.68	0.45–1.05	0.52	0.22–1.21
Non-fatal MI	0.68	0.45–1.05	0.39	0.21–0.73
Non-fatal stroke	0.51	0.29–0.91	0.55	0.29–1.01
Transient ischaemic attack	0.51	0.29–0.91	0.64	0.32–1.27
Death from CV causes	0.68	0.45–1.05	1	0.54–1.85

3.1.3 Comparative safety

Rosuvastatin was generally well tolerated in the entire JUPITER population; however, diabetes mellitus was reported in 54 more cases than placebo in patients with fasting glucose 5.6–6.9 mM (270/8901 patients receiving rosuvastatin compared to 216/8901 patients receiving placebo, p = 0.01)[13]. In the high-risk post-hoc analysis, the profile of adverse events (AEs), including the occurrence of diabetes, was similar in both treatment arms[14]. The statin therapies for elevated lipid levels compared across doses to rosuvastatin (STELLAR) trial studied the safety of several statins including rosuvastatin and pravastatin over a six-week period (LDL levels 4.14–6.5 mM). AEs were mild and similar across both groups, with 2.4% and 3% of patients discontinuing treatment due to AEs, respectively[18]. Brown and colleagues performed a 52-week trial comparing rosuvastatin, pravastatin and simvastatin in hypercholesterolaemia patients; the overall incidence and types of AEs were similar in all treatments arms[19].

3.2 WMP critique

- Care is advised when interpreting the primary and sensitivity analyses of the adjusted indirect comparison between rosuvastatin and pravastatin. Assumptions were required by the company in order to compare the range of heterogeneous endpoints from both trials, but efforts were made to obtain endpoints that offered comparability.
- Rosuvastatin is licensed to prevent future cardiovascular events; however, the median follow-up time in the high-risk JUPITER sub-group was only 1.8 years (maximum of 5 years). The long-term clinical effectiveness of rosuvastatin for the extended indication remains unclear.
- Only 56% of PROSPER subjects were in the primary prevention arm[16], in contrast to 100% of the JUPITER study population[13].
- JUPITER used two extended models of the original SCORE system in order to include patients > 64 years of age. No data has been provided to validate these.

- The JUPITER trial did not include men < 50 years and women < 60 years[13,14].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis of rosuvastatin 20 mg daily compared against pravastatin 40 mg daily in patients at high risk of a first CV event (≥ 20% over ten years), and who are intolerant of (or have contraindications to) simvastatin[2]. This represents a sub-group of the licensed indication of rosuvastatin.

The analysis is based on a Markov state transition model. Patients enter the model in a CVD-free health state, from which they can proceed to one of six primary CV events (unstable angina, non-fatal MI, TIA, non-fatal stroke, CVD death or death from other causes), or remain in the CVD-free state. Upon experiencing a primary CVD event, patients may remain in post-CV event states, proceed to a secondary CV event or die. Initial and subsequent probabilities of CV events are informed by data used in a 2007 economic evaluation of statins by Ward and colleagues[20]. The relative risks of primary CV events, used to adjust the probabilities of transition between CVD-free and CVD health states, are derived using an indirect comparison of data from sub-groups of the JUPITER and PROSPER trials[14,16]. The model assumes a one-year cycle and a lifetime horizon (see Appendix 1 for further details).

4.1.2 Results

The company reports base case results of cost-utility analysis based on the weighted distribution of gender, CVD-risk levels and age, according to the eligible Welsh population (Table 3).

Table 3. Company-reported weighted average results of cost-utility analyses of rosuvastatin 20 mg versus pravastatin 40 mg for patients with a starting 10-year CVD-risk of ≥ 20%.

Base case	Rosuvastatin 20 mg	Pravastatin 40 mg	Difference
Statin costs (£)	4,203.00	419.59	3,783.41
Total cost (£)	9,249.59	7,631.18	1,618.41
Life years gained	13.379	13.107	0.272
Total QALYs	9.755	9.431	0.324
ICER (£)			4,995

ICER: incremental cost-effectiveness ratio

Sub-group analyses presented by the company included male and female populations, four age groups (45, 55, 65 and 75 years old) and three different baseline 10-year CVD risk levels (20%, 25% and 30%). Summary results of these analyses are presented in Appendix 1, Table 2. Within these groups, the total cost of treatment was lower in older men with lower CVD risk and higher in younger women with higher CVD risk. The total cost of

treatment with rosuvastatin varied from £7,480 (in males aged 75 years with 10-year CVD risk > 20%) to £15,833 (in females aged 45 years with 10-year CVD risk > 30%), and the cost of treatment with pravastatin varied from £5,937 to £15,512 in these respective groups. The total QALYs were lower in older men with higher CVD risk and higher in younger women with lower CVD risk. The total QALYs per patient treated with rosuvastatin varied from 7.247 (in males aged 75 years with 10-year CVD risk 30%) to 16.672 (in females aged 45 years with 10-year CVD risk > 20%), and per patient treated with pravastatin from 6.966 to 16.041 (in these respective groups). The cost per QALY gained with rosuvastatin versus pravastatin varied from £129 for 55 year old women with CVD risk > 30% to £7,805 in 75 year old men with CVD risk of 20%.

The probability of rosuvastatin being cost-effective at a threshold of £20,000 per QALY is reported to vary from 66% (in males aged 75 years with 10-year CVD risk 20%) to 99.4% (in females aged 45 years with 10-year CVD risk > 30%); however, these must be interpreted with some caution. In all scenarios that are modelled, the majority of simulations suggest that rosuvastatin is more effective and more costly than pravastatin. As the baseline risk of CVD increases, the proportion of simulations in which rosuvastatin is more effective and less costly than pravastatin increases, and as the baseline cohort age increases the proportion of simulations in which rosuvastatin is less effective and more costly than pravastatin increases.

One-way sensitivity analysis demonstrated that variation in relative risk of non-fatal stroke for rosuvastatin versus pravastatin, and the cost of rosuvastatin after the first year were consistently among the most significant drivers of cost-effectiveness estimates, reflecting the high costs of ongoing care following non-fatal stroke, and the substantially greater acquisition costs of rosuvastatin compared with generic pravastatin. Other consistent drivers were the relative risk reductions of non-CVD death and CVD death for rosuvastatin versus pravastatin, and the relative risk reduction for non-fatal stroke for pravastatin versus placebo. Within the parameter values explored, the ICER remained below £20,000 per QALY gained in all sensitivity analyses.

Scenario analyses were conducted to address: lack of data to inform relative risk reductions for TIA and unstable angina (assumed in the base case analysis to be the same for 40 mg pravastatin and 20 mg rosuvastatin); delay in onset of efficacy (the time by which lipid titrations are expected to be reached) of 0, 3 and 6 months for both 40 mg pravastatin and 20 mg rosuvastatin; variation in starting dose of rosuvastatin (10 mg instead of 5 mg); variation in discount rate between 0% and 6%; and different time horizons (5, 10, 20, 30, 40 and 50 years). In general, the reported ICERs differ little from the base case analysis with the exception of the time horizon of analysis, in which the ICERs for patients with 10-year CVD risk > 20% varied from £3,078 for the lifetime horizon to £74,033 for the 5-year horizon in different population groups.

4.1.3 WMP critique

Strengths of the economic evidence include:

- A systematic review was conducted to inform the model design, and to identify CVD event rates and relevant utility values for different health states.
- In the absence of direct comparative data for rosuvastatin and pravastatin, the company has made efforts to conduct indirect comparisons of available trial data.
- A wide range of sensitivity analyses was performed to assess the uncertainty in parameter values and model outputs.

Limitations of the economic evidence include:

- There is a lack of direct comparative data for rosuvastatin and pravastatin in the primary prevention of CVD. Adjusted indirect comparisons have been conducted by the company but have inherent limitations, including the fact that the mean age of the sub-groups providing relative risk estimates was around 75 years and these have been assumed applicable to patients aged as young as 45 years, and inconsistent CVD event reporting between the trials. Collectively, there are several sources of uncertainty in the relative risk estimates.
- The model assumes that patients will take rosuvastatin and/or pravastatin continuously during their lifetime. This is in contrast to the 2008 NICE lipid modification costing template, which estimated that only 50% of patients at high risk of CVD persist with statin therapy[7]. The median follow-up of the relevant sub-group of the JUPITER trial was 1.8 years[14], and mean follow-up of all patients in PROSPER was 3.2 years[16], and only patients who successfully adhered to a four-week placebo run in period were included in the trials.
- There is a lack of evidence on the long-term adverse events for rosuvastatin and pravastatin.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published economic evidence on the cost-effectiveness of rosuvastatin 20 mg compared to pravastatin 40 mg in patients at high risk of a first CV event (≥ 20% over 10 years), who are also intolerant of, or have contraindications to, simvastatin.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimates that there are currently 232,451 adults aged 40–74 in Wales who are at > 20% risk of a first CV event (calculated as a proportion of the Welsh population using data from the NICE lipid modification costing template)[2,7]. This number is expected to increase to 246,083 by 2015 on the assumption of constant prevalence and incidence rates. It is assumed that 40% of these adults are diagnosed, of which 65% receive statin therapy. It is estimated that a further 80,634 patients over the age of 75 years are currently treated, based on the assumption that 46% of adults aged 75–84 and 40% of adults aged over 85 at high risk of a first CVD are offered statin therapy. The estimated number of patients over the age of 40 who are treated with statins for the primary prevention of CVD is therefore 141,071. Assuming that 95% of these patients would receive simvastatin (reportedly based on company sought Welsh expert opinion), and that 2% of these are intolerant or contraindicated to simvastatin, the number of people eligible for treatment with rosuvastatin in Wales is expected to be 2,680 in 2011, and to increase to 2,800 in 2015. Uptake in 2011 is expected to be 50%, rising to 100% in 2015. Drug costs and treatment outcomes modelled in the economic section are assumed in the budget impact. The estimated numbers of patients treated with rosuvastatin and the associated costs over the 5-year period are shown in Table 4.

Table 4. Company-reported costs associated with rosuvastatin treatment

	2011	2012	2013	2014	2015
Number of eligible patients	2,680	2,709	2,738	2,768	2,800
Uptake (%)	50	75	100	100	100
Number of treated patients	1,340	2,032	2,738	2,768	2,800
Drug costs (£)	384,530	604,335	818,103	838,090	847,547
Administration and monitoring costs (£)	172,840	88,507	90,080	2,486	2,552
Net savings (via reduction of CVD events, £)	36,906	188,071	305,044	300,729	331,825
Overall net costs (£)	**520,464**	**504,771**	**603,139**	**539,846**	**518,274**

A scenario analysis is provided, which assumes that the proportion of patients who are intolerant of, or have contraindications to simvastatin is 10% (2% in base-case analyses). This resulted in 13,402 patients being eligible for rosuvastatin in 2011 and an overall net cost of treatment of £2,602,321. A second scenario assumed a higher diagnosis rate (60% compared to 40%) for adults aged 40–74 who are at > 20% risk of a first CV event. This resulted in an increase in the number of eligible patients in 2011 to 3,254 with a corresponding increase in cost to £633,636.

5.1.2 WMP critique of the company's budget impact estimates

The company assumes a 50% uptake rate for rosuvastatin in year one and 100% by the year 2013, which implies a high degree of switching to rosuvastatin in patients who are already established on pravastatin. The probability of these patients switching to rosuvastatin is subject to considerable uncertainty and the company has not considered a scenario assuming lower uptake rates (e.g. limited to *de novo* patients and patients who failed titration with other statins). As the budget impact analysis employs costs of drugs and CV events estimated from the economic model, the limitations of the economic model highlighted above feed through to the budget impact analysis. Coupled with the alternative scenarios that have been presented in the submission, the company's budget impact analysis therefore appears subject to considerable uncertainty.

5.2 Comparative unit costs

Table 5. Examples of statin acquisition costs in adults

Regimen	Example of daily doses	Cost per year (£)
Rosuvastatin (Crestor®) tablets	20 mg once daily	338.26
Simvastatin (non-proprietary)* tablets	20–40 mg once daily	13.13–17.16
Pravastatin (non-proprietary)* tablets	40 mg once daily	36.14
Atorvastatin (Lipitor®) tablets	10 mg once daily	169.00

Costs are based on current BNF[21] list prices.
*Generic simvastatin and pravastatin are category M products in the NHS Drug Tariff and therefore list prices are subject to potential change every three months.
This table does not imply therapeutic equivalence of drugs or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

WMP is of the opinion that rosuvastatin (Crestor®) is suitable for shared care within NHS Wales for this indication.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 Other

The AWMSG template for the use of statins, as of June 2011, is under review.

GLOSSARY

Framingham risk: a coronary prediction algorithm based on data from the Framingham heart study[22]. Framingham risk scoring is based on age, gender, smoking, blood pressure, total and high-density cholesterol, and is commonly used to assess the 10-year cardiovascular risk of an individual.

SCORE (Systematic Coronary Risk Evaluation) risk: a coronary prediction algorithm, similar to the Framingham score, but based on specific data from European clinical practice. The following risk factors are incorporated into the SCORE calculation: age, gender, smoking, systolic blood pressure, total cholesterol and geographic region[6].

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Appendix 1. Additional health economic analysis information

Table 1. Health economic analysis detail

	Base case model	Appropriate?
Comparator(s)	Pravastatin 40 mg.	WMP originally requested simvastatin and atorvastatin as the relevant comparators for rosuvastatin in its licensed indication. However, the company has limited its submission to a sub-set of the licensed population that is either intolerant of simvastatin or has contraindications to simvastatin and atorvastatin (by virtue of a potential for drug interactions due to metabolism by CYP450 3A4). The company has therefore compared rosuvastatin against pravastatin, as agreed by WMP, on the basis that pravastatin is the most commonly prescribed statin in Wales for patients who are intolerant of or have contraindications to simvastatin.
Population	Patients at high risk of a first CV event (≥ 20% over 10 years), who are also intolerant or contraindicated to simvastatin.	Represents a sub-set of the licensed indication[1]. Sensitivity analysis considers difference in gender, age (45, 55, 65 and 75 years) and starting CVD risk level (20%, 25% and 30%).
Analysis type	A cost-utility analysis of primary prevention using rosuvastatin 20 mg versus pravastatin 40 mg is presented, based on a complex Markov model with a one-year cycle. Patients in a CVD-free state may transit to unstable angina, non-fatal stroke, non-fatal MI, TIA, CVD-death or non-CVD death states. Those who progress to CVD non-death states remain in those states for one year, before moving to post-CVD event states. All patients who experience a primary CVD event are assumed to be treated with pravastatin 40 mg daily for secondary prevention. Once in post-CVD event states they may experience further CVD events or death. Stable angina and peripheral arterial disease have been excluded from the model due to a reported lack of data with which to model these. A range of efficacy assumptions have been applied (see below).	Cost-utility analysis is the preferred type of analysis. The company has based their modelling approach on those of other models of statins and ezetimibe, identified from a literature review.
Perspective	Considers direct medical costs only, from the perspective of NHS Wales.	Yes.
Time horizon	The base case analysis assumes a lifetime horizon (until person dies or reaches 100 years old).	A lifetime time horizon of analysis is appropriate.
Discount rate	For the base case analysis a 3.5% p.a. discount rate is applied to both costs and outcomes. Sensitivity analysis includes 0% and 6% discount rates.	Yes.

Table 1. Continued

	Base case model	Appropriate?
Efficacy	Due to the lack of head-to-head comparative data for rosuvastatin 20 mg with pravastatin 40 mg, the relative risks of non-fatal MI, non-fatal stroke and CVD death were derived from adjusted indirect comparisons of data from sub-groups of patients enrolled in two trials: PROSPER comparing pravastatin 40 mg daily with placebo[16], and JUPITER comparing rosuvastatin 20 mg daily versus placebo[14]. The resultant relative risks have been applied to the annual event rates for CVD events employed in the independent model developed by the NICE technology appraisal group in their review of statins for the prevention of CV events[20]. Since no clinical data were available to inform the relative risk reduction in TIAs and unstable angina, for rosuvastatin and pravastatin in the current model, it has been assumed that the relative risk for unstable angina is equal to the relative risk for non-fatal MI, and that the relative risk for TIA is equal to the relative risk for non-fatal stroke. The uncertainty around this assumption was assessed by changing the relative risk for TIA and unstable angina to 1 (i.e. no difference in risk between rosuvastatin and pravastatin). Secondary CV event rates were derived from the same NICE Health technology appraisal of statins[20], adjusted by the relative risk of events when using pravastatin for secondary prevention. It is assumed that treatment benefit is delayed by three months due to titration of therapy. The proportion of patients that died from non-CVD were estimated from the 2007–2009 interim life tables for Wales by excluding CVD-related deaths taken from the 2008 cause of death statistics for Wales.	There are a number of limitations surrounding the relative efficacy estimates. Relative risks of CVD events assumed in the model have been derived from indirect comparisons of data from primary prevention sub-groups of the JUPITER and PROSPER trial populations. Indirect comparisons have a number of inherent limitations which warrants cautious interpretation of the resulting data. Although an adjusted indirect comparison has been reported, a limitation of this approach is the fact that not all reported CV events of interest were directly comparable between the JUPITER and the PROSPER trials; the composite endpoints in JUPITER trial were defined differently to those in the PROSPER trial. In a scenario analysis the company has attempted to derive comparable endpoint estimates by adjusting the trial reported outcomes by the proportion of patients experiencing individual events among the entire trial populations; however, the applicability of these relative risk estimates to the high risk primary prevention population is also uncertain. In addition, the JUPITER-derived relative risks have not all been verified from the published sources. Sensitivity analyses have been conducted to explore some of these areas of uncertainty. The model provides estimates of cost-effectiveness for different age groups at different levels of risk, ranging from 45 years and a 10-year CVD risk of 20% up to 75 year at 30% risk. The untreated risks of CVD events are based on registry data, which provide estimates for patients aged 45 years and over, but the JUPITER trial excluded males aged less than 50 years and females aged less than 60 years, and the PROSPER trial excluded patients aged less than 70 years. The company reports the mean age of the high risk primary prevention sub-groups used in the indirect comparison to be around 75 years. It is unclear how reliable the application of the relative risks derived from the JUPITER and PROSPER trial populations to the untreated CVD risk of patients aged much younger is, and how this has been achieved.

Table 1. Continued.

	Base case model	Appropriate?
		It is assumed in the base case analysis that treatment benefit is delayed by three months due to titration of therapy. However, it should be noted that only rosuvastatin is assumed to be titrated; pravastatin treatment is initiated and maintained at 40 mg daily. Deterministic sensitivity analysis indicates that the assumed delay has little impact upon the reported ICER, but this only explores simultaneous treatment benefit delay, rather than individual treatment benefit delay. Collectively, there are several areas of uncertainty in the relative efficacy estimates. Sensitivity analyses demonstrate that the model is sensitive to variation in relative risk parameters, in particular, for non-fatal stroke, CVD death and non-CVD death.
Adverse effects	No adverse events have been modelled.	The company reports that evidence from clinical trials and post-marketing surveillance data demonstrate that rosuvastatin 20 mg and pravastatin 40 mg are both well tolerated and have a comparable safety profile. In line with other models of statin therapy, AEs are therefore not modelled. However, it should be noted that the long-term effects of rosuvastatin and pravastatin have not been investigated, and the model assumes a lack of AEs over the life-time horizon.
Utility values	Since no HR-QoL data were collected in the JUPITER and PROSPER trials, the model used utility values from published sources. The age-specific, CVD-free utilities for a cohort were adjusted using EQ-5D utility values for the UK general population. Utility values for unstable angina, MI, stroke and TIA were taken from published studies. The utility values for post-unstable angina were assumed to be the same as for post-non-fatal MI. The utilities for post-non-fatal MI and post-non-fatal stroke were assumed to be the same as for non-fatal MI and non-fatal stroke, respectively.	A number of assumptions have been made with regard to utility values for post-CV health states (post-non-fatal stroke, post-unstable angina and post-non-fatal MI and post-TIA) due to a lack of published HR-QoL data. However, the model was not very sensitive to variation in utility values within the reported 95% CIs, as shown by the deterministic sensitivity analysis.
Resource use and costs	CVD-free costs include the costs of drugs and treatment monitoring for pravastatin and rosuvastatin and the cost of titration for rosuvastatin (assumed base case starting dose 5 mg, and a starting dose of 10 mg is considered in scenario analysis). Costs associated with treating CVD health states were taken from the 2009 PSSRU report and NICE TA reports.	Appropriate sources and items of resource use appear to have been used. A 5 mg starting dose for rosuvastatin would appear to be conservative, as it necessitates two up-titrations, with associated GP costs, to achieve 20 mg daily. Several assumptions have been made with regard to costs associated with the treatment of CVD health states, which is subject to uncertainty but the model appears relatively stable to these assumed costs when explored within the range of ± 20%. Generic pravastatin 40 mg unit costs assumed in the model are aligned with the current BNF list prices[21]. As generic pravastatin is a category M product in the NHS Drug Tariff its price is subject to potential variation every three months.

Table 1. Continued.

	Base case model	Appropriate?
Uncertainty and scenario analyses	To address the cost-effectiveness of rosuvastatin 20 mg versus pravastatin 40 mg in different population groups, sub-group analyses were conducted for male and female populations, in four age groups (45, 55, 65 and 75 years old), and across three different baseline 10-year CVD risk levels (20%, 25% and 30%). Probabilistic sensitivity analysis was conducted for these sub-groups to demonstrate the probabilities of rosuvastatin being cost-effective at thresholds of £10,000, £20,000 and £30,000 per QALY gained. One-way sensitivity analyses were conducted for key model parameters to identify their impact on the ICER for all groups of patients. Scenario analyses were conducted to address: lack of data for relative risk reduction for TIA and unstable angina for primary CVD prevention; delay in onset of efficacy; variation in starting dose of rosuvastatin; variation in discount rate and time horizon.	Due to the number of structural assumptions in the model and the limited data to inform relative risk reductions for some CVD health states, the results of the cost-utility analysis are subject to a high level of uncertainty. A wide range of sensitivity and sub-group analyses have been performed, which address many areas of uncertainty. However, no sensitivity analyses were conducted with respect to the drop-out of patients, such as those failing to reach lipid titration, or discontinuation of treatment due to non-adherence.
Model Provided?	Yes	Yes.

CV: cardiovascular; CVD: cardiovascular disease; TIA: transient ischaemic attack; MI: myocardial infarction; ICER: incremental cost-effectiveness ratio; AE: adverse event; CI: confidence interval; HR QoL: Health-related quality of life; PSSRU: Personal Social Services Research Unit.

Table 2. Base case results (discounted) for male and female population, with varying starting age and baseline CVD risk levels of cohort.

Starting age (years)	ICER (cost per QALY gained) for rosuvastatin 20 mg vs. pravastatin 40 mg, by baseline, 10-year CVD-risk (£)		
	20%	25%	30%
Male			
45	4,944	3,367	2,265
55	4,695	2,901	1,651
65	5,431	3,321	1,863
75	7,805	4,796	2,746
Female			
45	3,094	1,484	390
55	3,078	1,320	129
65	3,398	1,529	263
75	4,629	2,130	461