Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Re-submission

evolocumab 140mg solution for injection in pre-filled pen (Repatha® Sureclick) or pre-filled syringe (Repatha® PFS) SMC No. (1148/16)

Amgen Limited

13 January 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

evolocumab (Repatha®) is accepted for restricted use within NHS Scotland.

Indication under review: in adults with primary hypercholesterolaemia (heterozygous familial hypercholesterolaemia and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

• in combination with a statin or statin with other lipid lowering therapies in patients unable to reach low density lipoprotein-cholesterol (LDL-C) goals with the maximum tolerated dose of a statin or,

• alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

SMC restriction: for specialist use only, when administered at a dose of 140mg every two weeks, in patients at high cardiovascular risk as follows:

- patients with heterozygous familial hypercholesterolaemia (HeFH) and LDL-C ≥5.0mmol/L for primary prevention of cardiovascular events or,
- patients with HeFH and LDL-C ≥3.5mmol/L for secondary prevention of cardiovascular events or,
- patients at high risk due to previous cardiovascular events and LDL-C ≥4.0mmol/L or
- patients with recurrent/polyvascular disease and LDL-C ≥3.5mmol/L

In phase III clinical studies, treatment with evolocumab added to optimised background lipid-lowering therapy significantly improved mean percentage change in LDL-C from baseline to week 12, versus placebo and another lipid-lowering treatment, in patients with heterozygous familial and non-familial hypercholesterolaemia and mixed dyslipidaemia.

SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost effectiveness of evolocumab and is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

SMC cannot recommend the use of evolocumab in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies as the company's submission related only to its use in primary hypercholesterolaemia (heterozygous familial hypercholesterolaemia and non-familial) and mixed dyslipidaemia.

Published 13 February 2017

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Hypercholesterolaemia and mixed dyslipidaemia

In adults with primary hypercholesterolaemia (heterozygous familial hypercholesterolaemia [HeFH] and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

• in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,

• alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.[1]

Dosing Information

Primary hypercholesterolaemia and mixed dyslipidaemia in adults

The recommended dose of evolocumab is either 140mg every two weeks or 420mg once monthly; dose regimens are clinically equivalent.

Evolocumab is administered by subcutaneous injection. The 420mg dose should be delivered using three pre-filled syringes administered consecutively within 30 minutes. Evolocumab is intended for patient self-administration after proper training. Administration of evolocumab can also be performed by another individual who has been trained to administer the product.[1]

Product availability date

August 2015

Summary of evidence on comparative efficacy

Evolocumab is a human monoclonal immunoglobulin that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) which is an enzyme that targets low density lipoprotein (LDL) receptors on the liver cell surface, resulting in their degradation. Evolocumab binds to circulating PCSK9, inhibiting destruction of the hepatic LDL receptors and thereby reducing the concentration of circulating LDL cholesterol (LDL-C).[1] Inhibition of PCSK9 by evolocumab also reduces blood levels of total cholesterol, apolipoprotein B, non-high density lipoprotein cholesterol (non-HDL-C), very low density lipoprotein cholesterol, triglycerides and lipoprotein (a), total cholesterol/HDL-C, ApoB/apolipoprotein A1, and increases HDL-C and apolipoprotein A1.[2]

The submitting company has requested that SMC considers evolocumab only when administered at a dose of 140mg every two weeks, and for specialist use only, in patients at high cardiovascular risk as follows:

- Patients with heterozygous familial hypercholesterolaemia (HeFH) and LDL-C ≥5.0mmol/L for primary prevention of cardiovascular events
- Patients with HeFH and LDL-C ≥3.5mmol/L for secondary prevention of cardiovascular events
- Patients at high risk due to previous cardiovascular events and LDL-C ≥4.0mmol/L
- Patients with recurrent/polyvascular disease and LDL-C ≥3.5mmol/L

The main evidence supporting the marketing authorisation is from four phase III, double-blind, ezetimibe- or placebo-controlled studies (LAPLACE-2, GAUSS-2, RUTHERFORD-2 [all 12 weeks] and DESCARTES [52 weeks]) that included different patient populations (heterozygous familial and non-familial hyperlipidaemia) and background lipid-lowering treatments (with or without a statin or ezetimibe or other treatments).[3-6] The primary outcomes were percentage change in LDL-C from baseline at both week 12 and at the mean of weeks 10 and 12 in the three 12 week studies, and at 52 weeks in

DESCARTES. The primary analysis in all four studies was conducted in the modified intention to treat (ITT) population, defined as all randomised patients who received at least one dose of study treatment.[3-6] Supportive evidence for longer term use from the OSLER studies was also presented.[7]

LAPLACE-2 recruited patients 18 to 80 years old with primary hypercholesterolaemia and mixed dyslipidaemia who had the following LDL-C levels at screening: ≥3.9mmol/L if not treated with a statin; ≥2.6mmol/L if treated non-intensively with a statin; ≥2.1mmol/L if treated intensively with a statin. Triglyceride level was ≤4.5mmol/L. The study had two randomisation processes, resulting in 24 treatment groups. The first randomisation determined background statin therapy (atorvastatin [10mg or 80mg], simvastatin 40mg or rosuvastatin [5mg or 40mg]). After a 4-week lipid-stabilisation period, the second randomisation assigned patients in a 2:1 ratio to receive 12 weeks treatment with subcutaneous evolocumab (140mg every two weeks or 420mg monthly or placebo) or (in atorvastatin patients only) oral ezetimibe (10mg or placebo daily).[3]

From a mean baseline LDL-C of 2.8mmol/L in patients on background statin therapy, both evolocumab dose regimens significantly reduced LDL-C at week 12 and at the mean of weeks 10 and 12, compared with ezetimibe or with placebo; $p<0.05$ for all treatment differences, (n=1,896). See Table 1 for the co-primary outcome results for the modified ITT population. At the mean of weeks 10 and 12, in the groups receiving moderate intensity statins (atorvastatin 10mg, rosuvastatin 5mg or simvastatin 40mg), LDL-C <1.8mmol/L was achieved by 86% to 94% of patients in the evolocumab groups, by 17% to 20% of patients in the ezetimibe groups and by 1.9% to 7.0% of patients in the placebo groups. At the mean of weeks 10 and 12, in the groups receiving high intensity statins (atorvastatin 80mg or rosuvastatin 40mg), LDL-C <1.8mmol/L was achieved by 92% to 94% of patients in the evolocumab groups, by 51% to 62% of patients in the ezetimibe groups and by 9.3% to 40% of patients in the placebo groups.[3] The mean percentage changes from baseline to week 24 for the other secondary outcome lipid variables were numerically or statistically significantly improved in the evolocumab groups versus the comparator groups.[2,3] Pre-specified subgroup analyses found no notable differences in treatment effect versus ezetimibe or placebo.[3]

Table 1: Co-primary outcome results of LAPLACE-2 [3]

Evolocumab treatment group (statin)	**% change in LDL-C versus placebo at week 12 and at mean of weeks 10 and 12**	**% change in LDL-C versus ezetimibe at week 12 and at mean of weeks 10 and 12**
140mg fortnightly (atorvastatin 10mg)	-71% and -70%	-40% and -38%
420mg monthly (atorvastatin 10mg)	-59% and -63%	-41% and -44%
140mg fortnightly (atorvastatin 80mg)	-76% and -75%	-47% and -45%
420mg monthly (atorvastatin 80mg)	-70% and -75%	-39% and -44%
140mg fortnightly (rosuvastatin 5mg)	-68% and -67%	**-**
420mg monthly (rosuvastatin 5mg)	-64% and -67%	**-**
140mg fortnightly (rosuvastatin 40mg)	-68% and -66%	**-**
420mg monthly (rosuvastatin 40mg)	-55% and -63%	**-**
140mg fortnightly (simvastatin 40mg)	-71% and -69%	**-**
420mg monthly (simvastatin 40mg)	-60% and -68%	**-**

$p<0.05$ for all treatment differences versus placebo or versus ezetimibe

GAUSS-2 recruited patients 18 to 80 years old with LDL-C above treatment goal and intolerance to ≥2 statins, defined as inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects. Triglyceride level was ≤4.5mmol/L. Patients were randomised in a 2:2:1:1 ratio to 12 weeks' treatment with subcutaneous evolocumab 140mg every two weeks (n=103) or evolocumab 420mg every month (n=102), both with daily oral placebo, or to daily oral ezetimibe plus subcutaneous placebo every two weeks (n=51) or every month (n=51). Lipid-lowering therapy that was stable prior to screening was used by 33% of patients; 18% were receiving a low-dose statin.[4,]

From a mean baseline LDL-C of 5.0mmol/L, both evolocumab dose regimens significantly reduced LDL-C levels at week 12 and at the mean of weeks 10 and 12, compared with ezetimibe; adjusted p<0.001, see Table 2. At the mean of weeks 10 and 12, LDL-C <1.8mmol/L was achieved by 43% (88/205) of patients in the evolocumab groups and by 1.0% (1/102) of patients in the ezetimibe groups.[4] The mean percentage changes from baseline to week 24 for the other secondary outcome lipid variables were statistically significantly improved in the evolocumab groups versus the comparator groups.[2,4]

Table 2 Co-primary outcome results of GAUSS-2[4]

Evolocumab treatment group	**Evolocumab 140mg fortnightly**	**Evolocumab 420mg monthly**
% change in LDL-C versus ezetimibe at week 12	-38%	-38%
% change in LDL-C versus ezetimibe at mean of weeks 10 and 12	-37%	-39%

RUTHERFORD-2 recruited patients 18 to 80 years old with a clinical diagnosis of HeFH who were on a stable dose of a statin with or without other lipid-modifying therapy. Patients were randomised in a 2:2:1:1 ratio to receive 12 weeks' treatment with subcutaneous evolocumab 140mg every two weeks (n=111), evolocumab 420mg every month (n=110), subcutaneous placebo every two weeks (n=55) or subcutaneous placebo every month (n=55).[5]

From a mean baseline LDL-C of 4.0mmol/L, both dose regimens of evolocumab significantly reduced LDL-C levels at week 12 and at the mean of weeks 10 and 12, compared with placebo; p<0.0001, see table 3.[2,5] At week 12, LDL-C <1.8mmol/L was achieved by 68% (71/104) of patients in the evolocumab fortnightly group and by 63% (65/103) of patients in the evolocumab monthly group, compared with one patient (1.8%) in each of the placebo groups.[5] The mean percentage changes from baseline to week 24 for the other secondary outcome lipid variables were statistically significantly improved in the evolocumab groups versus the comparator groups.[2]

Table 3: Co-primary outcome results of RUTHERFORD-2 [5]

Evolocumab treatment group	**Evolocumab 140mg fortnightly**	**Evolocumab 420mg monthly**
% change in LDL-C versus placebo at week 12	-59%	-61%
% change in LDL-C versus placebo at mean of weeks 10 and 12	-60%	-66%

DESCARTES recruited patients 18 to 75 years old with LDL-C ≥1.9mmol/L, fasting triglyceride level ≤4.5mmol/L and a range of cardiovascular risks. A run-in phase of four to twelve weeks determined eligibility and specific background lipid-lowering treatment based on screening LDL-C level, previous use of statin therapy, and cardiovascular risk (as determined by the National Cholesterol Education Program [NCEP] Adult Treatment Panel [ATP]-III guidelines). Patients were assigned to one of four lipid-lowering regimens: diet alone; diet plus atorvastatin 10mg daily; diet plus atorvastatin 80mg daily; or diet plus atorvastatin 80mg daily plus ezetimibe 10mg daily. Patients with LDL-C ≥1.9mmol/L after

run-in treatment were randomised, in a 2:1 ratio, stratified according to NCEP risk category, to receive evolocumab 420mg or placebo every four weeks for 52 weeks.[6]

From a mean baseline LDL-C of 2.6mmol/L, patients receiving evolocumab had significantly greater mean percent reduction from baseline in the LDL-C level at week 52 compared with placebo; p<0.001 for all comparisons, see table 4. The proportion of patients with LDL-C <1.8mmol/L at week 52 was 82% in the evolocumab group and 6.4% in the placebo group. Compared with placebo, treatment with evolocumab produced significant least-squares mean percent improvements from baseline, for the other secondary outcome lipid variables.[6]

Table 4: Primary outcome results of DESCARTES Study [6]

	% change* in LDL-C at week 52 versus placebo
Background lipid-lowering treatment	**Evolocumab 420mg monthly**
Total population	-57%
Diet alone (n=111)	-56%
Diet +atorvastatin 10mg (n=383)	-62%
Diet +atorvastatin 80mg (n=218)	-57%
Diet + atorvastatin 80mg+ezetimibe 10mg (n=189)	-48%

***least squares mean percent change**

OSLER and OSLER-2 are ongoing long term, open-label, randomised studies including a total of 4,465 patients (1,324 and 3,141, respectively) who had previously completed one of 12 phase II or III evolocumab studies.[7] The pooled study population was varied in terms of LDL-C concentration, statin tolerance and background lipid-lowering treatment (none, statin, statin plus ezetimibe). Published integrated data from both studies after a median of 11.1 months are available. Patients were randomised (irrespective of prior treatment allocation in the initial study) in a 2:1 ratio to receive evolocumab (140mg every two weeks or 420mg monthly) plus standard therapy or standard therapy alone. The addition of evolocumab to standard therapy was associated with a mean reduction in LDL-C of 61% from the parent study baseline (p<0.001). Patients who had received evolocumab in the parent study had sustained LDL-C reduction up to 48 weeks. A pre-specified exploratory analysis of cardiovascular events was conducted. These included death, myocardial infarction, unstable angina requiring hospitalisation, coronary revascularisation, stroke, transient ischemic attack, and hospitalisation for heart failure. Events were reported in 29 out of 2,976 patients in the evolocumab group (Kaplan–Meier 1-year event rate, 0.95%) and in 31 out of 1,489 patients in the standard-therapy group (Kaplan–Meier 1-year event rate, 2.18%); hazard ratio in the evolocumab group, 0.47; (95% confidence interval [CI]: 0.28 to 0.78; p=0.003).[7]

Summary of evidence on comparative safety

The clinical study programme did not reveal any specific concerns about the safety profile of evolocumab, which was generally comparable to that of placebo or ezetimibe. The Summary of Product Characteristics (SPC) notes that the most commonly reported adverse drug reactions during the primary hypercholesterolaemia and mixed dyslipidaemia pivotal trials, at the recommended doses, were nasopharyngitis (4.8%), upper respiratory tract infection (3.2%), back pain (3.1%), arthralgia (2.2%), influenza (2.3%), and nausea (2.1%).

Summary of clinical effectiveness issues

There is clinical evidence that HMG-Co A reductase inhibitors (statins) reduce serum levels of LDL-C and reduce the risk of cardiovascular morbidity and mortality, with emerging evidence that ezetimibe also does this, to a lesser extent.[2] Statins are the first-line treatment for primary hypercholesterolaemia and mixed dyslipidaemia. Evolocumab is one of two medicines with a novel mode of lipid-lowering action (inhibition of the PCSK9 enzyme); the other is alirocumab, which has been accepted for restricted use by SMC (advice number 1147/16).

The submitting company has requested that SMC reviews evolocumab in a subset of the licensed indication (see efficacy section for details).

Clinical experts consulted by SMC considered that evolocumab is a therapeutic advancement as its mechanism of action differs from that of established therapies. Experts considered there to be an unmet need in patients with HeFH, and also in patients with non-familial hypercholesterolaemia with high cardiovascular risk, who have failed to reach lipid targets despite compliance with optimal treatment. Experts noted that patients with true statin intolerance have a particular unmet need.

The clinical studies demonstrated that, in patients with heterozygous familial and non-familial hypercholesterolaemia and mixed dyslipidaemia, treatment with evolocumab added to optimised background lipid-lowering therapy demonstrated statistically and clinically significant relative reductions in LDL-C levels (approximately 60 to 70% versus placebo, and nearly 40% versus ezetimibe).[2] Mean baseline LDL-C levels were 2.8mmol/L, 5.0mmol/L, 4.0mmol/L and 2.6mmol/L in the LAPLACE-2, GAUSS-2, RUTHERFORD-2 and DESCARTES studies, respectively. Patients included were at high cardiovascular risk and some were statin-intolerant.[3-6] Evolocumab has also been shown to improve the profile of other lipid parameters.[2] The addition of evolocumab, compared with placebo, to maximally tolerated statin treatment plus ezetimibe in a subgroup of 189 patients in the DESCARTES study reduced LDL-C at week 52 by 48%.[6]

The main limitation of the evidence is that LDL-C reduction is not a direct health outcome and there is a lack of evidence concerning clinical outcomes such as cardiovascular morbidity and mortality. Although LDL-C reduction is considered to be a surrogate marker for cardiovascular risk reduction, the main evidence is with statin therapy and there is as yet no robust evidence for evolocumab.[2] During the pooled long-term, randomised OSLER extension studies, a pre-specified exploratory analysis found that treatment with evolocumab significantly reduced the rate of cardiovascular events compared with standard therapy. However, the open label design of these studies was cited as a concern by the authors of the published report who noted that the most frequently reported cardiovascular event was coronary revascularisation and that a decision to conduct this procedure could potentially have been influenced by awareness of the patient's treatment. Additional limitations of this analysis were the small number of patients who had experienced cardiovascular events and the exclusion from the studies of patients who had previously discontinued study treatment due to adverse events in the parent study.[7] Other limitations include that three of the pivotal studies lasted only 12 weeks and long-term evidence is limited. All four pivotal studies excluded patients with Type 1 diabetes, or newly diagnosed or poorly controlled Type 2 diabetes. There was under-representation of patients over 75 years; evidence to date suggests similar efficacy to the wider adult population, but this has not been confirmed.[2] LAPLACE-2 enrolled some patients who were not on a maximum tolerated statin dose and the DESCARTES and OSLER studies included some patients without background lipid-lowering therapy; these patients would not be eligible to receive evolocumab in practice.[6,7]

As SMC has accepted alirocumab for restricted use in NHS Scotland, the submitting company presented a Bayesian network meta-analysis (NMA) comparing evolocumab subcutaneously 140mg every two weeks with alirocumab 75mg subcutaneously every two weeks (increasing to 150mg as per study protocol), alirocumab 150mg subcutaneously every two weeks, ezetimibe orally 10mg daily and placebo. Common comparators were pooled using random effects inverse-variance meta-analysis and effect sizes presented as forest plots (mean difference, 95% CI). The efficacy outcome measured was mean percentage change in LDL-C from baseline. If the mean of week 10 and 12 was available this was used, otherwise the week 12 result was used. For one study only the week 24 result was available. The base case NMA included 14 studies. The company concluded the NMA showed that evolocumab 140mg every two weeks compared favourably with alirocumab. Several limitations of the NMA were identified. The NMA population was broader than the proposed positioning; however, subgroup analyses by baseline characteristics and concomitant treatments suggest consistency of treatment effect. The inclusion of three Japanese studies and a single study with a higher inclusion criterion for LDL-C (>4.1mmol/L) than the rest of the studies, led to considerable statistical heterogeneity; sensitivity analyses excluding these studies supported the primary analysis. There were differences in background treatment: some patients were required to be on maximally tolerated statin dose and others were on a stable statin dose. This may have biased against alirocumab. There were differences in how the primary outcomes were reported; however, this seems unlikely to have introduced significant bias. Only LDL-C and no other lipid variables were included in the NMA. The comparison of safety data presented was naive. Despite the identified limitations, it is reasonable to conclude that evolocumab is at least at clinically effective as alirocumab with a similar safety profile.

The submitting company anticipates that evolocumab would be initiated and managed in secondary care in specialist lipid clinics. Training on administration of the injections would be required as current treatments for hypercholesterolaemia are administered orally.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis (CMA) comparing evolocumab, (administered at a dose of 140mg every 2 weeks) with alirocumab, with statins and/or ezetimibe in both arms, for use in the following patient groups:

- patients with HeFH and LDL-C ≥ 5.0 mmol/L for primary prevention of CV events or
- patients with HeFH and LDL-C ≥ 3.5 mmol/L for secondary prevention of CV events or
- patients at high risk due to previous CV events and LDL-C ≥ 4.0 mmol/L or
- patients with recurrent/polyvascular disease and LDL-C ≥ 3.5 mmol/L.

The above patient groups are a subset of the whole licensed indication. As an additional analysis, the company provided cost-utility analyses (CUAs) comparing evolocumab as an add-on to statins and/or ezetimibe in the same patient groups, additionally separating the non-FH groups into statin tolerant and intolerant.

The company considered that the appropriate comparator was alirocumab, but also acknowledged that ‘no treatment’ could also be the appropriate comparator (where evolocumab would be an add-on to established treatments) and so presented analyses for both scenarios.

The clinical data source underpinning the CMA was the NMA described above which found that evolocumab is at least as effective as alirocumab, and similar safety was established by a naive comparison and reference to a published meta-analysis. The model assumed equal efficacy and safety which, given that the two medicines have the same dosage regimen, meant identical health effects and costs other than the medicine cost itself. Therefore, the CMA consisted of comparing the prices of the two medicines. A PAS is in place for alirocumab and this was included in the analysis using an estimate of the PAS price.

The CUA was a lifetime Markov model including acute and long-term states for each cardiovascular event. The model was used for each patient group, though variables such as baseline risk differed by group. The CUA model used data on the effects of evolocumab on LDL-C levels and used this to estimate the effect of evolocumab on rates of various cardiovascular events, compared with a baseline obtained from a UK data registry. Data on the efficacy of evolocumab came from the LAPLACE-2 study, the GAUSS-2 study, and the RUTHERFORD-2 study, each of which compared evolocumab against either ezetimibe or placebo in at least one of the patient groups being considered.

The CUA derived utility scores from a systematic review of quality of life literature. These values were similar to those used in a NICE appraisal of alirocumab. Medicine costs were taken from NHS Drug Tariff and Scottish Drug Tariff, and a weighted average cost for statins was used.

A Patient Access Scheme (PAS) for evolocumab was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price of evolocumab. With the PAS, the results of the CMA model (with alirocumab as the comparator) report that evolocumab is a cost-effective treatment option. Given the simplicity of the model, no sensitivity analysis was conducted.

The results of the CUA model (where evolocumab would be an add-on to ezetimibe and/or statins) are as shown in table 5 below. A weighted average covering all indications under consideration was also presented: with the PAS, the incremental cost-effectiveness ratio (ICER) is £17,684 per quality adjusted life-year (QALY).

Table 5: Results of the CUA

Patient population	**Intervention** / **Comparator**	**Incremental costs with PAS**	**Incremental QALYs**	**ICER with PAS**
HeFH, primary prevention (LDL-C ≥5.0mmol/L)	evolocumab + statins + ezetimibe	£27,613	1.27	£21,726
	statins + ezetimibe			
HeFH, secondary prevention (LDL-C ≥3.5mmol/L)	evolocumab + statins + ezetimibe	£18,824	1.00	£18,860
	statins + ezetimibe			
High risk CVD (LDL-C ≥4.0mmol/L)	evolocumab + statins	£14,381	0.76	£18,847
	statins			
Recurrent/polyvascular disease (LDL-C ≥3.5mmol/L)	evolocumab + statins	£13,457	0.79	£17,046
	statins			

Statin intolerant - High risk CVD (LDL-C ≥4.0mmol/L)	evolocumab + ezetimibe	£14,829	0.93	£15,955
	ezetimibe			
Statin intolerant – recurrent/polyvascular disease (LDL-C ≥3.5mmol/L)	evolocumab + ezetimibe	£13,466	1.01	£13,377
	Ezetimibe			

Sensitivity analysis was performed on all six subgroup models. The models were frequently sensitive around the assumptions that translated lowering of LDL-C into lowering of risk of various events. Variation in the assumed treatment duration also commonly led to a large effect on the ICER. However, under all but one of the sensitivity scenarios in all subgroups, the with-PAS ICERs were under £25,000/QALY. One multivariate analysis was provided in which all rates converting lowering of LDL-C to risk reduction in various events were varied together. In this scenario, with-PAS subgroup ICERs could go up to £24k-£37k/QALY.

The main weaknesses and uncertainties with the economic analysis are as follows:

- The company considered that the most likely comparator is alirocumab. As alirocumab has only recently been accepted for use by SMC in NHS Scotland, it may not yet be established practice; therefore, alirocumab and no treatment (i.e. add-on to established treatments) could both be considered relevant comparators. The company has provided economic analyses which cover both scenarios.
- The estimation of long run CV outcomes was based on short 12 week follow-up using a single surrogate marker of LDL-C reduction. Whilst a relationship has been established between LDL-C change and CVD outcomes, this has been in the context of statin therapy, and there is an inherent uncertainty in the estimation of future CV events associated with such short term reductions in LDL-C.
- The company based the treatment effect for LDL-C reduction on the endpoint of the mean of week 10/12 change from baseline. A co-primary endpoint in the clinical studies was week 12 change.
- The ICERs for the model of evolocumab as an add-on to established treatment were lower than those presented in the original submission. The company explained that this came mainly from an amended method of factoring LDL-C levels in the model, and that this method was the same as the one used in the alirocumab submission previously accepted by SMC.

Despite these weaknesses and uncertainties, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

The Joint British Societies produced consensus recommendations for the prevention of cardiovascular disease in 2014 (JBS3).[8] Cholesterol lowering therapy is recommended in the following individuals:

- established cardiovascular disease (CVD)
- high risk of CVD: diabetes age >40 years, chronic kidney disease stages 3 to 5, or familial hypercholesterolaemia

- high 10-year CVD risk (threshold to be defined by National Institute of Health and Care Excellence [NICE] guidance)
- high lifetime CVD risk (JBS3 calculator) where lifestyle changes are insufficient

In all patients with familial hypercholesterolaemia, lifetime lowering of LDL-C is recommended to reduce CVD outcomes. Familial combined hyperlipidaemia cases should be managed by a lipid specialist.

Statins are recommended as a highly effective treatment and, with benefits evident at <2mmol/L LDL-C levels, intensive therapy is encouraged. JBS3 advises a 'lower is better' approach, supporting strategies to achieve non-HDL-C of <2.5mmol/L (equivalent to LDL of <1.8mmol/L) in those at high risk of cardiovascular events. Combination therapy with the addition of a bile sequestrant, ezetimibe or possibly nicotinic acid to statin therapy are suggested when increased statin dose is not tolerated. However, specialist lipid advice should be sought if there is a failure to establish statin therapy in patients with established CVD or with suspected familial hypercholesterolaemia, or if there is a rise in creatine kinase >5× upper limit of normal on a statin.

The JBS3 guideline refers to the development of PCSK9 inhibitors and the potential to produce benefits in patients with elevated LDL-C despite statin therapy and those with familial hypercholesterolaemia.[8]

In 2014, the National Institute for Health and Care Excellence (NICE) published clinical guideline (CG181); Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (CVD).[9] NICE recommends atorvastatin 20mg daily for primary prevention of CVD in the following groups:

- ≥10% ten year risk of developing CVD (QRISK2 tool)
- Type I diabetes who are over the age of 40, have had diabetes >10 years, have established neuropathy or have other CVD risk factors
- Type II diabetes who have ≥10% ten year risk of developing CVD
- Chronic kidney disease

Atorvastatin 20mg may also be considered in people ≥ 85 years old (possible reduction in non-fatal myocardial infarction) and in all adults with type I diabetes.

In patients with established CVD, including acute coronary syndrome, statins are recommended at the maximum tolerable dose (atorvastatin 80mg).

Specialist advice should be sought when patients with a high risk of CVD (primary or secondary) are intolerant to three different statins. Fibrates, nicotinic acid, bile sequestrants and omega-3 fatty compounds are not recommended as monotherapy or in combination with a statin for people being treated for primary or secondary CVD, those with chronic kidney disease or Type I or Type II diabetes.

In people with primary (heterozygous-familial and non-familial) hypercholesterolaemia, ezetimibe can be taken as monotherapy when statins are contraindicated or not tolerated, or in combination with a statin when cholesterol target levels have not been met despite increased statin dose or where increased statin dose is intolerable.[9]

NICE Clinical Guideline CG71 familial hypercholesterolaemia: identification and management was updated in July 2016.[10] The guideline recommends life-long lipid lowering treatment, initial treatment for all adults with statins. The maximum licensed/tolerated dose of statin should be considered to achieve a >50% reduction in LDL-C concentration from baseline. Ezetimibe monotherapy is recommended for patients with HeFH who are intolerant or have a contraindication to statins. Ezetimibe, co-administered with initial statin therapy, is recommended as an option for the treatment of adults with HeFH who have been initiated on statin therapy when serum LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance

to the initial statin therapy, and consideration is being given to changing from initial statin therapy to an alternative statin.
NICE recommends that adults with familial hypercholesterolaemia should be offered a referral to a specialist when:

- the recommended reduction in LDL-C concentration of greater than 50% from baseline has not been achieved despite maximum tolerated dose of a high intensity statin and ezetimibe or
- the patient has been assessed as being at very high risk of a coronary event (established coronary heart disease, family history or premature coronary heart disease or two or more other cardiovascular risk factors) or
- statin or ezetimibe therapy is contraindicated or not tolerated; (in this case treatment with a bile acid sequestrant, nicotinic acid or a fibrate may be considered).[10]

The Scottish Intercollegiate Guidelines Network (SIGN) is currently in the process of updating its cardiovascular disease guidelines.[11] The 2007 SIGN publication on risk estimation and the prevention of cardiovascular disease includes recommendations on lipid lowering. Simvastatin 40mg/day is recommended as primary prevention in all adults >40 years old who have a 10 year CV first event risk of ≥20% (ASSIGN risk tool). All adults with established atherosclerotic cardiovascular disease should be considered for intensive statin therapy. Patients with familial hypercholesterolaemia based on clinical or genetic evidence should be considered for aggressive statin therapy, irrespective of their calculated cardiovascular risk. An anion exchange resin or ezetimibe in combination with a statin is recommended when target cholesterol level has not been met and a higher dose of statin cannot be tolerated. No recommendation is made for monotherapy although the evidence statement notes treatment with a resin or ezetimibe may be useful when statins are not tolerated.[11]

The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) jointly published an updated guideline in 2016 on the management of dyslipidaemia. In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.[12]

Additional information: comparators

Evolocumab is likely to be added to established lipid-lowering treatments including statins and ezetimibe, rather than displacing current therapy. Alirocumab is another PCSK9 inhibitor that has been accepted for restricted use by SMC.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Evolocumab	**140mg subcutaneously every two weeks or 420mg subcutaneously every month**	**4,423 (fortnightly regimen) or 6,124 (monthly regimen)**
Alirocumab	75mg to 150mg subcutaneously every two weeks	4,368
Ezetimibe	10mg orally daily	342

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 20 October 2016. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 176 patients with HeFH and 1,240 patients with non-FH eligible for treatment with evolocumab in each year. This was estimated to rise over time in line with population growth. The estimated uptake rate was 10% in year 1 and 50% in year 5. This resulted in 18 HeFH patients and 124 non-FH patients estimated to receive treatment in year 1, rising to 90 HeFH patients and 633 non-FH patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 December 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice

Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.