NICE National Institute for Health and Care Excellence

NICE guidance

Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Evolocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:

- The dosage is 140 mg every 2 weeks.
- Low-density lipoprotein concentrations are persistently above the thresholds specified in table 1 despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached, or further titration is limited by intolerance (as defined in NICE's guideline on familial hypercholesterolaemia).
- The company provides evolocumab with the discount agreed in the patient access scheme.

Table 1 Low-density lipoprotein cholesterol concentrations above which evolocumab is recommended

	Without CVD	**With CVD**	
		High risk of CVD[1]	**Very high risk of CVD**[2]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre	

[1] High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.

[2] Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

1.2 This guidance is not intended to affect the position of patients whose treatment with evolocumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Evolocumab (Repatha, Amgen) is a monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme involved in down-regulation of low-density lipoprotein receptors. This increases receptor density and lowers low-density lipoprotein cholesterol (LDL-C). Evolocumab has a marketing authorisation in the UK for treating adults with primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin, or a statin plus 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 cannot tolerate or cannot be given statins.

Evolocumab is given by subcutaneous injection. The recommended dose in the summary of product characteristics is either 140 mg every 2 weeks or 420 mg once monthly.

2.2 Commonly reported adverse reactions with evolocumab include nasopharyngitis, upper respiratory tract infection, influenza, back pain, arthralgia (joint pain) and nausea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Evolocumab costs £170.10 for a 140-mg prefilled pen or syringe (excluding VAT; MIMS, March–May 2016). The annual cost of treatment per patient is about £4,422.60 for 140 mg every 2 weeks, and £6,123.60 for 420 mg monthly. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of evolocumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 7) considered evidence from a number of sources. See the committee papers for full details of the evidence.

Clinical effectiveness

3.1 The company did a systematic literature review, and identified 4 randomised controlled trials (RCTs) evaluating the efficacy and safety of evolocumab for primary hypercholesterolaemia or mixed dyslipidaemia: LAPLACE-2; RUTHERFORD-2; GAUSS-2; and DESCARTES. Of these, LAPLACE-2 and GAUSS-2 gave head-to-head evidence for evolocumab compared with ezetimibe, whereas RUTHERFORD-2 and DESCARTES compared evolocumab with placebo only. GAUSS-2 and RUTHERFORD-2 only studied evolocumab in subgroups specified in the scope; people who cannot tolerate statins (defined as people who had tried at least 2 statins, but could not tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects), and those with heterozygous-familial hypercholesterolaemia respectively.

3.2 All the trials were phase III, double-blind RCTs, including a combined total of 3500 patients who were included only if they had an low-density lipoprotein cholesterol (LDL-C) concentration equal to or greater than a certain concentration; this was 2.1 mmol/litre in LAPLACE-2, 2.6 mmol/litre in RUTHERFORD-2 and GAUSS-2, and 1.9 mmol/litre in DESCARTES. All patients had background therapy during the trials: moderate- to high-intensity statin therapy (LAPLACE-2), a statin with or without other lipid-lowering therapies (RUTHERFORD-2), non-ezetimibe lipid-lowering therapy (GAUSS-2), or diet alone or in combination with atorvastatin, ezetimibe, or both (DESCARTES). All trials except DESCARTES lasted for 12 weeks; DESCARTES was a long-term study that lasted for 52 weeks.

3.3 All the trials used a 2:1 randomisation to the evolocumab or control treatment arms. They gave evidence on the following treatment comparisons:

- LAPLACE-2 (n=1,899): eligible patients were randomised to 1 of 5 open-label statin cohorts; atorvastatin 10 mg or 80 mg, rosuvastatin 5 mg or 40 mg, or simvastatin 40 mg.
  - Within the atorvastatin cohorts: evolocumab 140 mg every 2 weeks or 420 mg monthly in combination with placebo was compared with placebo every 2 weeks or monthly in combination with ezetimibe or placebo respectively.
  - Within the rosuvastatin and simvastatin cohorts: evolocumab 140 mg 2 weekly or 420 mg monthly alone was compared with placebo every 2 weeks or monthly alone respectively.
- RUTHERFORD-2 (n=331): evolocumab 140 mg every 2 weeks or 420 mg monthly was compared with placebo every 2 weeks or monthly respectively.
- GAUSS-2 (n=307): evolocumab 140 mg every 2 weeks or 420 mg monthly in combination with placebo was compared with placebo every 2 weeks or monthly in combination with ezetimibe respectively.
- DESCARTES (n=905): evolocumab 420 mg monthly was compared with placebo monthly.

3.4 The co-primary end points in LAPLACE-2, RUTHERFORD-2 and GAUSS-2 were the percent change from baseline in LDL-C level at week 12, and the mean percent change from baseline in LDL-C level at weeks 10 and 12. In DESCARTES, the primary end point was the percent change from baseline in LDL-C level at week 52. Other lipid parameters (including triglycerides and high-density lipoprotein cholesterol implicated in mixed dyslipidaemia) were measured in the trials as secondary end points, but the company's submission did not focus on them. None of the trials collected data on health-related quality of life.

Evidence review group's comments

3.5 The ERG considered the trials identified for evolocumab to be relevant, good-quality RCTs. It noted that the patient and disease characteristics at baseline were generally well-balanced across treatment arms. However, all 4 trials excluded patients with type 1 diabetes, or newly diagnosed or poorly controlled type 2 diabetes. The ERG questioned

whether this could affect the generalisability of the trials because, in clinical practice, these patients are likely to present with co-morbid hypercholesterolaemia or mixed dyslipidaemia.

3.6 The ERG pointed out that the change in LDL-C concentration is clinically important if it can be used as a surrogate for cardiovascular disease (CVD). Although the effect of statins on cardiovascular (CV) events is established, that of evolocumab has not been robustly shown in purposely designed clinical trials. The ERG noted that the ongoing FOURIER RCT will test whether LDL-C is a valid surrogate for CV outcomes for evolocumab, which it considered to be a key area of uncertainty in the current evidence.

Clinical trial results

3.7 All efficacy and safety analyses were based on the modified intention-to-treat populations, that is, all patients who had at least 1 dose of study treatment. The results for the primary end points are shown in table 2 and table 3.

Table 2 Difference in percent change from baseline in LDL-C concentration at week 12 (week 52 in DESCARTES)

Evolocumab dosage	Cohort	Versus placebo (%, 95% CI)	Versus ezetimibe (%, 95% CI)
LAPLACE-2			
140 mg every 2 weeks	Atorvastatin 10 mg	−74* (−81 to −68)	−44* (−50 to −37)
	Atorvastatin 80 mg	−80* (−91 to −68)	−50* (−61 to −39)
	Any atorvastatin	N/A	−47* (−53 to −41)[1]
	Rosuvastatin 5 mg	−71* (−78 to −64)	N/A

	Rosuvastatin 40 mg	−71* (−80 to −63)	N/A
	Simvastatin 40 mg	−74* (−80 to −67)	N/A
	Any statin	−74* (−77 to −70)[1]	N/A
420 mg monthly	Atorvastatin 10 mg	−61* (−68 to −54)	−43* (−50 to −36)
	Atorvastatin 80 mg	−74* (−84 to −65)	−41* (−51 to −32)
	Any atorvastatin	N/A	−43* (−48 to −37)[1]
	Rosuvastatin 5 mg	−66* (−73 to −59)	N/A
	Rosuvastatin 40 mg	−59* (−70 to −48)	N/A
	Simvastatin 40 mg	−62* (−71 to −52)	N/A
	Any statin	−65* (−69 to −61)[1]	N/A
GAUSS-2			
140 mg every 2 weeks	N/A	N/A	−39* (−45 to −34)
420 mg monthly	N/A	N/A	−38* (−43 to −33)
RUTHERFORD-2			
140 mg every 2 weeks	N/A	−61* (−67 to −55)	N/A
420 mg monthly	N/A	−60* (−68 to −53)	N/A
DESCARTES			
420 mg monthly	N/A	−59* (−64 to −55)	N/A
*p<0.001			
[1] Using a fixed-effects model			

Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; N/A, not applicable.

Table 3 Difference in mean percent change from baseline in LDL-C concentration at weeks 10 and 12

Evolocumab dosage	Cohort	Versus placebo (%, 95% CI)	Versus ezetimibe (%, 95% CI)
LAPLACE-2			
140 mg every 2 weeks	Atorvastatin 10 mg	−73* (−78 to −67)	−41* (−47 to −35)
	Atorvastatin 80 mg	−78* (−88 to −68)	−48* (−58 to −38)
	Any atorvastatin	N/A	−45* (−50 to −39)[1]
	Rosuvastatin 5 mg	−70* (−76 to −63)	N/A
	Rosuvastatin 40 mg	−69* (−77 to −62)	N/A
	Simvastatin 40 mg	−73* (−78 to −67)	N/A
	Any statin	−72* (−75 to −69)[1]	N/A
420 mg monthly	Atorvastatin 10 mg	−65* (−71 to −58)	−45* (−52 to −39)
	Atorvastatin 80 mg	−78* (−86 to −70)	−46* (−54 to −38)
	Any atorvastatin	N/A	−46* (−51 to −41)[1]
	Rosuvastatin 5 mg	−69* (−75 to −62)	N/A
	Rosuvastatin 40 mg	−67* (−76 to −58)	N/A
	Simvastatin 40 mg	−70* (−79 to −61)	N/A
	Any statin	−70* (−73 to −66)[1]	N/A
GAUSS-2			
140 mg every 2 weeks	N/A	N/A	−38* (−44 to −33)
420 mg monthly	N/A	N/A	−39* (−44 to −35)
RUTHERFORD-2			

140 mg every 2 weeks	N/A	−61* (−67 to −55)	N/A
420 mg monthly	N/A	−66* (−72 to −61)	N/A
*p<0.001			
[1] Using a fixed-effects model			
Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; N/A, not applicable.			

3.8 The company presented subgroup analyses. It stated that in all of these evolocumab, compared with placebo or ezetimibe, was consistently effective in lowering LDL-C, with no notable differences between subgroups.

3.9 The company presented interim results from 2 ongoing, long-term, extension studies, OSLER and OSLER-2, which compared evolocumab plus standard of care (defined according to local guidelines) with standard of care alone. Eligible patients were those who completed treatment in a 'parent' study, including the RCTs identified for evolocumab. The company stated that OSLER and OSLER-2 showed that the effect of evolocumab continued for over 2 years. It also presented a pre-specified exploratory analysis, which combined data from OSLER and OSLER-2 (n=4465) on adjudicated CV events including death, myocardial infarction, unstable angina, coronary revascularisation, stroke, transient ischaemic attack, and heart failure. The rate of CV events at 1 year was 0.95% and 2.18% among patients randomised to evolocumab or standard of care respectively (hazard ratio 0.47, 95% CI 0.28 to 0.78; p=0.003).

3.10 TAUSSIG is an ongoing non-randomised, non-controlled, 5-year extension study of evolocumab for severe familial hypercholesterolaemia. Among 142 patients with severe heterozygous-familial hypercholesterolaemia, the percent reduction from baseline in LDL-C level at week 36 was 50.5%, with reductions ranging from 42.0% to 54.3% at earlier time points.

ERG's comments

3.11 The ERG noted that evolocumab, at both licensed doses, effectively reduced LDL-C concentration from baseline compared with ezetimibe or placebo ($p<0.001$), with consistent results seen across all subgroups, including patients who can or cannot tolerate statins.

3.12 The ERG noted that, although none of the RCTs studied evolocumab in combination with ezetimibe, RUTHERFORD-2 and DESCARTES included a subgroup in which patients had ezetimibe as background therapy with (DESCARTES) or without (RUTHERFORD-2) high-dose atorvastatin. The ERG reported the results for these subgroups:

- DESCARTES: The difference in percent change from baseline in LDL-C level at week 52 between evolocumab 420 mg monthly plus ezetimibe plus statin and placebo plus ezetimibe plus statin was −49.3% (95% CI −59.5 to −39.1; $p<0.001$) in favour of evolocumab.
- RUTHERFORD-2: At week 12, the percent change from baseline in LDL-C level favoured evolocumab 140 mg every 2 weeks plus ezetimibe compared with placebo plus ezetimibe, with a difference of −58.4% (95% CI −67.1 to −49.7; $p<0.001$). Evolocumab monthly plus ezetimibe was also more effective than placebo plus ezetimibe, with a difference of −60.9% (95% CI −71.0 to −50.8; $p<0.001$).

3.13 The ERG considered that the evidence from OSLER and OSLER-2 was arguably not relevant to this appraisal. This was because the studies included populations from trials that were themselves excluded from the systematic review of clinical evidence.

Adverse effects of treatment

3.14 In addition to the data on adverse effects from the individual studies for evolocumab, the company presented integrated analyses of safety data from 6,026 patients with primary hypercholesterolaemia or mixed dyslipidaemia who had any dose of evolocumab. The key results of these analyses are summarised below:

- Overall, evolocumab had a safety profile similar to the control treatment

(placebo or ezetimibe) arms, with the incidence of adverse events being 51.1% compared with 49.6%. Most adverse events were mildly to moderately severe.

- Serious adverse events occurred in 2.8% and 2.1% of patients who had evolocumab or any control treatment (placebo or ezetimibe) respectively.
- Of patients who had evolocumab, 1.9% stopped treatment because of an adverse event compared with 2.3% of those who had placebo or ezetimibe.
- The most common adverse events for evolocumab compared with placebo or ezetimibe were: nasopharyngitis (5.9% compared with 4.8%), upper respiratory tract infection (3.2% compared with 2.7%), headache (3.0% compared with 3.2%) and back pain (3.0% compared with 2.7%).
- The company stated that anti-evolocumab antibodies were infrequent, non-neutralising, and not associated with clinically relevant adverse events.

ERG's comments

3.15 The ERG stated that evolocumab seemed to have an acceptable safety profile.

Cost effectiveness

3.16 The company submitted a de novo Markov economic model to assess the cost effectiveness of evolocumab in reducing CVD for primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia. The perspective of the analysis was that of the NHS and personal social services. Costs and health effects were modelled over a lifetime time horizon, and discounted at an annual rate of 3.5%. The cycle length in the model was 1 year.

Population, intervention and comparators

3.17 The company modelled 3 separate subpopulations:

- non-familial hypercholesterolaemia without CVD
- non-familial hypercholesterolaemia with CVD

- heterozygous-familial hypercholesterolaemia (with or without CVD).

  The company modelled the 2 non-familial hypercholesterolaemia populations based on the characteristics of the respective populations in LAPLACE-2 with or without CVD. However, it only used data from the subset of patients who had an LDL-C concentration over 2.5 mmol/litre to represent a population at high risk of CVD. For patients with heterozygous-familial hypercholesterolaemia, the company used the modified intention-to-treat population in RUTHERFORD-2.

3.18 The intervention modelled in the base case was evolocumab 140 mg every 2 weeks; the company explored using the monthly dosage of evolocumab in scenario analyses (see section 3.48). For each population modelled, the company presented separate results for 4 treatment comparisons; 2 relevant to patients who can tolerate statins (who had atorvastatin as background therapy), and 2 relevant to those who cannot (who did not have any background lipid-lowering therapy):

- For patients who can tolerate statins:
  - evolocumab plus atorvastatin compared with ezetimibe plus atorvastatin
  - evolocumab plus ezetimibe plus atorvastatin compared with ezetimibe plus atorvastatin.
- For patients who cannot tolerate statins:
  - evolocumab compared with ezetimibe
  - evolocumab plus ezetimibe compared with ezetimibe.

    The company represented statins with atorvastatin because this is the statin recommended in NICE's guideline on lipid modification for people with or without CVD.

ERG's comments

3.19 The ERG's clinical advisers suggested that modelling a non-familial hypercholesterolaemia population with an LDL-C concentration over 2.5 mmol/litre only was likely to have excluded many patients within this

population. This was because many UK patients will have an LDL-C concentration lower than 2.5 mmol/litre after taking statins.

3.20 The ERG noted that the company assumed that patients who can tolerate statins have the same characteristics as those who cannot. However, the risk of CVD was likely to be related to whether LDL-C concentration can be controlled on statins. The ERG advised that GAUSS-2 would have better represented patients with non-familial hypercholesterolaemia who cannot tolerate statins than LAPLACE-2, noting that the company's analyses reflected the overall populations in LAPLACE-2 and RUTHERFORD-2, which included both patients who can and cannot tolerate statins, rather than either of these individual groups.

3.21 The ERG noted that the modelled heterozygous-familial hypercholesterolaemia population included patients with, and those without, CVD. It advised that modelling these groups separately may be more clinically appropriate.

Model structure

3.22 The company's model consisted of 24 mutually exclusive states:

- 3 acute states (in which the patient could stay for a maximum of 1 year unless the same event occurred in the next cycle)
  - acute coronary syndrome (including myocardial infarction and unstable angina)
  - ischaemic stroke
  - heart failure
- 5 chronic states
  - no CVD
  - established CVD (including patients who had a history of stable angina, transient ischaemic attack, carotid stenosis, revascularisation without a history of myocardial infarction, abdominal aortic aneurism, or peripheral vascular disease)

  - 3 post-event states
    - post-acute coronary syndrome
    - post-ischaemic stroke
    - post-heart failure
- 13 composite CVD states (formed of a combination of 2 or 3 acute and post-event states; these were used to remember the history of CV events and model the corresponding outcomes of recurring CV events)
- 3 death states: death from coronary heart disease, death from stroke and death from other causes.

  Patients who had CVD could have either 1 of the events modelled separately (acute coronary syndrome, ischaemic stroke or heart failure), or 1 of the events in the established CVD state. This was because the events in the established CVD state were less severe than those modelled separately, and so would be associated with lower costs and better health outcomes. The company assumed that patients who started treatment in the model had it continuously over their lifetime.

3.23 Patients entered the model in different states depending on the population to which they belonged:

- All patients with non-familial hypercholesterolaemia who did not have CVD entered the model in the no CVD state.
- Patients with non-familial hypercholesterolaemia who had CVD entered the model in one of the 3 post-event states, or the established CVD state.
- Patients with heterozygous-familial hypercholesterolaemia (with or without CVD) entered the model in one of the 3 post-CVD event states, the established CVD state, or the no CVD state.

  Patients who entered the model in the no CVD state stayed in this state until they had CVD (that is, acute coronary syndrome, ischaemic stroke, heart failure, or one of the events in the established CVD state), or died. After the first CV event, patients could have no further CV events and move to the corresponding post-event state, have the same event again and stay in the

same acute event state, have a different acute event and move to a composite state representing the post-event state for previous events and the new event, or die. Patients in a post-event state could have the same acute event and move to the corresponding acute state or composite state (if the patient had had other CV events), a different acute event and move to the relevant composite state, or die.

ERG's comments

3.24 The ERG considered that the company did not describe how it selected the states in the model, nor did it explain why they were more relevant than those used in previous models for primary hypercholesterolaemia or mixed dyslipidaemia, including the model for the NICE clinical guideline on lipid modification. The ERG was particularly concerned about the composite states in the model. This was because there were no data to inform them, and the company made several arbitrary assumptions about the costs and health effects in these states, which the ERG considered to have increased the uncertainty in the model.

Estimation of CVD risks

3.25 To estimate the risk of CVD in the model, the company used a 3-step approach. First, it predicted the risk of CVD before treatment in patients in LAPLACE-2 with an LDL-C concentration at baseline over 2.5 mmol/litre (non-familial hypercholesterolaemia), and the modified intention-to-treat population in RUTHERFORD-2 (heterozygous-familial hypercholesterolaemia). To do so, the company used published risk equations from the Framingham Heart Study for patients without CVD, and the REACH registry for patients with CVD. Second, the company estimated calibration (adjustment) factors from an analysis of data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES). Third, it adjusted the predicted risks of CVD based on the Framingham and REACH registry equations using these calibration factors to reflect real-world data (CPRD and HES data). Because there was no CV risk equation specifically for patients with heterozygous-familial hypercholesterolaemia, the company adjusted the predicted risks of CVD in this population using a rate ratio of 7.1 (relative to patients without heterozygous-familial hypercholesterolaemia) derived from a

study by Benn et al. (2012).

ERG's comments

3.26 The ERG considered the process by which the company estimated the risks of CVD to be circular, and unnecessarily complicated, with several assumptions and adjustments needed to estimate these risks. The ERG noted that the company used published equations to predict risks and then adjusted these to reflect real-world data, although it could have estimated the risks directly from the analysis of real-world data (CPRD and HES) without using risk equations. In the ERG's opinion, the company's approach did not add information compared with the CPRD and HES data.

3.27 The ERG stated that the company did not sufficiently justify why it selected the US-based Framingham risk equations for patients without CVD, instead of alternative equations such as the QRISK2 assessment tool, which was used in the model for NICE's guideline on lipid modification.

3.28 The ERG noted that the company added several constraints to prevent the model from generating negative transition probabilities. It considered that some of these constraints seemed arbitrary, and it was difficult to follow the logic supporting them from the information given by the company.

3.29 The ERG noted that the company predicted the risks of CVD in the heterozygous-familial hypercholesterolaemia population using the Framingham and REACH registry risk equations based on the entire RUTHERFORD-2 population (which included patients with or without CVD). It did not consider this to be appropriate because these equations were only created for patients with or without a history of CVD. Also, the company used the study by Benn et al. (2012) to adjust the risk of CVD at baseline in patients with heterozygous-familial hypercholesterolaemia. The ERG noted that this study compared the risk of CV events between the general population and patients with heterozygous-familial hypercholesterolaemia. However, in the model, the rate ratio was not applied to the general population, but to the RUTHERFORD-2 trial

population, which was already at high risk of CVD. This was likely to overestimate the risk of CVD, and produce more favourable incremental cost-effectiveness ratios (ICERs) for evolocumab. The ERG also highlighted other studies, which suggested that the rate ratio derived from Benn et al. was likely to be an overestimate (see section 3.42).

Treatment effect

3.30 The objective of the model was to capture the lifetime progression of CVD among adults with primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia. Because none of the clinical trials for evolocumab had data on the direct effect of evolocumab on CVD, the company used estimates from the Cholesterol Treatment Trialists' (CTT) meta-analysis to convert the surrogate outcomes measured in the trials (LDL-C concentration) to 'real-world' outcomes (CV events).

3.31 The company used the estimates of treatment effect on LDL-C concentrations from the head-to-head RCTs comparing evolocumab with ezetimibe. The data on other lipid parameters were not included in the model. For patients with non-familial hypercholesterolaemia, the company used LAPLACE-2 for the treatment comparisons relevant to patients who can tolerate statins, and GAUSS-2 for the comparisons relevant to those who cannot (see section 3.18). To source the clinical effectiveness in patients with heterozygous-familial hypercholesterolaemia who can tolerate statins, the company used RUTHERFORD-2 for evolocumab and LAPLACE-2 for ezetimibe because RUTHERFORD-2 compared evolocumab with placebo only. For patients with heterozygous-familial hypercholesterolaemia who cannot tolerate statins, the company used GAUSS-2. The company assumed that the treatment effect in the model lasted throughout the time horizon.

ERG's comments

3.32 The ERG noted that the company used LDL-C concentration as a surrogate for CVD. It considered that, without robust data on the effect of evolocumab on CV outcomes, relying on a surrogate end point could be uncertain.

3.33 The ERG was concerned about the following assumptions in the model, which it considered uncertain:

- For patients with non-familial hypercholesterolaemia who can tolerate statins, the treatment effect from LAPLACE-2 could be generalised to the subset of patients with an LDL-C concentration over 2.5 mmol/litre.
- The treatment effects from LAPLACE-2 and GAUSS-2 would be the same in all patients whether or not they have diabetes or other risk factors for CVD.
- The treatment effect would last indefinitely in the model.

3.34 The ERG considered the following assumptions made by the company to estimate the relationship between changes in LDL-C concentration and CV events to be arbitrary, implausible or uncertain:

- The relationship between LDL-C concentration and CVD was the same for patients with or without a history of CVD.
- The effect of reducing LDL-C concentration on non-fatal myocardial infarction was the same as that on heart failure (first event). The ERG also noted that the company assumed that reducing LDL-C concentration in patients with heart failure (either acute, post-event state or combined state) would reduce death from coronary heart disease even though it recognised the lack of benefit for lipid-lowering therapies once patients had heart failure.
- The relationship between LDL-C concentration and non-fatal myocardial infarction (secondary prevention) would apply to patients moving from the no CVD state to the established CVD state.
- Reducing LDL-C concentration had no effect on death from stroke.

Health-related quality of life and costs

3.35 To populate the base-case model with utility data, the company used the utility values informing the model developed for NICE's guideline on lipid modification, with some adjustments to match the states in the model:

- Established CVD: in the company's model, this state included various CV events, 1 of which was stable angina. The original utility value for stable angina

was 0.808 (for both acute and post event). This was unexpectedly lower than the value for post myocardial infarction (0.880) and post unstable angina (0.880), which are considered more severe than stable angina. Because of this, the company used the utility value for the post-acute coronary syndrome state (0.880) for the established CVD state.

- Acute states: in the model, the acute coronary syndrome state included myocardial infarction and unstable angina. The original utility values for the acute events of these 2 diseases were 0.760 and 0.77 respectively. The company chose the higher utility value (0.77) for the acute coronary syndrome state. The utility values for the ischaemic stroke and heart failure were 0.63 and 0.68 respectively.
- Post-event states: the utility value was 0.88 for acute coronary syndrome, 0.63 for ischaemic stroke, and 0.68 for heart failure.
- Composite states: the company assumed the lowest utility value in the individual acute or post-event states included in that composite state.

In line with NICE's guideline on lipid modification, the company assumed that the utility depends on age, and so it multiplied the utility values (multipliers) by age-adjusted utility values for the general population based on a study by Dolan et al. (1996). The company also gave details of a company-sponsored study that used the time trade-off method to estimate utility values for patients with CVD. It explored using utility values from this study in scenario analyses (see section 3.48).

3.36 The company's model included treatment and monitoring costs, and those associated with the model health states. The cost of evolocumab in the model included the patient access scheme discount. The company assumed that patients who started treatment with evolocumab had 1-hour training by a nurse to self-administer the treatment at a cost of £84.00; no additional monitoring was assumed for patients having evolocumab compared with those having ezetimibe. The company equated the costs in the composite states to the highest cost in the individual states included in that state.

ERG's comments

3.37 The ERG stated that, of the 7 acute and post-event states in the model,

only 3 states (acute coronary syndrome, heart failure and post heart failure) were based on the EQ-5D questionnaire. The other utility multipliers were taken from studies that used the time trade-off method, and so did not meet the NICE reference case (the methods considered by NICE to be the most appropriate for technology appraisals). The ERG also noted that some of the utility multipliers did not match the states in the model for which they were used.

3.38 Overall, the ERG did not have major concerns about the costs used in the company's model.

Original base-case results (including the patient access scheme)

3.39 In its patient access scheme submission accompanying the original submission, the company presented incremental cost-effectiveness analyses for all 3 populations. The original base-case ICERs, including the patient access scheme, are shown in table 4. All of these ICERs are based on the every 2 weeks dosage of evolocumab 140 mg.

Table 4 Company's original base-case ICERs (including the patient access scheme)

Treatment comparison	**ICER (£/QALY)**		
	Non-familial hypercholesterolaemia		Heterozygous-familial hypercholesterolaemia
	Without CVD	With CVD	With or without CVD
Ezetimibe plus statin	N/A	N/A	N/A
Evolocumab plus statin	74,331	46,005	22,902
Ezetimibe	N/A	N/A	N/A
Evolocumab	78,879	49,278	23,927
Ezetimibe	Not presented	N/A	N/A
Evolocumab plus ezetimibe		52,811	25,609

Ezetimibe plus statin	Not presented	N/A	N/A
Evolocumab plus ezetimibe plus statin		50,880	24,826
Abbreviations: CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALY, quality-adjusted life year.			

The company also presented sensitivity analyses (deterministic and probabilistic), scenario analyses, and subgroup analyses for selected populations and treatment comparisons. All the analyses presented in the company's patient access scheme submission accompanying the original submission were superseded by the company's new evidence in response to consultation (see sections 3.44–3.50).

3.40 At the start of treatment evolocumab is prescribed in specialist secondary care clinics, but people may move from secondary to primary care after 2–3 years because routine lipid management is an area of standard GP practice. This has potential implications for the proposed simple discount patient access scheme because simple discounts do not apply when drugs are prescribed by GPs using FP10 prescriptions. In response to a request from NICE, the company presented sensitivity analyses varying the proportion of patients who may move from secondary care to primary care (after which point the simple discount does not apply), and the time patients spend in secondary care before this happens.

ERG's comments

3.41 In summary, the ERG advised some caution in the interpretation of the company's results because of:

- the selected populations used in the model (see sections 3.19–3.21)
- the use of multiple composite states, which were populated using many assumptions and little evidence (see section 3.24)
- the circular approach used by the company to predict risks of CVD (see section 3.26)
- the likely overestimation of the risk of CVD in the heterozygous-familial

hypercholesterolaemia population (see section 3.29)

- the uncertainty about the relationship between LDL-C reduction and reductions in CV events (see section 3.32).

3.42 The ERG stated that calibration rate of 7.1, which was likely to be overestimated (see section 3.29), was a key driver of the cost effectiveness of evolocumab for heterozygous-familial hypercholesterolaemia. It noted that the company estimated that about 50% of the patients having statins would have a CV event or die from other causes 8–9 years after starting treatment. In comparison, a long-term cohort study identified by the ERG (Versmissen et al. 2008) indicated that, within the same time period, 10% of patients with heterozygous-familial hypercholesterolaemia having statins would have coronary heart disease. The ERG also highlighted other studies, which suggested that the rate of death from cardiovascular or coronary artery disease may increase in patients with heterozygous-familial hypercholesterolaemia, although not to the extent assumed by the company; these studies also reported no statistically significant difference for all-cause mortality. Specifically, a UK study by Neil et al. (2008) reported standardised mortality ratios in patients with heterozygous-familial hypercholesterolaemia treated with statins of 1.03 (primary prevention) and 3.88 (secondary prevention) for death from coronary artery disease, and 0.94 for all-cause mortality, which was not statistically significant (p=0.31). Similar results were also reported by a recent Norwegian study by Mundal et al. (2014).

3.43 The ERG did a threshold analysis to determine the minimum calibration factor that must be applied to the predicted CV risks in the heterozygous-familial hypercholesterolaemia population for the ICER comparing evolocumab with ezetimibe to be below £30,000 per quality-adjusted life year (QALY) gained. This suggested that the ICER increased considerably as the assumed calibration factor decreased, with calibration factors greater than 4.5–5.6 needed for evolocumab compared with ezetimibe to have an ICER below £30,000 per QALY gained.

Company's new evidence in response to consultation

3.44 In response to consultation on the first appraisal consultation document, in which evolocumab was not recommended for primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia, the company was permitted to submit revised cost-effectiveness analyses. These incorporated the following changes, which reflected the committee's preferred analyses in the first appraisal consultation document:

- Use of the baseline characteristics of the population in GAUSS-2 to model patients with non-familial hypercholesterolaemia who cannot tolerate statins.
- Modelling of the heterozygous-familial hypercholesterolaemia population with or without CVD separately.
- Use of the QRISK2 assessment tool to estimate the level of CVD risk in people without CVD (non-familial or heterozygous-familial hypercholesterolaemia).
- Adjustment of the risk of CVD in the heterozygous-familial hypercholesterolaemia population using a rate ratio of 6.1 derived from Benn et al. (2012).
- Use of the equation from the Health Survey for England to inform the relationship between age and background health-related quality of life.
- Modelling of subgroups reflecting all the characteristics of the actual subgroup in clinical trials.

3.45 The company's revised base-case ICERs, including the patient access scheme, are presented in table 5. All of these ICERs are based on the every 2 weeks' dosage of evolocumab 140 mg.

Table 5 Company's revised base-case ICERs (including the patient access scheme)

Treatment comparison	ICER (£/QALY)	
	Non-familial hypercholesterolaemia	Heterozygous-familial hypercholesterolaemia

	Without CVD	With CVD	Without CVD	With CVD
Ezetimibe plus statin	N/A	N/A	N/A	N/A
Evolocumab plus statin	69,249	45,439	23,536	29,910
Ezetimibe	N/A	N/A	N/A	N/A
Evolocumab	38,458	30,985	21,921	25,293
Ezetimibe	N/A	N/A	N/A	N/A
Evolocumab plus ezetimibe	41,911	33,814	23,602	27,390
Ezetimibe plus statin	N/A	N/A	N/A	N/A
Evolocumab plus ezetimibe plus statin	78,459	50,257	25,583	32,698
Abbreviations: CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALY, quality-adjusted life year.				

3.46 The company revised its deterministic sensitivity analyses, varying the input values in the model for 1 parameter at a time. Among the most influential parameters were the treatment duration assumed in the model, the effect of reducing LDL-C concentration on death from coronary heart disease or ischaemic stroke, and the heterozygous-familial hypercholesterolaemia calibration rate ratio.

3.47 The company revised its probabilistic sensitivity analyses, varying parameters simultaneously with values from a probability distribution. The probabilistic ICERs were slightly higher than the deterministic ones. The company reported the following probabilities of evolocumab being cost effective:

- Non-familial hypercholesterolaemia population without CVD: 0% compared with any comparator at a maximum acceptable ICER of £30,000 per QALY gained.
- Non-familial hypercholesterolaemia population with CVD: 0% compared with ezetimibe plus statin at a maximum acceptable ICER of £30,000 per QALY gained. Compared with ezetimibe alone, the probability was 5.4% when used as an add-on to ezetimibe, and 30.1% when used as an alternative to ezetimibe.

- Heterozygous-familial hypercholesterolaemia without CVD: there was a low probability of evolocumab being cost effective at a maximum acceptable ICER of £20,000 per QALY gained (less than 20%). At a maximum acceptable ICER of £30,000 per QALY gained, the probability exceeded 85% for all comparisons.
- Heterozygous-familial hypercholesterolaemia with CVD: there was a low probability of evolocumab being cost effective at a maximum acceptable ICER of £20,000 per QALY gained (less than 5%). At a maximum acceptable ICER of £30,000 per QALY gained, the probability ranged from 15% to 42% compared with ezetimibe plus statin, and from 69% to 84% compared with ezetimibe alone.

3.48 The company revised its scenario analyses, varying the input values for certain parameters. The model was most sensitive to applying alternative discount rates (0% for costs, and 0% or 6% for health effects), having evolocumab monthly (as opposed to every 2 weeks), having treatment for a shorter duration of 5 or 10 years, and using utility values from the company-sponsored time trade-off study.

Subgroups

3.49 The company presented a range of subgroup analyses based on actual patient-level characteristics when possible. It used LAPLACE-2 and GAUSS-2 for the subgroups of the non-familial hypercholesterolaemia population with CVD who can or cannot tolerate statins respectively, and RUTHERFORD-2 for the subgroups of the heterozygous-familial hypercholesterolaemia population. For the subgroups of the non-familial hypercholesterolaemia population with CVD who can tolerate statins, the company also used CPRD data to model additional high-risk subgroups. The company presented results for the following subgroups:

- Non-familial hypercholesterolaemia population with CVD who can tolerate statins:
  - People with 1, and separately those with 2, of the following risk factors:
    - Based on LAPLACE-2: mean LDL-C concentration of 3.0–6.0 mmol/litre (intervals of 0.5 mmol/litre), diabetes, and acute coronary syndrome.
    - Based on CPRD: mean LDL-C concentration of 3.0–6.0 mmol/litre

(intervals of 0.5 mmol/litre), diabetes, 2 vascular beds, 3 vascular beds, atrial fibrillation, and acute coronary syndrome.

- People with 3 of the following risk factors (based on CPRD): mean LDL-C concentration of 3.0–6.0 mmol/litre (intervals of 0.5 mmol/litre), diabetes, 2 vascular beds, 3 vascular beds, atrial fibrillation, and acute coronary syndrome.

- Non-familial hypercholesterolaemia population with CVD who cannot tolerate statins:
  - People with 1, and separately those with 2, of the following risk factors (based on GAUSS-2): mean LDL-C concentration of 3.0–6.0 mmol/litre (intervals of 0.5 mmol/litre), diabetes, and acute coronary syndrome.

- Heterozygous-familial hypercholesterolaemia population with or without CVD who can tolerate statins:
  - People with 1 risk factor (based on RUTHERFORD-2): mean LDL-C concentration of 3.0–6.0 mmol/litre (intervals of 0.5 mmol/litre).

3.50 The ICER ranges from the company's analyses are presented below:

- Non-familial hypercholesterolaemia population with CVD who can tolerate statins (evolocumab plus statin compared with ezetimibe plus statin; base-case ICER £45,439 per QALY gained):
  - People with 1 risk factor:
    - Based on LAPLACE-2: from £34,277 to £51,571 per QALY gained (mean LDL-C concentrations of 6.0 mmol/litre and 3.0 mmol/litre respectively).
    - Based on CPRD: from £32,622 (mean LDL-C concentration of 6.0 mmol/litre) to £49,404 (diabetes) per QALY gained.
  - People with 2 risk factors:
    - Based on LAPLACE-2: from £31,340 (mean LDL-C concentration of 4.5 mmol/litre and diabetes) to £41,509 (mean LDL-C concentration of 3.5 mmol/litre and acute coronary syndrome) per QALY gained.

◇ Based on CPRD: from £21,203 (mean LDL-C concentration of 4.5 mmol/litre and 3 vascular beds) to £33,631 (mean LDL-C concentration of 3.5 mmol/litre and diabetes) per QALY gained.

— People with 3 risk factors (based on CPRD): from £18,343 (mean LDL-C concentration of 4.0 mmol/litre, acute coronary syndrome and 3 vascular beds) to £30,524 (mean LDL-C concentration of 3.0 mmol/litre, diabetes and 2 vascular beds) per QALY gained.

- Non-familial hypercholesterolaemia population with CVD who cannot tolerate statins (evolocumab compared with ezetimibe; base-case ICER £30,985 per QALY gained):

  — People with 1 risk factor (based on GAUSS-2): from £24,007 (acute coronary syndrome) to £43,180 (mean LDL-C concentration of 3.0 mmol/litre) per QALY gained.

  — People with 2 risk factors (based on GAUSS-2): from £25,347 (mean LDL-C concentration of 4.5 mmol/litre and diabetes) to £31,842 (mean LDL-C concentration of 3.5 mmol/litre and acute coronary syndrome) per QALY gained.

- Heterozygous-familial hypercholesterolaemia population without CVD who can tolerate statins (evolocumab plus statin compared with ezetimibe plus statin; base-case ICER £23,536 per QALY gained):

  — People with 1 risk factor (based on RUTHERFORD-2): from £18,436 to £29,304 per QALY gained (mean LDL-C concentrations of 6.0 mmol/litre and 3.0 mmol/litre respectively).

- Heterozygous-familial hypercholesterolaemia population with CVD who can tolerate statins (evolocumab plus statin compared with ezetimibe plus statin; base-case ICER £29,910 per QALY gained):

  — People with 1 risk factor (based on RUTHERFORD-2): from £23,244 to £38,133 per QALY gained (mean LDL-C concentrations of 6.0 mmol/litre and 3.0 mmol/litre respectively).

ERG's critique of the company's new evidence

3.51 The ERG noted that although the company appeared to have used the

QRISK2 assessment tool appropriately, several assumptions and adjustments were still needed to estimate and apply the calibration factors for the non-familial hypercholesterolaemia population.

3.52 The ERG was concerned about the rate ratio of 6.1 used to adjust the risk of CVD for heterozygous-familial hypercholesterolaemia, reiterating that this was inappropriately applied to the RUTHERFORD-2 trial population, which was already at high risk of CVD (see section 3.29). The ERG maintained that it would be more appropriate to estimate the risk of CVD directly from the CPRD and HES data, or other routine data.

3.53 The ERG considered that the company's revised subgroup analyses were broadly reasonable. However, it highlighted uncertainties relating to the following:

- Applying the same calibration factors from the whole non-familial hypercholesterolaemia population with CVD to the subgroups of that population.
- Assuming that the association between reduced LDL-C concentrations and improved CV outcomes did not depend on risk factors.
- Assuming that the treatment effect in subgroups was the same as in the full trial populations.

4 Consideration of the evidence

The appraisal committee reviewed the data available on the clinical and cost effectiveness of evolocumab, having considered evidence on the nature of primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia and the value placed on the benefits of evolocumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee considered the aim of treating primary hypercholesterolaemia or mixed dyslipidaemia. It heard from the patient experts that having primary hypercholesterolaemia or mixed dyslipidaemia affects day-to-day life, impinging also on family and friends. The committee was aware that the recommendations in NICE's guideline on lipid modification place greater emphasis on managing cardiovascular risk than meeting target cholesterol concentrations, although cholesterol targets are routinely used in clinical practice. The committee understood from the clinical experts that treating people with familial hypercholesterolaemia is a priority because lifelong exposure to high concentrations of low-density lipoprotein cholesterol (LDL-C) increases the risk of cardiovascular disease (CVD), even if these concentrations are not very high. The committee heard from patient experts that in their experience diet and lifestyle changes, in addition to medication, were important to lose weight and further reduce the risk of CVD. The committee concluded that in clinical practice, lowering LDL-C concentrations in people with primary hypercholesterolaemia or mixed dyslipidaemia aims primarily to prevent CVD, as recommended in the NICE guideline on lipid modification.

4.2 The committee noted that the scope for this appraisal included people with primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia for whom lipid-modifying therapies, in line with current NICE guidance, would be considered. This was consistent with the marketing authorisation for evolocumab, which recommends treatment, as an adjunct to diet, for primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia. The committee discussed whether evolocumab would be

used for mixed dyslipidaemia, which is also associated with elevated LDL-C concentrations. It understood from the clinical experts that although evolocumab was likely to mainly be used for primary hypercholesterolaemia in clinical practice, it may also be used for mixed dyslipidaemia when LDL-C concentrations remain very high despite maximum statin and ezetimibe management.

4.3 The committee considered the current treatment pathway and comparators for people with primary hypercholesterolaemia. It was aware that statins (particularly atorvastatin) are the mainstay of treatment for familial and non-familial hypercholesterolaemia (as described in NICE's guideline on familial hypercholesterolaemia and on lipid modification), but that some people may not tolerate them. The committee noted that NICE technology appraisal guidance on ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia recommends ezetimibe monotherapy for primary hypercholesterolaemia when statin therapy is contraindicated or not tolerated. It also recommends ezetimibe, co-administered with initial statin therapy, when cholesterol levels are not low enough, even when the dose is increased, or if a person is unable to tolerate higher doses of the statin. The committee concluded that ezetimibe is used to treat primary hypercholesterolaemia (heterozygous-familial and non-familial) in adults who are unable to have a statin, or need to supplement statin therapy, and therefore was an appropriate comparator for evolocumab in this appraisal.

4.4 The committee discussed the prevalence of statin intolerance among people with primary hypercholesterolaemia, noting that in NICE's guideline on familial hypercholesterolaemia intolerance to initial statin therapy was defined as 'the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may compromise adherence to therapy'. The committee understood from the clinical experts that absolute statin intolerance is rare, accounting for less than 5% of people. However, the clinical experts pointed out that up to 25% of people may have some degree of muscle pain that they perceive as being caused by statin intolerance. The committee concluded that absolute statin intolerance was in line with the definition in NICE's guideline on familial

hypercholesterolaemia, and that only a few people would have it.

4.5 The committee discussed the clinical situations in which treatment with evolocumab would be started. It heard from the clinical experts that evolocumab would be used in people with a high clinical unmet need such as people with severe forms of heterozygous-familial hypercholesterolaemia, and those who cannot tolerate statins and who are benefitting only marginally from ezetimibe, which will leave them with a high residual risk of CVD. For these people the only option was lipoprotein apheresis, which has its disadvantages (see section 4.6), and so evolocumab would be a welcome alternative. The committee heard that clinicians were likely to use evolocumab as an add-on, rather than an alternative, to statins and ezetimibe because statins and ezetimibe have well-established safety data, are not expensive, and have been robustly shown to improve cardiovascular (CV) outcomes. The committee concluded that, in clinical practice, evolocumab was likely to be reserved for people who are at a high risk of CVD as an add-on to statins and ezetimibe.

4.6 The committee discussed the place of lipoprotein apheresis in managing primary hypercholesterolaemia. The committee was aware that, although apheresis is recommended in the NICE guideline on familial hypercholesterolaemia as an option for severe heterozygous-familial hypercholesterolaemia, it is not only costly and onerous for the patient, but also difficult to access because only a few centres offer it. The committee noted that current guidelines recommend lipoprotein apheresis for patients with heterozygous-familial hypercholesterolaemia or other forms of severe hypercholesterolaemia and with progressive coronary heart disease whose low-density lipoprotein cholesterol (LDL-C) remains above 5.0 mmol/litre or decreases by less than 40% on maximally tolerable doses of combined drug therapy. The committee concluded that treatments that avoid the need for lipoprotein apheresis would be welcomed.

Clinical effectiveness

4.7 The committee considered the randomised controlled trials (RCTs) for evolocumab, noting that the company's submission focussed on the

results for LDL-C. It was aware that 2 of the 4 RCTs (LAPLACE-2 and GAUSS-2) compared evolocumab directly with ezetimibe, the sole comparator treatment in the scope. However, this was only for the non-familial hypercholesterolaemia population, and none of the trials compared evolocumab with ezetimibe for heterozygous-familial hypercholesterolaemia. RUTHERFORD-2 and GAUSS-2 studied evolocumab in 2 subgroups defined in the scope: people with heterozygous-familial hypercholesterolaemia, and those who cannot tolerate statins. The committee was aware that none of the trials studied evolocumab plus ezetimibe in any population. The committee agreed that the RCTs were otherwise relevant, and of good quality. It concluded that the trials were suitable for assessing the clinical effectiveness of evolocumab for primary hypercholesterolaemia (non-familial and heterozygous-familial).

4.8 The committee discussed whether the RCTs for evolocumab represented people who present with primary hypercholesterolaemia in clinical practice in England. It noted that the trials did not include some people with diabetes (see section 3.5), who may also have primary hypercholesterolaemia or mixed dyslipidaemia. The clinical experts did not consider this to have affected the generalisability of the trial results because, in clinical practice, people with diabetes would have their blood glucose levels controlled before being treated for primary hypercholesterolaemia. In general, the clinical experts agreed that the trials included people who reflected those with primary hypercholesterolaemia seen in clinical practice in England. The committee concluded that the trial results could be generalised to clinical practice.

4.9 The committee noted that at both dosages (140 mg every 2 weeks and 420 mg monthly), evolocumab effectively reduced LDL-C by 60–70% compared with placebo, and around 40% compared with ezetimibe. Consistent results were seen across high-risk subgroups including people with heterozygous-familial hypercholesterolaemia, and those who cannot tolerate statins. The committee also noted that evolocumab was well tolerated. The committee concluded that, compared with placebo or ezetimibe, evolocumab was clinically effective in reducing LDL-C in people with primary hypercholesterolaemia.

4.10 The committee discussed the effect of evolocumab on CVD in people with primary hypercholesterolaemia. It noted that the RCTs primarily measured surrogate end points (such as LDL-C), and were not powered to measure CV outcomes, which the committee considered to be an important limitation of the evidence base. The committee was aware that the reduction in CV events with statins has been confirmed by many large RCTs. By contrast, adding other lipid-modifying drugs to statins has not consistently been shown to further decrease CV events. The clinical experts generally considered LDL-C to be a reasonable surrogate for future CV events, although they advised that this relationship was uncertain when the LDL-C concentration at baseline is low (below 2.0 mmol/litre). The committee understood that the currently accepted relationship between LDL-C and CV events is based on the Cholesterol Treatment Trialists' (CTT) meta-analysis of statin trials. Further data on the benefit of non-statins on CVD came from RCTs of ileal bypass surgery (POSCH), and recently of ezetimibe (IMPROVE-IT), which showed that when ezetimibe was added to a statin, this further reduced CV events compared with statins alone. The committee noted the consultation comments suggesting that the association between reduced LDL-C concentrations and improved CV outcomes was well established and shown in many clinical trials. The committee understood that evolocumab should have a beneficial effect on CV outcomes because it has the same ultimate mechanism for LDL-C reduction as statins. The committee noted the data from OSLER and OSLER-2 on CV events (see section 3.9). However, it considered that these data were based on an exploratory analysis with few events, and were yet to be validated in larger trials. The committee noted that an ongoing RCT, FOURIER, would test whether or not LDL-C is a valid surrogate for CV outcomes for evolocumab. It agreed that this trial would give useful data on the direct effect of evolocumab on CVD, and recommended that the consideration of the review of the guidance is scheduled so that the results of FOURIER could be taken into account. The committee concluded that, although it was reasonable to infer that evolocumab would reduce CVD, the extent of this reduction was still uncertain, particularly with low concentrations of LDL-C at baseline.

4.11 The committee discussed the long-term effects of evolocumab. It heard from the clinical experts that the treatment effect could gradually

weaken over time, and more likely so when people start treatment with relatively low LDL-C concentrations, but the committee agreed that evolocumab is only likely to be targeted to people with LDL-C concentrations at the high end of the spectrum. However, the committee also noted the statement from clinical experts suggesting that with evolocumab, there is a theoretical potential for neutralising antibodies to develop and for treatment to lose its effectiveness, although there was no positive evidence that this would be the case. The committee was aware that long-term data were limited, but what data there were did not show that evolocumab may lose its effect over long treatment durations because of neutralising antibodies. The committee heard from the company that in an integrated safety analysis of more than 6000 patients (representing 7,235 patient years of exposure), anti-evolocumab antibodies were infrequent, non-neutralising, and not associated with clinically relevant adverse events. However, the committee did not consider this analysis to have followed up people for long enough to draw firm conclusions about the long-term effect of evolocumab. Without robust, long-term data the committee could not ascertain whether the effect of evolocumab would be maintained over time at the same level as when therapy was started, although the limited evidence available suggested that any loss of effect would be likely to be infrequent.

Cost effectiveness

4.12 The committee considered the company's model, noting that this reflected the effect of evolocumab on LDL-C, but not on other lipid parameters, including those implicated in mixed dyslipidaemia. The evidence review group (ERG) was concerned about the overall structure of the model, and in particular the 13 composite states, which it considered to be based on many arbitrary assumptions and little evidence (see section 3.24). The committee agreed that the composite states reflected specific combinations of CV events, which were unlikely to be robustly modelled given the existing evidence. The committee acknowledged the company's response to consultation suggesting that the composite states prevented clinically implausible scenarios from occurring in the model, and used assumptions that were endorsed by expert opinion. Although the committee appreciated the logic of using

the composite states, it concluded that, without evidence to support the modelling of these states, the internal validity of the model was unclear.

4.13 The committee discussed the modelled populations (that is, non-familial hypercholesterolaemia and heterozygous-familial hypercholesterolaemia). It understood that the company initially assumed that people who can tolerate statins have the same characteristics as those who cannot, although the risk of CVD is likely to be affected by whether or not the person can tolerate statins. In response to consultation, the company used GAUSS-2, which only included people who could not tolerate statins, to model people with non-familial hypercholesterolaemia who cannot tolerate statins. The committee concluded that it was more appropriate to model people with non-familial hypercholesterolaemia who can or cannot tolerate statins separately.

4.14 The committee discussed the heterozygous-familial hypercholesterolaemia population for which cost-effectiveness results were originally presented (see section 3.39). It noted that the company had modelled patients with or without CVD together. The committee heard from the clinical experts that, in clinical practice, people with CVD are treated more intensively than those without, and so it would be useful to separate the results for each of these groups. In response to consultation, the company split the heterozygous-familial hypercholesterolaemia population by whether or not people had CVD (see section 3.45). The committee concluded that the company's revised analyses more appropriately reflected clinical practice.

4.15 The committee discussed how the company estimated the risk of CVD in the model. It noted the ERG's comment that several assumptions and adjustments were needed to predict the risk of CVD before treatment, even though the company could have estimated the risks directly from its analysis of real-world data (Clinical Practice Research Datalink [CPRD] and Hospital Episode Statistics) without using risk equations that needed secondary modification. The committee heard from the company that it used risk equations to be able to model the profiles of specific high-risk populations, such as those with CVD who have additional risk factors. The committee concluded that using published risk equations, although introducing additional uncertainty, could be accepted if these reliably

estimated the risks of CVD.

4.16 The committee discussed whether the risk equations used by the company to predict the risks of CVD at baseline were appropriate. It noted that the company initially used the Framingham Heart Study risk equations for patients without CVD, and the REACH registry risk equations for patients with CVD. The committee was aware that extensive validation studies had shown that the Framingham risk equations systematically overestimated the risk of CVD in UK patients. In response to consultation, the company used the QRISK2 assessment tool for the non-familial and heterozygous-familial hypercholesterolaemia populations without CVD. The committee was aware that QRISK2 was more widely used in the UK, being recommended in NICE's guideline on lipid modification, and targeted to UK patients. It concluded that QRISK2 was more appropriate than the Framingham risk equations for patients without CVD, acknowledging that neither was derived from people with heterozygous-familial hypercholesterolaemia.

4.17 The committee discussed how the company adjusted the risks of CVD predicted from the Framingham and REACH registry risk equations for the heterozygous-familial hypercholesterolaemia population. It noted that the company applied a rate ratio of 6.1, derived from a study by Benn et al. (2012), to reflect the increased risk of CVD in this population. The committee was aware that the model was highly sensitive to this parameter (see section 3.43). The committee heard from the ERG that this adjustment was not appropriate mainly because Benn et al. compared the risk of CV events between people with heterozygous-familial hypercholesterolaemia and those with non-familial hypercholesterolaemia. However, the company applied the rate ratio estimated from Benn et al. to the RUTHERFORD-2 trial population, who were already at high risk of CVD from having heterozygous-familial hypercholesterolaemia. Furthermore, the clinical experts considered that the estimate based on Benn et al. was likely to have significantly overestimated the risk of CVD in patients with heterozygous-familial hypercholesterolaemia, although they acknowledged that there was no robust evidence on the increased risk of CVD in these patients compared with the general population. The committee also heard from the ERG that the risk of CVD predicted by the model for people with heterozygous-

familial hypercholesterolaemia, both with or without CVD, was much higher than the risks for the same populations in 'real-world' databases, including the CPRD. The committee concluded that the rate ratio from Benn et al. highly overestimated the risk of CVD among people with heterozygous-familial hypercholesterolaemia, and cast doubt about the validity of the estimated cost effectiveness of evolocumab for this population.

4.18 The committee considered how the company captured the lifetime progression of CVD among people with primary hypercholesterolaemia. It noted that the company used estimates from the Cholesterol Treatment Trialists' (CTT) meta-analysis to convert the surrogate outcomes measured in the trials (LDL-C concentration) to 'real-world' outcomes (CV events). However, the company did not use the 21 trials of 'statin versus control'. Instead, it used the 5 trials of 'more versus less intensive statin therapy' for most CV events from the CTT meta-analysis published in 2010. The committee was aware that a more recent CTT meta-analysis (including a total of 27 trials) was published in 2012. The committee considered that, without a justification for not doing so, the most recent analysis should be used because it provides the most mature data. It also heard from the clinical experts that using the 2012 meta-analysis was preferable. The committee concluded that the 2012 meta-analysis would be more appropriate than earlier data.

4.19 The committee considered how the company applied the treatment effect in the model. It noted that patients in the model had treatment continually over their lifetime, and that the treatment effect lasted throughout the time horizon at the same level as that observed in the short-term trials. The committee agreed that there were no long-term data on the extent to which evolocumab could reduce CVD, or whether this effect would be sustained over time (see sections 4.10 and 4.11). It noted the company's response to consultation suggesting that there was no evidence that the treatment effect diminished over time, or that neutralising antibodies developed with evolocumab. The committee would have liked the company to have explored further the uncertainty in the long-term effects of evolocumab. The committee concluded that the company's modelling of the treatment effect was uncertain, although the available evidence suggested that it was unlikely to have a significant

impact on the cost effectiveness of treatment.

4.20 The committee considered the utility multipliers used in the model. It agreed that these were generally in line with other values used for people with primary hypercholesterolaemia. However, the committee noted that the relationship assumed between age and utility was based on a study by Dolan et al. (1996), which the ERG considered to be crude and outdated by a more recent equation based on the Health Survey for England. In response to consultation, the company used the equation from the Health Survey for England to inform the relationship between age and background health-related quality of life. The committee concluded that the utility multipliers could be accepted in this appraisal.

4.21 The committee considered the cost effectiveness of the 2 dosages of evolocumab (140 mg every 2 weeks and 420 mg monthly). It recognised that the available cost-effectiveness evidence related to the every 2 weeks dosage and that the company had not presented evidence, apart from a scenario analysis, for the monthly dosage. The committee was aware that evolocumab 420 mg monthly was more expensive than evolocumab 140 mg every 2 weeks. Without evidence for the monthly dosage, the committee was unable to recommend evolocumab 420 mg monthly.

4.22 The committee discussed the company's revised incremental cost-effectiveness ratios (ICERs), including the patient access scheme, presented as part of the company's new evidence in response to consultation (see section 3.45). It discussed the ICERs for evolocumab 140 mg every 2 weeks in people without CVD and, separately, in those with CVD, noting that they all needed considerable caution in their interpretation:

- Non-familial hypercholesterolaemia population: the committee noted that the company's base-case ICERs with the patient access scheme for the non-familial hypercholesterolaemia population with or without CVD (£31,000–78,500 per quality-adjusted life year [QALY] gained) were all above the maximum acceptable ICERs normally considered to represent a cost-effective use of NHS resources (£20,000–30,000 per QALY gained).
- Heterozygous-familial hypercholesterolaemia population: the committee noted

that the ICERs for people without CVD (£21,900–25,600 per QALY gained) were lower than those for people with CVD (£25,300–32,700 per QALY gained). This was inconsistent with the results for the non-familial hypercholesterolaemia population, and counter-intuitive because people with CVD have a higher risk of CV events, and so would be expected to gain more QALYs from treatment than those without CVD. The committee heard from the company that people without CVD may be benefitting from the prevention of a first CV event. However, it considered that this did not explain why the non-familial hypercholesterolaemia population without CVD would not benefit in the same manner, and have lower ICERs than the population with CVD. The committee heard from the ERG that different CV events were assumed for the non-familial and heterozygous-familial hypercholesterolaemia populations and, further, the calibration of CV events for the non-familial hypercholesterolaemia population was event-specific, whereas a single rate ratio (6.1) from Benn et al. (2012) was applied to all CV events for the heterozygous-familial hypercholesterolaemia population. Therefore, the committee had doubts about the resulting ICERs and their face validity, especially those for people without CVD.

In addition to the magnitude of the company's ICERs, and the concerns about their validity for certain subpopulations, the committee recalled its misgivings about using the composite states in the model (see section 4.12), and modelling treatment continually over the person's lifetime, while assuming that its effect would be maintained throughout the time horizon (see section 4.19). Furthermore, the committee had concerns about using Benn et al. (2012) to reflect the increased risk of CVD for heterozygous-familial hypercholesterolaemia (see section 4.17). Because of this, it concluded not to recommend evolocumab 140 mg every 2 weeks for the primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia population as a whole.

Subgroups

4.23 The committee considered the cost effectiveness of evolocumab in clinically relevant subgroups. It agreed that the company's analyses had limitations, which made the committee question the validity of the results, particularly those for heterozygous-familial hypercholesterolaemia. Nevertheless, the committee agreed that there was merit in exploring potential subgroups of patients with the highest

need. It also noted that most responses to consultation advocated using evolocumab in selected subgroups. The committee considered how it could reconcile the uncertainty in the evidence base with the clinical unmet need in the primary hypercholesterolaemia or mixed dyslipidaemia population. It noted the consistent trend in the company's results suggesting that the cost effectiveness of evolocumab would improve within a given population as the risk of CVD increases (see section 3.50). The committee acknowledged that evolocumab is a new therapy with a novel mechanism of action, which consistently reduced LDL-C concentrations compared with placebo and ezetimibe, while also being well-tolerated by patients. Taken together, the committee concluded that, although the ICERs were not as robust as it would have liked, they could be used to check a proposed set of recommendations guided by the clinical unmet need in the primary hypercholesterolaemia or mixed dyslipidaemia population.

4.24 The committee discussed which subgroups would have a high clinical unmet need. It noted that the Royal College of Pathologists and a clinical expert considered that evolocumab would be particularly valued for:

- non-familial hypercholesterolaemia with progressive, symptomatic CVD, and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy
- heterozygous-familial hypercholesterolaemia with progressive, symptomatic CVD, and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy
- severe heterozygous-familial hypercholesterolaemia with pre-treatment LDL-C concentrations above 8.0 mmol/litre and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy.

  The committee understood that 'persistent' LDL-C means on-treatment LDL-C concentrations confirmed by repeated measures. Other consultation comments received also suggested specific subgroups. However, these suggestions would be difficult to implement in the NHS because the subgroups did not reflect clinical practice. The committee agreed that the suggestions from the Royal College of Pathologists and the clinical expert highlighted the areas

where the clinical unmet need was highest, concluding that it would be appropriate to use them as a starting point in its decision-making.

4.25 The committee was aware that there was an ongoing NICE appraisal of another PCSK9 inhibitor (alirocumab) and that the evidence submitted for that appraisal differed from this one in a number of ways. Firstly, the risks of CVD at baseline for most populations were estimated directly from observational data without using risk equations, and then modifying the estimated risks to approximate the characteristics of the respective population. Secondly, the 2012 CTT meta-analysis was used to convert the surrogate outcomes measured in the trials to 'real world' outcomes, which the committee agreed was more appropriate than using the earlier meta-analysis published in 2010 (see section 4.18). Thirdly, the ICERs were for triple therapy (that is, alirocumab plus statin plus ezetimibe), which the committee heard was likely to be the combination in which PCSK9 inhibitors would be mainly used. For these reasons, the committee was generally satisfied that the ICERs in the appraisal of alirocumab were suitable for decision-making. The committee recognised that evolocumab and alirocumab had similar efficacy in clinical trials, and that clinicians generally regarded them as being clinically equivalent. Because of this, the committee concluded that it should refer to the appraisal of alirocumab in its discussion about the subgroups of people who would be prioritised for treatment with PCSK9 inhibitors.

4.26 The committee considered the subgroups identified as being at high risk of CVD in the appraisal of alirocumab. It was aware that that appraisal defined 2 levels of CVD risks:

- High risk of CVD: previous acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke, or peripheral arterial disease.
- Very high risk of CVD: recurrent CV events or CV events in more than 1 vascular bed (that is, polyvascular disease).

The committee noted that the CV events defining these risk levels meant that the definition of CVD was more restricted in the appraisal of alirocumab than in this appraisal (see section 3.22). The committee concluded that it would be

mindful of the distinction between high and very high risk of CVD in the appraisal of alirocumab when considering subgroups with a high unmet need.

Non-familial hypercholesterolaemia with CVD

4.27 The Royal College of Pathologists and the clinical expert recommended persistently high LDL-C concentrations above 4.0 mmol/litre for non-familial hypercholesterolaemia with progressive, symptomatic CVD. The committee understood that most people in this subgroup will not have been able to tolerate statins, and would consequently have a high residual risk of CVD. The committee agreed that the company's subgroup with acute coronary syndrome could be considered a reasonable proxy for progressive, symptomatic CVD. The company estimated that people with a mean LDL-C concentration of 4.0 mmol/litre and acute coronary syndrome who can tolerate statins had ICERs of £37,700 (LAPLACE-2) and £29,200 (CPRD) per QALY gained for evolocumab plus statin compared with ezetimibe plus statin. These ICERs would be lower for a minimum, as opposed to a mean, LDL-C concentration of 4.0 mmol/litre. The committee recognised that the company's ICERs for evolocumab were high. However, it noted from the ongoing appraisal of alirocumab that when a more restricted definition of CVD is used, the ICERs were likely to decrease. The committee agreed that the remaining uncertainty around the ICER could be accepted because evolocumab would represent an important treatment option for this group of patients, who have a relatively high risk of CVD and few treatment options. The committee concluded that it could recommend evolocumab 140 mg every 2 weeks for primary non-familial hypercholesterolaemia with CVD in people with LDL-C concentrations persistently above 4.0 mmol/litre.

4.28 The committee discussed whether there would be people with LDL-C concentrations below 4.0 mmol/litre at very high risk of CVD who could benefit from evolocumab. It considered the response to the second appraisal consultation document, which suggested that specifying a minimum LDL-C concentration above 4.0 mmol/litre to start treatment would exclude some people at high risk of CVD because of a poor response to statins, statin intolerance, or a high pre-treatment LDL-C concentration. The response noted that in one-sixth of people, high-dose statins will reduce LDL-C concentrations by less than 39%. The

committee heard from the clinical experts that LDL-C concentrations below 4.0 mmol/litre in themselves would not pose as high a risk of CVD as those above 4.0 mmol/litre, but other factors will sometimes increase the risk of CVD. The committee recalled that in the ongoing appraisal of alirocumab, a group considered to be at even higher risk of CVD than the non-familial hypercholesterolaemia population with CVD as a whole was defined (group at 'very high risk of CVD'; see section 4.26). The committee accepted that requiring a minimum LDL-C concentration of 4.0 mmol/litre may exclude a small group with additional risk factors for CVD who do not have an effective option to reduce their risk of CVD. It revisited the company's subgroup analyses, noting that these suggested that evolocumab would be cost effective for people with more than 1 risk factor, or with disease in multiple vascular beds (see section 3.50). The committee discussed whether a lower LDL-C concentration of 3.5 mmol/litre for starting treatment would be more appropriate than 4.0 mmol/litre for that group. It heard from the clinical experts that the benefit of treatment on CV outcomes below an LDL-C concentration of 3.5 mmol/litre was still being researched. Therefore, the committee concluded that for primary non-familial hypercholesterolaemia with very high risk of CVD (as defined in section 4.26), evolocumab 140 mg every 2 weeks could be recommended in people with LDL-C concentrations persistently above 3.5 mmol/litre.

Heterozygous-familial hypercholesterolaemia with CVD

4.29 The Royal College of Pathologists and the clinical expert recommended persistently high LDL-C concentrations above 4.0 mmol/litre for heterozygous-familial hypercholesterolaemia with progressive, symptomatic CVD. The committee recognised that people in this subgroup with LDL-C concentrations above 5.0 mmol/litre would be eligible for apheresis according to the current guidelines (see section 4.6), reflecting a high clinical unmet need. Although it recalled its misgivings about the calculations, the committee noted that the company's ICER for people with an LDL-C concentration above 4.0 mmol/litre would be lower than £30,200 per QALY gained. It also considered responses to the second appraisal consultation document, suggesting that a minimum LDL-C concentration above 4 mmol/litre to start treatment would exclude some people at high risk of CVD. The

committee noted that the company's ICER for heterozygous-familial hypercholesterolaemia with CVD in people with a mean LDL-C concentration of 3.5 mmol/litre was £33,600 per QALY gained, but would be lower for people with progressive symptomatic CVD whose minimum, rather than mean, LDL-C concentration was 3.5 mmol/litre. Also, restricting the definition of CVD as in the appraisal of alirocumab would further reduce the ICER. The committee, accepting that a minimum LDL-C concentration of 4 mmol/litre may exclude a group at high risk of CVD, agreed that a lower LDL-C concentration of 3.5 mmol/litre for starting treatment would be more appropriate than 4.0 mmol/litre for heterozygous-familial hypercholesterolaemia with CVD. The committee concluded that for this population, it could recommend evolocumab 140 mg every 2 weeks in people at high risk, or very high risk, of CVD (as defined in section 4.26) with LDL-C concentrations persistently above 3.5 mmol/litre.

Heterozygous-familial hypercholesterolaemia without CVD

4.30 For the subgroup with heterozygous-familial hypercholesterolaemia without CVD, the Royal College of Pathologists and the clinical expert recommended a pre-treatment LDL-C concentration above 8.0 mmol/litre, and a persistently high LDL-C concentration above 4.0 mmol/litre. The company's estimated ICER for people with a mean LDL-C concentration of 4.0 mmol/litre was less than £23,500 per QALY gained. However, the committee had doubts about the validity of the ICERs for the heterozygous-familial hypercholesterolaemia population without CVD (see section 4.22). The committee was aware that in the ongoing appraisal of alirocumab the risks of CVD for most populations were estimated directly from real-world data without using the rate ratio from Benn et al., and the ICERs for heterozygous-familial hypercholesterolaemia were higher for people without CVD than those with CVD. The committee noted the response to the second appraisal consultation document suggesting that the 4.0 mmol/litre threshold already defined a higher risk subgroup within the heterozygous-familial hypercholesterolaemia population, and that the additional criterion for pre-treatment LDL-C concentration (above 8.0 mmol/litre) would exclude some people at high risk of CVD in whom evolocumab would be cost effective. The committee understood from the clinical experts that the

risk of CVD varies widely among people with heterozygous-familial hypercholesterolaemia. A pre-treatment LDL-C concentration above 8 mmol/litre, corresponding to the 90th percentile, has historically been used to define 'severe heterozygous-familial hypercholesterolaemia', which reflects long exposure to high LDL-C concentrations. This is associated with an increased risk of CVD of 25% compared with non-severe heterozygous-familial hypercholesterolaemia. The committee agreed that a minimum LDL-C concentration on repeated measures, rather than a single pre-treatment measure, would capture severe heterozygous-familial hypercholesterolaemia with less potential to exclude people at high risk of CVD (young people, for example, because LDL-C concentrations increase with age). The committee was aware that the current criteria for apheresis require the LDL-C concentration to remain above 5.0 mmol/litre. Without further evidence on how to identify people at high risk of CVD within this subgroup, the committee agreed that this threshold would adequately capture such people. The committee concluded that it could recommend evolocumab 140 mg every 2 weeks for heterozygous-familial hypercholesterolaemia without CVD in people with LDL-C concentrations persistently above 5.0 mmol/litre.

Overall conclusion

4.31 The committee agreed that evolocumab would be a clinically and cost-effective use of NHS resource in certain subgroups. It concluded that it could recommend evolocumab, only if:

- the dosage is 140 mg every 2 weeks
- the person has primary non-familial hypercholesterolaemia and
  - a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; or peripheral arterial disease and
  - an LDL-C concentration persistently above 4.0 mmol/litre
- the person has primary non-familial hypercholesterolaemia and

  - recurrent CV events or CV events in more than 1 vascular bed (that is, polyvascular disease) and
  - an LDL-C concentration persistently above 3.5 mmol/litre
- the person has primary heterozygous-familial hypercholesterolaemia and
  - a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; or peripheral arterial disease and
  - an LDL-C concentration persistently above 3.5 mmol/litre
- the person has primary heterozygous-familial hypercholesterolaemia and
  - no CVD and
  - an LDL-C concentration persistently above 5.0 mmol/litre
- the company provides evolocumab with the discount agreed in the patient access scheme.

  Without evidence for the monthly dosage, the committee was unable to recommend evolocumab 420 mg monthly for primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia.

4.32 The committee was aware that the company's model did not include people with mixed dyslipidaemia. It discussed whether its recommendations for primary hypercholesterolaemia could be generalised to mixed dyslipidaemia. The committee recalled its conclusion that evolocumab may be used for mixed dyslipidaemia when LDL-C concentrations remain very high despite maximum statin and ezetimibe management (see section 4.2). The committee was aware that people with mixed dyslipidaemia also have elevated LDL-C concentrations, and that treatment for mixed dyslipidaemia is partly determined by the LDL-C concentration. The committee was aware that people with heterozygous-familial hypercholesterolaemia are considered to be at high risk of CVD not only because of the high LDL-C concentrations, but also because of the lifelong exposure to such concentrations. Because of this, the committee concluded that the

recommendations for mixed dyslipidaemia should follow those for non-familial hypercholesterolaemia because mixed dyslipidaemia is not associated with additional risk factors that warrant intervention at lower LDL-C concentrations.

4.33 The committee was aware that the Royal College of Pathologists and the clinical expert recommended that LDL-C concentrations had to be persistently high despite maximal tolerated lipid-lowering therapy. It recalled that statins with or without ezetimibe are the mainstay of treatment for primary hypercholesterolaemia. However, some people may be misidentified as being unable to tolerate statins (see section 4.4), and this may worsen the cost effectiveness of subsequent treatment. Because of this, the committee emphasised that its recommendations for evolocumab should only apply when maximal tolerated lipid-lowering therapy has failed. It clarified that this meant that either the maximum dose has been reached or further titration is limited by intolerance (as defined in NICE's guideline on familial hypercholesterolaemia). The committee was aware that there may also be people in whom statins are contraindicated. These people have the same unmet clinical need as those who cannot tolerate statins, and so should have the same treatment options. In addition, there is no biologically plausible reason for the effect to differ between these 2 groups. Because of this, the committee concluded that its recommendations should also apply to people in whom statins are contraindicated.

4.34 The committee discussed whether the ICERs presented reflect the cost of evolocumab to the NHS. It understood that the actual discount received by the NHS may be less than the percentage discount offered in the patient access scheme. This is because people may move from secondary to primary care after 2–3 years, and simple discounts do not apply when drugs are prescribed through GP's FP10 prescriptions. The committee considered that the subgroups for which evolocumab is recommended have severe hypercholesterolaemia and a high risk of CVD, so people should continue treatment under secondary care where simple patient access schemes apply. The committee concluded that the discounted patient access scheme price of evolocumab would be consistently applied for all people for whom evolocumab is recommended.

4.35 The committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising evolocumab. The committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of evolocumab. It therefore concluded that the PPRS payment mechanism was not applicable for considering the cost effectiveness of evolocumab.

Summary of appraisal committee's key conclusions

TA394	Appraisal title: Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia	Section
Key conclusion		

Evolocumab is recommended, only if: • the dosage is 140 mg every 2 weeks and • the person has primary non-familial hypercholesterolaemia or mixed dyslipidaemia and — a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; or peripheral arterial disease and — a low-density lipoprotein cholesterol (LDL-C) concentration persistently above 4.0 mmol/litre • the person has primary non-familial hypercholesterolaemia or mixed dyslipidaemia and — recurrent cardiovascular (CV) events or CV events in more than 1 vascular bed (that is, polyvascular disease) and — an LDL-C concentration persistently above 3.5 mmol/litre • the person has primary heterozygous-familial hypercholesterolaemia and — a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke, or peripheral arterial disease and — an LDL-C concentration persistently above 3.5 mmol/litre • the person has primary heterozygous-familial hypercholesterolaemia and — no cardiovascular disease (CVD) and — an LDL-C concentration persistently above 5.0 mmol/litre • the company provides evolocumab with the discount agreed in the patient access scheme. The committee agreed that the company's analyses had limitations, which made the committee question the validity of the results. Nevertheless, the	1.1, 4.23, 4.25, 4.31

committee agreed that there was merit in exploring potential subgroups of patients with the highest need. To reconcile the uncertainty in the evidence base with the clinical unmet need in the primary hypercholesterolaemia population, the committee concluded that the incremental cost-effectiveness ratios (ICERs) could be used to check a proposed set of recommendations guided by the clinical unmet need in this population. The committee also concluded that it should refer to the appraisal of alirocumab in its discussion about the subgroups of people who would be prioritised for treatment with PCSK9 inhibitors because evolocumab and alirocumab belonged to the same class of drugs, and were regarded as being clinically equivalent.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee heard that the clinical unmet need was high in some groups, such as people with severe forms of heterozygous-familial hypercholesterolaemia, and those who cannot tolerate statins and who are benefitting only marginally from ezetimibe. The committee was aware that lipoprotein apheresis is not only costly and onerous for the patient, but also difficult to access. It concluded that treatments that avoid the need for lipoprotein apheresis would be welcomed.	4.5, 4.6
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee acknowledged that evolocumab is a new therapy with a novel mechanism of action, which consistently reduced LDL-C concentrations compared with placebo and ezetimibe, while also being well-tolerated by patients.	4.23

What is the position of the treatment in the pathway of care for the condition?	The committee concluded that, in clinical practice, evolocumab was likely to be reserved for people who are at a high risk of CVD as an add-on to statins and ezetimibe.	4.5
Adverse reactions	The committee noted that evolocumab was well tolerated.	4.9
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee was aware that 2 of the 4 randomised controlled trials (RCTs) for evolocumab gave direct evidence for the comparison with ezetimibe, although this was only for the non-familial hypercholesterolaemia population, and 2 RCTs studied evolocumab in subgroups defined in the scope. The committee agreed that the RCTs were relevant, and of good quality. The committee noted that the RCTs primarily measured surrogate end points, and were not powered to measure CV outcomes, which the committee considered to be an important limitation of the evidence base.	4.7, 4.10
Relevance to general clinical practice in the NHS	The committee concluded that the trial results could be generalised to clinical practice in England.	4.8
Uncertainties generated by the evidence	The committee concluded that the extent to which evolocumab could reduce CVD was still uncertain, particularly with low concentrations of LDL-C at baseline. Without robust, long-term data the committee could not ascertain whether the effect of evolocumab would be maintained over time at the same level as when therapy was started.	4.10, 4.11

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee noted that the clinical trial results were consistent across high-risk subgroups including people with heterozygous-familial hypercholesterolaemia, and those who cannot tolerate statins.	4.9
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee noted that evolocumab effectively reduced LDL-C by 60–70% compared with placebo, and around 40% compared with ezetimibe.	4.9
Evidence for cost effectiveness		
Availability and nature of evidence	The committee concluded that the internal validity of the model was unclear because the composite states were unlikely to be robustly modelled given the existing evidence.	4.12
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee concluded that the rate ratio from Benn et al. (2012) highly overestimated the risk of CVD among people with heterozygous-familial hypercholesterolaemia, and cast doubt about the validity of the estimated cost effectiveness of evolocumab for this population. The committee concluded that the company's modelling of the treatment effect was uncertain because there were no long-term data on the extent to which evolocumab could reduce CVD, or whether this effect would be sustained over time.	4.17, 4.19

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee concluded that the utility multipliers were generally in line with other values used for people with primary hypercholesterolaemia, and could be accepted in this appraisal.	4.20
Are there specific groups of people for whom the technology is particularly cost effective?	The committee noted the consistent trend in the company's results suggesting that the cost effectiveness of evolocumab would improve within a given population as the risk of CVD increases.	4.23
What are the key drivers of cost effectiveness?	The committee was aware that the model was highly sensitive to the rate ratio used to reflect the increased risk of CVD in the heterozygous-familial hypercholesterolaemia population.	4.17

Most likely cost-effectiveness estimate (given as an ICER)	The company estimated the following ICERs for the subgroups for whom evolocumab is recommended: • Non-familial hypercholesterolaemia or mixed dyslipidaemia with CVD in people at high risk of CVD whose LDL-C concentrations are persistently above 4.0 mmol/litre: lower than £37,700 (based on the LAPLACE-2 population) and £29,200 (based on the Clinical Practice Research Datalink population) per quality-adjusted life–year (QALY) gained. • Non-familial hypercholesterolaemia or mixed dyslipidaemia with CVD in people at very high risk of CVD whose LDL-C concentrations are persistently above 3.5 mmol/litre: no specific ICER reported. • Heterozygous-familial hypercholesterolaemia with CVD in people whose LDL-C concentrations are persistently above 3.5 mmol/litre: lower than £33,600 per QALY gained. • Heterozygous-familial hypercholesterolaemia without CVD in people whose LDL-C concentrations are persistently above 5.0 mmol/litre: no specific ICER reported.	4.27–4.30
Additional factors taken into account		
Patient access schemes (PPRS)	The company has agreed a simple discount patient access scheme with the Department of Health.	2.3
End-of-life considerations	Not applicable.	–

Equalities considerations and social value judgements	The clinical experts noted that community nursing support will be needed if patients cannot self-inject. They also noted that patients in geographically remote areas may have difficulty accessing specialist care to start therapy. None of these was considered an equality issue according to the legislation, and so the committee did not need to change its recommendations in any way.	–

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has primary hypercholesterolaemia or mixed dyslipidaemia and the doctor responsible for their care thinks that evolocumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Amgen have agreed that evolocumab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Amgen on 01223 436762, email repathaukcommercial@amgen.com.

6 Recommendations for research

6.1 The committee was aware that an ongoing randomised controlled trial, FOURIER, would test whether or not low-density lipoprotein cholesterol (LDL-C) is a viable surrogate for cardiovascular outcomes for evolocumab. The committee agreed that this trial would give useful data on the direct effect of evolocumab on cardiovascular disease.

7 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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