NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using evolocumab in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 10) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using evolocumab in the NHS in England.

For further details, see the Guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 26 February 2016

Second Appraisal Committee meeting: 9 March 2016

Details of membership of the Appraisal Committee are given in section 9, and a list of the sources of evidence used in the preparation of this document is given in section 10.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Recommendations

1.1 Evolocumab, alone or in combination with other lipid-lowering therapies, is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:

- the dosage is 140 mg every 2 weeks **and**
- the person has:
  - primary non-familial hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic cardiovascular disease (CVD), and persistently high low-density lipoprotein cholesterol (LDL-C) concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy **and**
    - ◊ statin therapy is not tolerated (as defined in NICE's guideline on familial hypercholesterolaemia: identification and management) **or**
    - ◊ initial statin therapy is contraindicated
  - primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic CVD, and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy
  - severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD, 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 **and**

- ◊ statin therapy is not tolerated (as defined in NICE's guideline on familial hypercholesterolaemia: identification and management) **or**
- ◊ initial statin therapy is contraindicated **and**

- the company provides evolocumab with the discount agreed in the patient access scheme.

1.2 People whose treatment with evolocumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment 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 statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,

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

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, September–November 2015). The annual cost of treatment per patient is about £4448.60 for 140 mg every 2 weeks, and £6123.60 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 9) considered evidence submitted by Amgen and a review of this submission by the Evidence Review Group (ERG; section 10).

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 and 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=1899): eligible patients were randomised to one 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. 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 and 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 company reported the following results for the primary end points:

- Difference in percent change from baseline in LDL-C level at week 12 (week 52 in DESCARTES) between evolocumab and placebo or ezetimibe:
  - LAPLACE-2
    - 140 mg every 2 weeks: −71% (95% confidence interval [CI] −78 to −64) to −80% (95% CI −91 to −68) compared with placebo, and −44% (95% CI −50 to −37) to −50% (95% CI −61 to −39) compared with ezetimibe.
    - 420 mg monthly: −59% (95% CI −70 to −48) to −74% (95% CI −84 to −65) compared with placebo, and −41% (95% CI −51 to −32) to −43% (95% CI −50 to −36) compared with ezetimibe.
  - GAUSS-2
    - 140 mg every 2 weeks: −39% (95% CI −45 to −34) compared with ezetimibe.
    - 420 mg monthly: −38% (95% CI −43 to −33) compared with ezetimibe.
  - RUTHERFORD-2

  - ◊ 140 mg every 2 weeks: −61% (95% CI −67 to −55) compared with placebo.
  - ◊ 420 mg monthly: −60% (95% CI −68 to −53) compared with placebo.
- DESCARTES (evolocumab 420 mg monthly): −59% (95% CI −64 to −55) compared with placebo.

- Difference in mean percent change from baseline in LDL-C level at weeks 10 and 12 between evolocumab and placebo or ezetimibe:
  - LAPLACE-2
    - ◊ 140 mg every 2 weeks: −69% (95% CI −77 to −62) to −78% (95% CI −88 to −68) compared with placebo, and −41% (95% CI −47 to −35) to −48% (95% CI −58 to −38) compared with ezetimibe.
    - ◊ 420 mg monthly: −65% (95% CI −71 to −58) to −78% (95% CI −86 to −70) compared with placebo, and −45% (95% CI −52 to −39) to −46% (95% CI −54 to −38) compared with ezetimibe.
  - GAUSS-2
    - ◊ 140 mg every 2 weeks: −38% (95% CI −44 to −33) compared with ezetimibe.
    - ◊ 420 mg monthly: −39% (95% CI −44 to −35) compared with ezetimibe.
  - RUTHERFORD-2
    - ◊ 140 mg every 2 weeks: −61% (95% CI −67 to −55) compared with placebo.

- 420 mg monthly: −66% (95% CI −72 to −61) compared with placebo.

All the differences were statistically significant at the 0.01 level (that is, there was strong evidence that the effect of evolocumab differed from that of placebo or ezetimibe).

3.8 The company presented subgroup analyses, focussing on the subgroups of patients who are at high risk of a CV event (this is also a subgroup specified in the scope) because these patients would be prioritised for having evolocumab. It stated that in all the subgroup analyses, 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 6026 patients with primary hypercholesterolaemia and 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) and 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 a history of 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 only a non-familial hypercholesterolaemia population with an LDL-C concentration over 2.5 mmol/litre was likely to have excluded many patients within this population. This was because many UK patients can have an LDL-C concentration lower than 2.5 mmol/litre on 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 CHD, 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 and 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 hypercholesterolaemia (heterozygous-

familial and non-familial) and 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 from the head-to-head RCTs comparing evolocumab with ezetimibe. For patients with non-familial hypercholesterolaemia, it 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 sections 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 1. All of these ICERs are based on the every 2 weeks dosage of evolocumab 140 mg.

Table 1 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 Although at the start, evolocumab will be used in specialist secondary care clinics, 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 through

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 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 incorporating 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 2. All of these ICERs are based on the every 2 weeks dosage of evolocumab 140 mg.

Table 2 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: there was a 0% probability of evolocumab being cost effective compared with any comparator at a maximum acceptable ICER of £30,000 per QALY gained.
- Non-familial hypercholesterolaemia population with CVD: there was a 0% probability of evolocumab being cost effective compared with ezetimibe plus statin at a maximum acceptable ICER of £30,000 per QALY gained. Compared with ezetimibe alone, the probability of evolocumab being cost effective 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 the CPRD 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 of the following 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 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.

3.54 Full details of all the evidence are in the Committee papers.

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 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 heard from the patient experts about the nature of the condition and their experience with treatment. It heard that, although hypercholesterolaemia can be life threatening, some people are diagnosed by chance after a routine blood test; these people risk developing heart disease before diagnosis. The patient experts noted that having hypercholesterolaemia affects day-to-day life, impinging also on family and friends. The Committee noted that the patient expert was being treated with simvastatin and had no side effects. In addition to medication, the patient experts stated that diet and lifestyle changes were important to lose weight and further reduce the risk of cardiovascular disease (CVD). The Committee concluded that primary hypercholesterolaemia increases the risk of CVD but, with early diagnosis, it can be managed with medication and lifestyle changes.

4.2 The Committee considered the aim of treating primary hypercholesterolaemia. It 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 CVD, even if these concentrations are not very high. The Committee concluded that treatment for hypercholesterolaemia in clinical practice aims primarily to prevent CVD, as recommended in the NICE guideline on lipid modification.

4.3 The Committee considered the current treatment pathway for 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. It was also aware that fibrates, nicotinic acid and bile acid sequestrants (anion exchange resins) are not routinely used to treat primary hypercholesterolaemia, although they may be used for mixed dyslipidaemia. The Committee noted that final draft 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 statins are the main option for treating primary hypercholesterolaemia (heterozygous-familial and non-familial), and that ezetimibe is used to treat primary hypercholesterolaemia in adults who are unable to have a statin, or need to supplement statin therapy.

4.4 The Committee discussed the place of lipoprotein apheresis in managing primary hypercholesterolaemia, noting that this was not included as a comparator in the final scope for this appraisal. 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 lipoprotein apheresis would mainly be used in this group, which reflected people with a high unmet clinical need.

4.5 The Committee discussed the clinical situations in which 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 (LDL-C concentration above 8.0 mmol/litre), and those who cannot tolerate statins at all and who are benefitting only marginally from ezetimibe, which will leave them with a high residual risk of CVD. The Committee understood that, for these people, the only option was apheresis, which has its disadvantages (see section 4.4), and so evolocumab would be a welcome alternative. The Committee concluded that, in clinical practice, evolocumab was likely to be reserved for people who are at a particularly high risk of CVD.

4.6 The Committee discussed how statin intolerance is defined in clinical practice. It noted that there were no clear diagnostic criteria

to identify people who cannot tolerate statins, although for the purposes of NICE's guideline on familial hypercholesterolaemia: identification and management, 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. Adverse effects include evidence of new-onset muscle pain (often associated with blood levels of muscle enzymes indicative of muscle damage), significant gastrointestinal disturbance or alterations in liver function tests. Without other established definitions of statin intolerance, the Committee concluded that the same definition in the NICE guideline would be used in this appraisal.

4.7 The Committee noted that the scope for this appraisal included people with primary hypercholesterolaemia (heterozygous-familial and non-familial) and 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 and mixed dyslipidaemia. The Committee discussed whether evolocumab would be used for mixed dyslipidaemia. It was aware that people with mixed dyslipidaemia also have elevated LDL-C concentrations. Because of this, the Committee concluded that, although evolocumab was likely to mainly be used for primary hypercholesterolaemia in clinical practice, it may also be used for mixed dyslipidaemia.

Clinical effectiveness

4.8 The Committee considered the randomised controlled trials (RCTs) for evolocumab. It noted that 2 of the 4 RCTs gave head-to-head evidence for the comparison with ezetimibe, the sole comparator for evolocumab 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 noted the Evidence Review Group's (ERG) comment 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. The Committee concluded that the trials were suitable for assessing the clinical effectiveness of evolocumab.

4.9 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, who may also have hypercholesterolaemia. The clinical experts did not consider this to have affected the generalisability of the trials because in clinical practice, people with diabetes would have their blood glucose levels controlled before being treated for hypercholesterolaemia. In general, the clinical experts agreed that the trials included people who reflected those with hypercholesterolaemia seen in clinical practice in England. The

Committee concluded that the trial results could be generalised to clinical practice.

4.10 The Committee discussed the RCT evidence for evolocumab in people with primary hypercholesterolaemia. It 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, with consistent results seen across subgroups. The Committee also noted that evolocumab was well tolerated by people. The Committee concluded that, compared with placebo or ezetimibe, evolocumab was clinically effective in reducing LDL-C in people with primary hypercholesterolaemia.

4.11 The Committee discussed the effect of evolocumab on CVD in people with hypercholesterolaemia. It noted that the RCTs primarily measured surrogate end points (such as LDL-C), and were not powered to measure cardiovascular outcomes, which the Committee considered to be an important limitation of the evidence base. The Committee was aware that the reduction in cardiovascular (CV) events with statins was well established in many large RCTs. By contrast, adding other lipid-modifying drugs to statins was not consistently shown to further decrease CV events. The clinical experts highlighted the Cholesterol Treatment Trialists' (CTT) meta-analysis, which followed 169,138 people from 26 interventional trials for a median of 4.9 years, and showed that non-statin therapy reduced CV events. Further data on the benefit of non-statins on CVD came from RCTs of ileal bypass surgery (POSCH), and recently ezetimibe (IMPROVE-IT), which showed

that when ezetimibe was added to a statin, this further reduced CV events compared with statins alone. The clinical experts generally considered LDL-C to be a reasonable surrogate for future CV events, although they indicated that this relationship was uncertain when the LDL-C concentration at baseline is low (below 2.0 mmol/litre). The Committee also 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 cardiovascular outcomes for evolocumab. It agreed that this trial would give useful data on the direct effect of evolocumab on CVD, and recommended that the review of the guidance is scheduled so that the results of FOURIER could be taken into account (see section 8.1). 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.

4.12 The Committee discussed the long-term effects of evolocumab. It heard from the clinical experts that the treatment effect could gradually lessen, 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 the effect of evolocumab weakened over long treatment durations. The Committee heard from the company that in an integrated safety analysis of more than 6000 patients (representing 7235 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 that this analysis followed up people 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 it would. The Committee agreed that any loss of effect would be likely to be infrequent.

Cost effectiveness

4.13 The Committee considered the structure of the model developed by the company. It noted that this differed from the model used for primary hypercholesterolaemia in the NICE clinical guideline on lipid modification. The 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.

4.14 The Committee discussed the modelled populations. It understood that the company initially assumed that people who can tolerate statins have the same characteristics, and hence the same risks of CVD, 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 each of these groups within the non-familial hypercholesterolaemia population separately.

4.15 The Committee discussed the heterozygous-familial hypercholesterolaemia population for which cost-effectiveness results were originally presented. 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. The Committee concluded that the company's revised analyses more appropriately reflected clinical practice.

4.16 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 was aware that the company's analysis of real-world data was not peer reviewed. Because of this, it concluded that using published risk equations, although introducing some uncertainty, was, in principle, acceptable if these reliably estimated the risks of CVD.

4.17 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, instead of the Framingham risk equations, 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.

4.18 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 7.1, 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 for several reasons. Firstly, Benn et al. compared the risk of CV events between the general population and patients with heterozygous-familial hypercholesterolaemia. However, the company applied the rate ratio from the study to the RUTHERFORD-2 trial population, who were already at high risk of CVD. Secondly, the estimate from Benn et al. was not event-specific, so it increased the risk of all CV events by a factor of 7.1.

Thirdly, the rate ratio was derived from a pooled analysis of patients who could and could not, tolerate statins, although the difference between the rate ratios for these 2 groups was large (1.7 and 10.5 respectively). 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 to show the increased risk of CVD in these patients compared with the general population. Because of this, the Committee would have preferred to have seen analyses that adjusted the risk of CVD in people with heterozygous-familial hypercholesterolaemia, with sensitivity analyses, based on a well-conducted systematic review of the literature, and taking into account the studies identified by the ERG about the natural history of heterozygous-familial hypercholesterolaemia (see section 3.50). In response to consultation, the company presented a systematic review of the literature from which it maintained that Benn et al. represented the best available estimate of the increased risk of CVD for heterozygous-familial hypercholesterolaemia, but revised the rate ratio derived from this study from 7.1 to 6.1. The Committee did not, however, consider this to have appropriately addressed its previous concerns about the methodological limitations in the analysis. Furthermore, it 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 maintained its previous

conclusion that the rate ratio from Benn et al., even reduced from 7.1 to 6.1, 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.

4.19 The Committee considered how the company applied the treatment effect in the model. It noted that patients in the model had treatment continuously 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 4.11 and 4.12). 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 data used in the model. It heard from the ERG that only 3 of the 7 utility multipliers used in the acute and post-event states were based on the EQ-5D, NICE's preferred measure of health-related quality of life in adults. Furthermore, the utility multipliers applied in 3 states related to people who had had a myocardial infarction, and so may not be

relevant. The Committee also 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 were generally in line with other values used for people with hypercholesterolaemia, and accepted them in this appraisal.

Non-familial hypercholesterolaemia population

4.21 The Committee considered 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. It discussed the ICERs for evolocumab 140 mg every 2 weeks in people without CVD and separately, in those with CVD:

- People without CVD:
  - People who can tolerate statins:
    - for evolocumab plus statin compared with ezetimibe plus statin, the ICER was £69,200 per quality-adjusted life year (QALY) gained
    - for evolocumab plus statin compared with ezetimibe plus statin, the ICER was £78,500 per QALY gained.
  - People who cannot tolerate statins:

- ◊ for evolocumab compared with ezetimibe, the ICER was £38,500 per QALY gained
- ◊ for evolocumab plus ezetimibe compared with ezetimibe, the ICER was £42,900 per QALY gained.

- People with CVD:
  - People who can tolerate statins:
    - ◊ for evolocumab plus statin compared with ezetimibe plus statin, the ICER was £45,400 per QALY gained
    - ◊ for evolocumab plus statin plus ezetimibe compared with ezetimibe plus statin, the ICER was £50,300 per QALY gained.
  - People who cannot tolerate statins:
    - ◊ for evolocumab compared with ezetimibe, the ICER was £31,000 per QALY gained
    - ◊ for evolocumab plus ezetimibe compared with ezetimibe, the ICER was £33,800 per QALY gained.

4.22 The Committee discussed these ICERs. It noted that all of them were above the maximum acceptable ICERs normally considered to represent a cost-effective use of NHS resources (£20,000–30,000 per QALY gained). For both people with or without CVD, evolocumab therapy generally had a low probability of being cost effective compared with ezetimibe, alone or in combination with statin, at a maximum acceptable ICER of £30,000 per QALY gained (see section 3.46). The Committee recalled its previous conclusions that the effect of using the composite states was unclear because these states had a weak evidential basis (see section 4.13). In addition, the company's modelling of the treatment

effect was somewhat uncertain (see section 4.19). The Committee therefore agreed that the company's base-case ICERs with the patient access scheme for the non-familial hypercholesterolaemia population with or without CVD, which were already unacceptably high, could be different from those presented. The Committee concluded not to recommend evolocumab 140 mg every 2 weeks for the primary non-familial hypercholesterolaemia population (with or without CVD) as a whole.

Heterozygous-familial hypercholesterolaemia population

4.23 The company presented the following revised ICERs, including the patient access scheme, for evolocumab 140 mg every 2 weeks in people without CVD and, separately, in those with CVD:

- People without CVD:
  - People who can tolerate statins:
    - for evolocumab plus statin compared with ezetimibe plus statin, the ICER was £23,500 per QALY gained
    - for evolocumab plus statin compared with ezetimibe plus statin, the ICER was £25,600 per QALY gained.
  - People who cannot tolerate statins:
    - for evolocumab compared with ezetimibe, the ICER was £21,900 per QALY gained
    - for evolocumab plus ezetimibe compared with ezetimibe, the ICER was £23,600 per QALY gained.
- People with CVD:
  - People who can tolerate statins:

- ◊ for evolocumab plus statin compared with ezetimibe plus statin, the ICER was £29,900 per QALY gained
- ◊ for evolocumab plus statin plus ezetimibe compared with ezetimibe plus statin, the ICER was £32,700 per QALY gained.

– People who cannot tolerate statins:

- ◊ for evolocumab compared with ezetimibe, the ICER was £25,300 per QALY gained

– for evolocumab plus ezetimibe compared with ezetimibe, the ICER was £27,400 per QALY gained.

4.24 The Committee discussed these ICERs, noting that evolocumab therapy generally had a low probability of being cost effective compared with ezetimibe, alone or in combination with statin, at a maximum acceptable ICER of £20,000 per QALY gained, although the probability exceeded 80% for most comparisons at a maximum acceptable ICER of £30,000 per QALY (see section 3.47). The Committee noted that the ICERs for people without CVD were actually lower than those for people with CVD. This was inconsistent with the results for non-familial hypercholesterolaemia population, and counter-intuitive because people with CVD have a higher risk of CVD, 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 event of CVD. 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 CVD events were assumed for the non-familial and heterozygous-familial hypercholesterolaemia populations and, further, the calibration of CVD 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, and agreed that these should be treated with caution. Importantly, the Committee had concerns about how the company estimated the risks of CVD for the heterozygous-familial hypercholesterolaemia, particularly in relation to increasing the risk of all CV events for this population by an overestimated factor of 6.1. Because of these limitations, the Committee concluded not to recommend evolocumab 140 mg every 2 weeks for the primary heterozygous-familial hypercholesterolaemia population as a whole.

Subgroups

4.25 The Committee considered the subgroup analyses presented by the company in response to consultation. It was aware that the company's original subgroup analyses had methodological limitations in that the company manually changed the subgroup variable for the entire population while holding the other characteristics at their observed values. In the first appraisal consultation document, the Committee agreed that evolocumab might be cost effective in specific subgroups, but it was not satisfied that the ICERs were reliable enough for decision-making.

In response to consultation, the company revised its subgroup analyses by modelling within-trial subgroups. The Committee concluded that the company's revised analyses were more appropriate because they reflected the patient characteristics of the subgroups more accurately.

4.26 The Committee discussed whether it could consider the cost effectiveness of evolocumab in clinically relevant subgroups. It recognised that the analyses presented by the company had several limitations, and sometimes produced ICERs that varied inconsistently in different directions. This made the Committee unsure about the overall validity of the results, particularly those for the heterozygous-familial hypercholesterolaemia without CVD. Nevertheless, the Committee agreed that there was merit in exploring potential subgroups of patients with the highest need. It also noted that most comments received during 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 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. 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 precise 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 population.

4.27 The Committee considered the subgroups with 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.

Other consultation comments received also suggested specific subgroups. However, these suggestions were 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 reflected the areas where the clinical unmet need was highest, concluding that it would be appropriate to use them in its decision-making.

4.28 **Non-familial hypercholesterolaemia with progressive, symptomatic CVD, and persistently high LDL-C concentrations above 4.0 mmol/litre**: the Committee discussed which of the company's modelled subgroups reflected patients with 'progressive, symptomatic CVD'. It agreed that 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. The Committee recognised that these ICERs would be lower for a minimum, as opposed to a mean, LDL-C concentration of 4.0 mmol/litre. It also recognised, however, that they could be higher because the effect of using the composite states was unclear, and the company's modelling of the long-term effect of evolocumab was not certain. The Committee recalled the statement from the clinical expert that people who cannot tolerate statins will have a high residual risk of CVD, and may have apheresis as their only remaining treatment option (see section 4.4). It also noted that the comments from the Royal College of Pathologists and the clinical expert advised that most people in this subgroup (that is, people with persistently high LDL-C concentrations above 4.0 mmol/litre) will not have been able to tolerate statins. The Committee therefore considered the company's ICER for patients who cannot tolerate statins within this subgroup. This was £28,700 per QALY gained for evolocumab compared with ezetimibe, but would be lower for a minimum LDL-C concentration of 4.0 mmol/litre. 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. The Committee concluded that it could recommend evolocumab 140 mg every 2 weeks for primary non-familial hypercholesterolaemia and mixed dyslipidaemia with progressive, symptomatic cardiovascular disease, and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy in adults who cannot tolerate statins.

4.29 **Heterozygous-familial hypercholesterolaemia with progressive, symptomatic CVD, and persistently high LDL-C concentrations above 4.0 mmol/litre**: the Committee recognised that most patients in this subgroup would be eligible for apheresis according to the current guidelines (see section 4.4), reflecting a high clinical unmet need. The company's ICER for the heterozygous-familial hypercholesterolaemia population with CVD and a mean LDL-C concentration of 4.0 mmol/litre was £30,200 per QALY gained. This would be lower for people with 'progressive, symptomatic CVD' because their risk of subsequent CVD would be higher than the general heterozygous-familial hypercholesterolaemia population with CVD, and so treatment would be expected to be more cost effective. It would also be lower for an LDL-C concentration above, rather than equal to, 4.0 mmol/litre. The Committee agreed that people with heterozygous-familial hypercholesterolaemia and mixed dyslipidaemia with progressive, symptomatic CVD, and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximal

tolerated lipid-lowering therapy have a high residual risk of CVD and suboptimal treatment options. The Committee concluded to recommend evolocumab 140 mg every 2 weeks for this subgroup.

4.30 **Severe heterozygous-familial hypercholesterolaemia (without CVD) with pre-treatment LDL C concentrations above 8.0 mmol/litre and persistently high LDL C concentrations above 4.0 mmol/litre**: the Committee understood from the clinical experts that the risk of CVD in this subgroup increases by 25% compared with the general heterozygous-familial hypercholesterolaemia population without CVD. The Committee noted that there were no ICERs for the heterozygous-familial hypercholesterolaemia population without CVD who have an LDL-C concentration above 8.0 mmol/litre. The ICER for people who have a mean LDL-C concentration of 6.0 mmol/litre was £18,400 per QALY gained. However, the Committee had serious doubts about the face validity of the ICERs for the heterozygous-familial hypercholesterolaemia population without CVD, mainly because the ICERs were inconsistent with the results for non-familial hypercholesterolaemia population, and counter-intuitive (see section 4.24). Because of this, it concluded to recommend evolocumab 140 mg every 2 weeks only for the subset of patients with severe heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia who have the highest clinical unmet need; that is, people who cannot tolerate statins.

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 to recommend evolocumab, only if:

- the dosage is 140 mg every 2 weeks and
- the person has an LDL-C concentrations persistently above 4.0 mmol/litre and
  - primary non-familial hypercholesterolaemia or mixed dyslipidaemia and
    - ◊ CVD and
    - ◊ statin therapy is not tolerated
  - primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia and
    - ◊ CVD
  - severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD and
    - ◊ pre-treatment LDL-C concentrations are above 8.0 mmol/litre and
    - ◊ statin therapy is not tolerated and
- the company provides evolocumab with the discount agreed in the patient access scheme.

4.32 The Committee discussed whether its recommendations for people who cannot tolerate statins also apply to those in whom statins are contraindicated. It considered that the latter group also have limited treatment options, and the same unmet need as people who cannot tolerate statins. In addition, there was no biologically plausible

reason for the effect to differ between these 2 groups. Because of this, the Committee concluded that its recommendations for people who cannot tolerate statins also apply to those in whom statins are contraindicated.

4.33 The Committee discussed whether the ICERs it considered reflected 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 was because people may move from secondary to primary care after 2–3 years, and simple discounts do not apply when drugs are prescribed through FP10 prescriptions. The Committee agreed in the first appraisal consultation document that up to 90% of people may have evolocumab through FP10 prescriptions in primary care after 2 years. The Committee took note of the company's consultation comments about the implementation of the PAS, and agreed to discuss this issue in the context of the new recommendations. It considered that the subgroups for which evolocumab is recommended have severe hypercholesterolaemia and a high risk of CVD, and so would continue treatment under secondary care. The Committee concluded that the discounted price of evolocumab would apply to all people for whom evolocumab is recommended in this appraisal consultation document.

4.34 The Committee considered whether it could make recommendations for evolocumab 420 mg monthly. It recognised that the cost-effectiveness evidence considered 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 concluded not to recommend evolocumab 420 mg monthly for primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia.

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 Appraisal 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

TAXXX	**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 an LDL-C concentrations persistently above 4.0 mmol/litre and
  – primary non-familial hypercholesterolaemia or mixed dyslipidaemia and
  ◊ CVD and
  ◊ statin therapy is not tolerated or contraindicated
  – primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia and
  ◊ CVD
  – severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD and
  ◊ pre-treatment LDL-C concentrations are above 8.0 mmol/litre and
  ◊ statin therapy is not tolerated or contraindicated and
• the company provides evolocumab with the discount agreed in the patient access scheme.
 	
The Committee recognised that the analyses presented by the company had several limitations, which made the Committee unsure about the overall validity of the results. Nevertheless, the 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 ICERs could be used to check a
	1.1, 4.26

proposed set of recommendations guided by the clinical unmet need in this population.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee was aware that lipoprotein apheresis is not only costly and onerous for the patient, but also difficult to access. It concluded that patients eligible for apheresis according to current guidelines had a high unmet clinical need. The Committee heard that there is a high clinical unmet need in people with severe forms of heterozygous-familial hypercholesterolaemia, and those who cannot tolerate statins at all and who are benefitting only marginally from ezetimibe.	4.4, 4.5
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.	4.26
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 particularly high risk of CVD.	4.5
Adverse reactions	The Committee noted that evolocumab was well tolerated by people.	4.10
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that 2 of the 4 randomised controlled trials (RCTs) for evolocumab gave head-to-head 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	4.8, 4.11

	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 cardiovascular outcomes, which the Committee considered to be an important limitation of the evidence base.	
Relevance to general clinical practice in the NHS	The Committee concluded that the trial results could be generalised to clinical practice in England.	4.9
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.	4.11, 4.12

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 subgroups.	4.10
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.	4.10
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee concluded that the internal validity of the model was unclear because there was no evidence to support the modelling of these states.	4.13
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee concluded that using published risk equations introduced some uncertainty. The Committee concluded that the rate ratio from Benn et al., even reduced from 7.1 to 6.1, highly overestimated the risk of CVD among people with heterozygous-familial hypercholesterolaemia, and cast doubt about	4.16, 4.18, 4.19

	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.	
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 hypercholesterolaemia, and accepted them 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.	4.26
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.	4.18
Most likely cost-effectiveness estimate (given as an ICER)	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, the company's ICERs were lower than £37,700 (based on the LAPLACE-2 population) and £29,200 (based on the Clinical Practice Research Datalink population) per QALY gained. In the subset of this subgroup who cannot tolerate statins, the ICER was lower than £28,700 per QALY gained. For heterozygous-familial hypercholesterolaemia with progressive, symptomatic CVD, and persistently high	4.28–4.30

	LDL-C concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy, the company's ICER was lower than £30,200. For 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 company's ICER was lower than £18,400 per QALY gained. In the subset of this subgroup who cannot tolerate statins, the ICER would be even lower.	
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 [NICE to add details at time of publication].

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 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Cardiovascular disease: risk assessment and reduction, including lipid modification. (2014) NICE guideline CG181
- Familial hypercholesterolaemia: identification and management. (2008) NICE guideline CG71
- Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. (2007) NICE technology appraisal guidance 132

Under development

- Ezetimibe for treating primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132) NICE technology appraisal guidance (publication expected February 2016)
- Hypercholesterolaemia (primary) and dyslipidaemia (mixed) – alirocumab. NICE technology appraisal guidance (publication expected June 2016)
- Familial hypercholesterolaemia (standing committee update). NICE guideline (publication expected January 2016)

8 Proposed date for review of guidance

8.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive when the FOURIER trial is

completed (planned for February 2018) so that the results of the trial can be taken into account. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens
Chair, Appraisal Committee
January 2016

9 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
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Medical Director, NHS South Yorkshire and Bassetlaw

Mr David Chandler

Lay Member

Mrs Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Department of Primary Care and Population Health, University College London

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Nigel Langford

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Patrick McKiernan

Consultant Paediatrician, Birmingham Children's Hospital

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Dr Iain Miller

Founder and Chief Executive Officer, Health Strategies Group

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Dr Anna O'Neill

Deputy Head of Nursing & Health Care School, Senior Clinical University Teacher, University of Glasgow

Dr Claire Rothery

Research Fellow in Health Economics, University of York

Professor Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Dr Judith Wardle

Lay Member

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.

Ahmed Elsada

Technical Lead

Nicola Hay

Technical Adviser

Lori Farrar and **Stephanie Yates**

Project Managers

10 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by School of Health and Related Research:

- Carroll C, Tappenden P, Rafia R et al. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: A Single Technology Appraisal. School of Health and Related Research (ScHARR), September 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Amgen

II. Professional/expert and patient/carer groups:

- HEART UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- UK Clinical Pharmacy Association

III. Other consultees:

- Department of Health
- NHS Barking and Dagenham Clinical Commissioning Group
- NHS England
- NHS Walsall Clinical Commissioning Group
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Merck Sharp & Dohme
- Sanofi

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Professor Antony Wierzbicki, Consultant in Metabolic Medicine, nominated by HEART UK – clinical expert
- Dr Handrean Soren, Consultant Physician and Endocrinologist, nominated by HEART UK – clinical expert
- Steve Forster, nominated by HEART UK – patient expert

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Amgen