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: 08 December 2015

Second Appraisal Committee meeting: 13 January 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 Appraisal Committee's preliminary recommendations

1.1 Evolocumab, alone or in combination with lipid-lowering therapies, is not recommended within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia in adults.

1.2 Adults whose treatment with evolocumab 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 is either 140 mg 2-weekly 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. If evolocumab had been recommended, this scheme would provide 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 would not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee (section 9) considered evidence submitted by Amgen and a review of this submission by the Evidence Review Group (section 10).

Clinical-effectiveness evidence

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. Patients were included only if they had an 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 (RUTHERFOED-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 2-weekly or 420 mg monthly in combination with placebo was compared with placebo 2-weekly 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 2-weekly or monthly alone respectively.
- RUTHERFORD-2 (n=331): evolocumab 140 mg 2-weekly or 420 mg monthly was compared with placebo 2-weekly or monthly respectively.
- GAUSS-2 (n=307): evolocumab 140 mg 2-weekly or 420 mg monthly in combination with placebo was compared with placebo 2-weekly 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 Evidence Review Group (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, a group which the ERG considered highly likely to have co-morbid hypercholesterolaemia and mixed dyslipidaemia.

3.6 The ERG noted that none of the trials studied evolocumab compared with ezetimibe in patients with heterozygous-familial hypercholesterolaemia, or evolocumab in combination with ezetimibe in any population.

3.7 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 shown. 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

3.8 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 2-weekly: −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 2-weekly: −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 2-weekly: −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 2-weekly: −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 2-weekly: −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 2-weekly: −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).

3.9 The company presented subgroup analyses that were pre-specified in the study protocols of the trials, 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. However, how 'high risk' is defined may vary across countries, and so the company presented pre-specified subgroup analyses that were done to give data on 5 different subgroups of high-risk patients. The company also did post hoc subgroup analyses (that is, after the trial results had been compiled). These explored whether the effect of evolocumab depended on the presence of a broad range of CV events, or the severity of hypercholesterolaemia. The company 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.

3.10 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. The company 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 ischemic 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).

3.11 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

3.12 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.

3.13 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 2-weekly 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).

3.14 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

3.15 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 (51.1% compared with 49.6%), with most adverse events being mildly to moderately severe. Across year 1 of the extension studies (controlled period), the frequency of adverse events associated with evolocumab increased to 65.4%.
- 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

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

Cost-effectiveness evidence

3.17 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

3.18 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.

3.19 The intervention modelled in the base case was evolocumab 140 mg 2-weekly; the company explored using the monthly dose of evolocumab in scenario analyses (see sections 3.45 and 3.46). 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

3.20 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 most patients within this population. This was because most UK patients can have an LDL-C concentration of 2.0 mmol/litre on statins.

3.21 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.

3.22 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

3.23 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.

3.24 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

3.25 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

3.26 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 relative risk of 7.1 (relative to patients without heterozygous-familial hypercholesterolaemia) derived from a study by Benn et al. (2012).

ERG's comments

3.27 The ERG considered the process by which the company estimated the risks of CVD to be circular, unnecessarily complicated and counter-intuitive, with several assumptions and adjustments needed to estimate these risks. The ERG considered that, whereas the company used published equations to predict risks then adjusted these to reflect real-world data, it could have estimated

the risks directly from the real-world data (CPRD and HES analysis) without using risk equations, which in the ERG's opinion did not add information compared with the CPRD and HES data.

3.28 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, which was used in the model for NICE guideline on lipid modification.

3.29 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.

3.30 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 relative risk was not applied to the general population, but to the RUTHERFORD-2

trial population that was already at high risk of CVD. This was likely to overestimate the risk of CVD, and produce more favourable ICERs for evolocumab. The ERG also highlighted other studies, which suggested that the relative risk derived from Benn et al. was likely to be an overestimate (see section 3.50).

Treatment effect

3.31 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).

3.32 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 3.19). 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

3.33 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.

3.34 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.

3.35 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

3.36 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 3.45 and 3.46).

3.37 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

3.38 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.

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

Company's base-case results and sensitivity analysis

3.40 In its patient access scheme submission, the company presented the base-case analyses for all 3 populations as incremental cost-effectiveness analyses. It also presented deterministic and probabilistic sensitivity analyses, and scenario analyses for the non-familial hypercholesterolaemia population with CVD and the heterozygous-familial hypercholesterolaemia population. These analyses were only done for the comparison of evolocumab plus statin with ezetimibe plus statin, except for the probabilistic sensitivity analysis, which also included the comparison of evolocumab with ezetimibe. Also, the company presented

subgroup analyses for the comparison of evolocumab plus statin with ezetimibe plus statin in the non-familial hypercholesterolaemia population with CVD. All the analyses used the 2-weekly dose of evolocumab, except the scenario analysis in which the company explored using the monthly dose (see sections 3.45 and 3.46).

Base-case analysis

3.41 The company's base-case ICERs including the patient access scheme are presented in table 1 for all 3 populations. The total and incremental costs for evolocumab were commercial in confidence.

Table 1 Company's 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.			

Deterministic sensitivity analyses (non-familial hypercholesterolaemia with CVD and heterozygous-familial hypercholesterolaemia: evolocumab plus statin compared with ezetimibe plus statin only)

3.42 The company presented deterministic sensitivity analyses in which it varied input values in the model for 1 parameter at a time. Among the most influential parameters were the effect of reducing LDL-C concentration on death from coronary heart disease or ischemic stroke, the effect of ezetimibe on LDL-C in patients at high risk of CVD, and the CPRD and heterozygous-familial hypercholesterolaemia calibration rate ratios.

Probabilistic sensitivity analyses (non-familial hypercholesterolaemia with CVD and heterozygous-familial hypercholesterolaemia: evolocumab plus statin compared with ezetimibe plus statin, and evolocumab compared with ezetimibe)

3.43 The company did probabilistic sensitivity analyses varying parameters simultaneously with values from a probability distribution. The probabilistic ICERs were slightly higher than the deterministic ones (see table 2). At a maximum acceptable ICER of £30,000 per QALY gained, there was a 0% probability of evolocumab being cost effective compared with ezetimibe for the non-familial hypercholesterolaemia population with CVD. For heterozygous-familial hypercholesterolaemia (with or without CVD), there was a low probability of evolocumab (alone or in combination with statins) being cost effective at a maximum acceptable ICER of £20,000 per QALY gained (less than 10%). However, at a maximum acceptable ICER of £30,000 per QALY gained, the probability exceeded 90%.

Table 2 Probabilistic and deterministic ICERs (including the patient access scheme)

Population	Intervention	Comparator	ICER (£/QALY)	
			Deterministic	Probabilistic
Non-FH with CVD	Evolocumab plus statin	Ezetimibe plus statin	46,005	47,079
	Evolocumab	Ezetimibe	49,278	50,321
HeFH	Evolocumab plus statin	Ezetimibe plus statin	22,902	23,504
	Evolocumab	Ezetimibe	23,927	24,604
Abbreviations: CVD, cardiovascular disease; HeFH, heterozygous-familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; Non-FH, non-familial hypercholesterolaemia; QALY, quality-adjusted life year.				

Scenario analyses: severity of hypercholesterolaemia (non-familial hypercholesterolaemia with CVD and heterozygous-familial hypercholesterolaemia: evolocumab plus statin compared with ezetimibe plus statin only)

3.44 The company explored how the severity of hypercholesterolaemia, as reflected in the LDL-C concentration at baseline, affected the cost effectiveness of evolocumab plus statin compared with ezetimibe plus statin. Results suggested that the higher the concentration of LDL-C at baseline, the more cost effective evolocumab is. The company reported the following results, which included the patient access scheme for evolocumab:

- **Non-familial hypercholesterolaemia with CVD**: when the company assumed a baseline LDL-C concentration of 3.0 mmol/litre, the ICER for evolocumab plus statin compared with ezetimibe plus statin was £52,222 per QALY gained. This

decreased to £34,685 per QALY gained at a baseline LDL-C concentration of 6.0 mmol/litre.

- **Heterozygous-familial hypercholesterolaemia**: at baseline LDL-C concentrations of 3.0 mmol/litre and 6 mmol/litre, the ICERs for evolocumab plus statin compared with ezetimibe plus statin were £29,250 and £17,328 per QALY gained respectively.

Other scenario analyses (non-familial hypercholesterolaemia with CVD and heterozygous-familial hypercholesterolaemia: evolocumab plus statin compared with ezetimibe plus statin only)

3.45 The company did further scenario analyses to assess the impact of having evolocumab monthly (as opposed to 2-weekly), having treatment for 5, 10 and 20 years, applying alternative discount rates, capping the risk at age 75, applying costs derived from NICE's guideline on lipid modification, using utility values from the company-sponsored time trade-off study, and making alternative assumptions about nurse training.

3.46 The company reported the following results, which included the patient access scheme:

- **Non-familial hypercholesterolaemia with CVD**: compared with the base-case ICER of £46,005 per QALY, the lowest ICER was £34,450 per QALY gained when using the utility values from the company's time trade-off study, and the highest was £104,346 per QALY gained when applying an annual discount rate of 0% and 6% for costs and health effects respectively. Evolocumab monthly increased the base-case ICER to £69,229 per QALY gained.

- **Heterozygous-familial hypercholesterolaemia**: compared with the base-case ICER of £22,902 per QALY gained, the company obtained the lowest and highest ICER (£17,555 and £58,252 per QALY gained) when it varied the annual discount rate for costs and health effects. Evolocumab monthly increased the base-case ICER to £34,037 per QALY gained. Using the utility values from company's time trade-off study had little impact on the ICER in this population.

Subgroup analyses (non-familial hypercholesterolaemia with CVD only: evolocumab plus statin compared with ezetimibe plus statin only)

3.47 The company presented 3 sets of subgroup analyses based on the following variables in LAPLACE-2:

- Patients with individual risk factors for CVD, including LDL-C concentration of 3.0–6.0 mmol/litre (in increments of 0.5 mmol/litre), sex, diabetes, vascular beds (2 or 3), atrial fibrillation, and CV events that happened in the previous year.
- Patients with individual risk factors for CVD (diabetes, atrial fibrillation, number of vascular beds, or history of CVD events) combined with LDL-C concentration at baseline (3.5–4.5 mmol/litre), age and sex.
- Patients with 2 individual risk factors for CVD (including diabetes, atrial fibrillation, number of vascular beds, and history of acute coronary syndrome) combined with baseline LDL-C (3.0–4.0 mmol/litre), age and sex.

3.48 The company reported the following results for the non-familial hypercholesterolaemia population with CVD:

- **Patients with individual risk factors for CVD**: the ICERs for evolocumab plus statin compared with ezetimibe plus statin ranged from £28,550 per QALY gained (patients with 3 vascular beds) to £98,139 per QALY gained (when all patients were assumed to have ischemic stroke when they started treatment).
- **Patients with individual risk factors for CVD combined with LDL-C concentration at baseline, age and sex**: the ICERs ranged from £22,138 per QALY gained (men with LDL-C concentration of 4.5 mmol/litre and 3 vascular beds who are 10 years older than the average cohort age) to £100,609 per QALY gained (women of the average age of the cohort with LDL-C concentration of 3.5 mmol/litre and a history of ischemic stroke).
- **Patients with 2 individual risk factors combined with baseline LDL-C concentration at baseline, age and sex**: the ICERs ranged from £18,784 per QALY gained (men with LDL-C concentration of 4.0 mmol/litre, diabetes and 3 vascular beds who are 10 years older than the average cohort age) to £42,418 per QALY gained (women of the average age of the cohort with LDL-C concentration of 3.0 mmol/litre, heart failure and 2 vascular beds).

ERG's comments

3.49 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 3.20–3.22)

- the use of multiple composite states, which were populated using many assumptions and little evidence (see section 3.25).
- the circular approach used by the company to predict risks of CVD (see section 3.27)
- the likely overestimation of the risk of CVD in the heterozygous-familial hypercholesterolaemia population (see section 3.30)
- the uncertainty about the relationship between LDL-C reduction and reductions in CV events (see section 3.33)

3.50 The ERG stated that calibration rate of 7.1, which was likely to be overestimated (see section 3.30), 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).

3.51 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 sensitivity analyses around the patient access scheme

3.52 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. The company reported the following ICER ranges for the comparison of evolocumab plus statin with ezetimibe plus statin:

- **Non-familial hypercholesterolaemia without CVD**: £85,869 to £197,191 per QALY gained, compared with a base-case ICER of £74,331 per QALY gained.
- **Non-familial hypercholesterolaemia with CVD**: £53,491 to £126,845 per QALY gained, compared with a base-case ICER of £46,005 per QALY gained.
- **Heterozygous-familial hypercholesterolaemia**: £26,898 to £65,624 per QALY gained, compared with a base-case ICER of £22,902 per QALY gained.

3.53 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 are at risk of 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 using medication and lifestyle changes.

4.2 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 statins. 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 ezetimibe monotherapy is used to treat primary hypercholesterolaemia when a statin is considered inappropriate or is not tolerated, and that ezetimibe in combination with a statin is used in people 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.

4.3 The Committee considered the aim of treating primary hypercholesterolaemia. It was aware that the recommendations in the NICE guideline on lipid modification place greater emphasis on managing cardiovascular risk than meeting target cholesterol concentrations. The NICE guideline on lipid modification recommends offering statins for treating hypercholesterolaemia for primary prevention of CVD in people with a 10% or greater 10−year risk of developing CVD for many clinical scenarios. However, the decision to treat hypercholesterolaemia for the primary prevention of CVD sometimes happens when the 10-year risk of developing CVD is higher than 10%. The guideline also recommends starting statin treatment (normally atorvastatin 80 mg) in all people with CVD (that is, for secondary prevention). The Committee understood from the clinical experts that treating people with familial hypercholesterolaemia was also a priority because the lifelong exposure to high concentrations of 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 would start as recommended in the NICE guideline on lipid modification, with the primary aim of preventing CVD.

4.4 The Committee discussed the clinical situations in which evolocumab would be started. It heard from the clinical experts that the clinical unmet need is highest in 2 subgroups of people who are considered to have a different prognosis from the typical person:

- People with heterozygous-familial hypercholesterolaemia, particularly those who have an LDL-C concentration above 8 mmol/litre and in whom the risk of CVD is considered to

increase by 25% compared with the general heterozygous-familial hypercholesterolaemia population.

- People 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, although this was not widely available, and so evolocumab would be a welcome alternative. The Committee concluded that evolocumab was likely to be reserved for people who are at a particularly high risk of CVD, including people with heterozygous-familial hypercholesterolaemia, and those who cannot tolerate statins and in whom ezetimibe does not adequately control LDL-C.

4.5 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 was aware that the marketing authorisation for ezetimibe did not include treatment of mixed dyslipidaemia. It asked the clinical experts whether evolocumab would be equally used for primary hypercholesterolaemia and mixed dyslipidaemia in clinical practice. It heard that evolocumab would be used only for primary hypercholesterolaemia, and that alternative options would be considered for mixed dyslipidaemia. The Committee concluded

that evolocumab would be predominantly used for primary hypercholesterolaemia (heterozygous-familial and non-familial) in clinical practice.

Clinical effectiveness

4.6 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 in combination with ezetimibe in any population. The Committee agreed that the RCTs were relevant, and of good quality, although they primarily measured surrogate end points (such as LDL-C). The Committee concluded that the trials were suitable for assessing the clinical effectiveness of evolocumab.

4.7 The Committee discussed whether the RCTs for evolocumab represented people who present with primary hypercholesterolaemia in clinical practice in England. The ERG 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 considered 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.

4.8 The Committee discussed the RCT evidence for evolocumab in people with primary hypercholesterolaemia. It noted that at both dosages (140 mg 2-weekly 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.

4.9 The Committee discussed the effect of evolocumab on CVD in people with hypercholesterolaemia. It noted that the RCTs mainly gave data on 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 Committee noted that the clinical experts generally considered LDL-C to be a reasonable surrogate for future CV events, although this relationship was uncertain when the LDL-C concentration at baseline is low (below 2.0 mmol/litre). It also heard from them 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 3.10). However, it was aware 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 a key area of uncertainty, particularly with low concentrations of LDL-C at baseline.

4.10 The Committee discussed the long-term effects of evolocumab. It heard from the clinical experts that the treatment effect was more likely to gradually lessen when people start treatment with relatively low LDL-C concentrations. However, the Committee also noted the statement from clinical experts suggesting that with evolocumab, neutralising antibodies can develop and treatment may lose its effectiveness. 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 concluded that the effect of evolocumab over time was still unknown.

Cost effectiveness

4.11 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 3.25). The Committee agreed that the composite states reflected specific combinations of CV events,

which were unlikely to be robustly modelled given the existing evidence. Because the effect of using the composite states was unclear, the Committee expressed its concern about the internal validity of the model.

4.12 The Committee considered the following parameters in the model:

- the modelled populations
- the general approach to estimating the risk of CVD
- the risk equations used to predict the risks of CVD at baseline
- the estimation of the risks of CVD for people with heterozygous-familial hypercholesterolaemia
- the adjustment of the predicted risks of CVD for the heterozygous-familial hypercholesterolaemia population
- the treatment effect
- the utility data.

4.13 The Committee discussed the modelled populations. It understood that the company modelled all populations based on LAPLACE-2 (non-familial hypercholesterolaemia) or RUTHERFORD-2 (heterozygous-familial hypercholesterolaemia), which included people who could, and those who could not, tolerate statins. This implicitly assumed that these 2 groups have the same characteristics and risks of CVD at baseline. The Committee was aware that GAUSS-2 only included people who could not tolerate statins, although the company chose not to use it to source data for this group. The Committee heard from the clinical experts that separating out these 2 groups would have been desirable because the risk of CVD was likely to be affected by whether or not the

person can tolerate statins. The Committee concluded that each of these groups should have been modelled separately. In addition, the Committee considered issues specific to the populations with non-familial, or heterozygous-familial, hypercholesterolaemia:

- Non-familial hypercholesterolaemia: the Committee noted that the company modelled only the subset of patients in LAPLACE-2 with an LDL-C concentration above 2.5 mmol/litre. It heard from the clinical experts that in clinical practice, evolocumab would not be used in people with an LDL-C concentration below 2.5 mmol/litre. The Committee concluded that it was appropriate for the company to have modelled a non-familial hypercholesterolaemia population with an LDL-C concentration above 2.5 mmol/litre.
- Heterozygous-familial hypercholesterolaemia: the Committee noted that the company modelled patients with or without CVD together, which the ERG did not consider to be clinically appropriate. 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. The Committee concluded that splitting the heterozygous-familial hypercholesterolaemia by whether or not people had CVD would better reflect clinical practice.

4.14 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 the real-world data (Clinical Practice Research Datalink and Hospital Episode Statistics analysis) 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 analysis of real-world data was not peer reviewed. Because of this, it concluded that using published risk equations was, in principle, acceptable if these were relevant to the population being modelled and reliably estimated the risks of CVD.

4.15 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 used the Framingham Heart Study risk equations for patients without CVD, and the REACH registry risk equations for patients with CVD. The Committee questioned why the company did not use the QRISK2 assessment tool for people without CVD. It did not consider the company to have sufficiently justified why it used the Framingham risk equations because the company stated that the predicted CV events would need to be calibrated whether the Framingham equations or QRISK2 tool were selected. The Committee was aware that extensive validation studies on the US-based Framingham risk equations had shown that they systematically overestimated the risk of CVD. Although the Committee recognised that the company calibrated the predicted risks, it did not agree that the Framingham equations should have been used at the outset when these were known to

produce inaccurate predictions. The Committee was aware that the QRISK2 assessment tool was more widely used in the UK, being recommended in NICE's guideline on lipid modification, and targeted to UK patients. The company stated that the Framingham equations had the advantage of including a broader definition of CV events, and needing fewer variables. However, the Committee considered that the trials collected data for enough variables to inform the QRISK2 tool, and that for the variables for which data were not collected, the average value for the specific UK population that reflects this variable could be used. The Committee concluded that the QRISK2 assessment tool would have been more appropriate than Framingham risk equations to estimate the risks of CVD in people without CVD.

4.16 The Committee discussed whether the estimated risks of CVD in people with heterozygous-familial hypercholesterolaemia were appropriate. The ERG noted that the company applied the Framingham and REACH registry equations formulated for people with or without CVD to the population in RUTHERFORD-2, which included a mix of the 2 groups. Furthermore, neither set of equations was applicable for heterozygous-familial hypercholesterolaemia. The Committee recalled its previous conclusion that the QRISK2 assessment tool was more appropriate than the Framingham risk equations for people without CVD (see section 4.16), acknowledging that neither was derived from people with heterozygous-familial hypercholesterolaemia. It concluded that the REACH registry and QRISK2 assessment tool could be used for heterozygous-familial hypercholesterolaemia in this appraisal,

but only for the subsets in RUTHERFORD-2 with or without CVD respectively.

4.17 The Committee discussed how the company adjusted the risks of CVD predicted from the Framingham and REACH registry risk equations for the heterozygous-familial hypercholesterolaemia population. It understood that the company applied a relative risk of 7.1, which was derived from a study by Benn et al. (2012), to reflect the increased risk of CVD in this population. The Committee heard from the ERG that this adjustment was not appropriate for several reasons. First, Benn et al. compared the risk of CV events between the general population and patients with heterozygous-familial hypercholesterolaemia. However, the company applied the relative risk from the study to the RUTHERFORD-2 trial population, who were already at high risk of CVD. Second, 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. Third, the relative risk was derived from a pooled analysis of patients who could, and those who could not, tolerate statins, whereas the difference in relative risk between these 2 groups was large (1.7 and 10.5 respectively). The Committee noted the studies highlighted by the ERG (see section 3.50), which suggested that the rate of death from CVD in patients with heterozygous-familial hypercholesterolaemia was unlikely to be as high as that assumed by the company. It also noted the ERG's exploratory analyses, which implied that the model was highly sensitive to the relative risk applied for this population (see section 3.51). The Committee heard from the clinical experts that there was no robust evidence to show the

increased risk of CVD in patients with heterozygous-familial hypercholesterolaemia compared with the general population. However, they considered that the estimate based on Benn et al. was likely to have significantly overestimated the risk of CVD in these patients. The Committee concluded that, given the methodological limitations highlighted by the ERG and the existing evidence, the relative risk from Benn et al. highly overestimated the risk of CVD among people with heterozygous-familial hypercholesterolaemia.

4.18 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. The Committee agreed that, given the existing data, the extent to which evolocumab could reduce CVD was uncertain (see section 4.9). Also, it was unknown whether the effect of evolocumab would continue over time because long-term data were limited (see section 4.10). Because of this, the Committee concluded that the company did not sufficiently explore alternative scenarios reflecting different assumptions about future treatment effects.

4.19 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. The Committee agreed that the utility multipliers were generally in line with other values used for people with hypercholesterolaemia, and accepted them in this appraisal. However, it concluded that the equation from the Health Survey for England would better show the relationship between age and health-related quality of life.

Non-familial hypercholesterolaemia population

4.20 The Committee considered the company's incremental cost-effectiveness ratios (ICERs) for people without CVD and separately, for those with CVD.

- People without CVD: The base-case deterministic ICERs with the patient access scheme were £74,300 per quality-adjusted life year (QALY) gained for evolocumab plus statin compared with ezetimibe plus statin (people who can tolerate statins), and £78,800 per QALY gained for evolocumab compared with ezetimibe (people who cannot tolerate statins). The company did not present any further analyses with the patient access scheme for this population.
- People with CVD: The company estimated the following ICERs with the patient access scheme:
  - People who can tolerate statins:
    - for evolocumab plus statin compared with ezetimibe plus statin, the ICERs were £46,000 per QALY gained (deterministic) and £47,100 per QALY gained (probabilistic)

- ◊ for evolocumab plus statin plus ezetimibe compared with ezetimibe plus statin, the ICERs were £50,900 per QALY gained (deterministic); no probabilistic ICER was presented for this comparison.

– People who cannot tolerate statins:
  - ◊ for evolocumab compared with ezetimibe, the ICERs were £49,300 per QALY gained (deterministic), and £50,300 per QALY gained (probabilistic)
  - ◊ for evolocumab plus ezetimibe compared with ezetimibe, the ICERs were £52,800 per QALY gained (deterministic); no probabilistic ICER was presented for this comparison.

The Committee was aware that the probabilistic sensitivity analysis for people with CVD suggested that there was a 0% probability of evolocumab alone or with statin being cost effective compared with ezetimibe alone or with statin at a maximum acceptable ICER of £30,000 per QALY gained.

4.21 The Committee discussed these ICERs. It recalled that in the model, patients who can, and those who cannot, tolerate statins had the same risks of CVD at baseline, whereas future CV events were likely to be influenced by whether or not the person can tolerate statins. Furthermore, the company used the Framingham risk equations to predict the risk of CVD before treatment, although these have been shown to overestimate the risk of CVD. The company then assumed that the effect of evolocumab would last indefinitely in the model, which the Committee considered to be uncertain because there was no robust evidence on the effect of evolocumab on CVD, or on the long-term effect of evolocumab.

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 could be substantially higher than those presented, which were already above the maximum acceptable ICERs normally considered to represent a cost-effective use of NHS resources (£20,000–30,000 per QALY gained). The Committee concluded not to recommend evolocumab for primary non-familial hypercholesterolaemia with or without CVD.

4.22 The Committee considered the company's subgroup analyses for people with CVD (see sections 3.47 and 3.48). It noted that these suggested that the cost effectiveness of evolocumab might improve in certain subgroups at a particularly high risk of CVD, such as those with multiple risk factors for CVD for whom the company estimated ICERs for evolocumab plus statin compared with ezetimibe plus statin as low as £18,800 per QALY gained, compared with the base-case ICER of £46,000 per QALY gained. The Committee was aware that these analyses had the same limitations as the primary analysis (see section 4.21). Also, the ERG highlighted additional methodological limitations in that the company manually changed the subgroup variable for the entire population and held the other characteristics at their observed values, instead of modelling the subgroups who actually had these characteristics in the trial. The Committee was aware that some variables may be correlated in subgroups, and so within-trial subgroups would reflect the subgroup characteristics more accurately. The Committee did not preclude that evolocumab might

be cost effective in specific subgroups with CVD. However, given the limitations of the analyses, it was not satisfied that the ICERs were reliable enough for its decision-making, and concluded not to recommend evolocumab for any of the subgroups.

Heterozygous-familial hypercholesterolaemia population

4.23 The Committee noted the following ICERs with the patient access scheme estimated by the company:

- People who can tolerate statins:
  - for evolocumab plus statin compared with ezetimibe plus statin, the ICERs were £22,900 per QALY gained (deterministic) and £23,500 per QALY gained (probabilistic)
  - for evolocumab plus statin plus ezetimibe compared with ezetimibe plus statin, the ICERs were £24,800 per QALY gained (deterministic); no probabilistic ICER was presented for this comparison.
- People who cannot tolerate statins:
  - for evolocumab compared with ezetimibe, the ICERs were £23,900 per QALY gained (deterministic), and £24,600 per QALY gained (probabilistic)
  - for evolocumab plus ezetimibe compared with ezetimibe, the ICERs were £25,600 per QALY gained (deterministic); no probabilistic ICER was presented for this comparison.

There was a low probability of evolocumab alone or with statin being cost effective compared with ezetimibe alone or with statin at a maximum acceptable ICER of £20,000 per QALY (less than 10%), although the probability exceeded 90% at a maximum

acceptable ICER of £30,000 per QALY. The Committee noted that the company's scenario analyses suggested that the ICER for evolocumab plus statin compared with ezetimibe plus statin could be as low as £17,300 per QALY gained when the LDL-C concentration at baseline is 6 mmol/litre (see section 3.44).

4.24 The Committee discussed these ICERs. It was aware that they reflected both patients with and without CVD, although it was more clinically appropriate to model each group separately. Also, people who can, and those who cannot, tolerate statins were assumed to have the same characteristics. Importantly, the Committee had concerns about how the company estimated the risks of cardiovascular for this population. This was because the company used the Framingham risk equations, which were not appropriate for heterozygous-familial hypercholesterolaemia, then increased the risk of all CV events by a highly overestimated factor of 7.1, independent of whether or not the patient can tolerate statins. Because of these limitations, the Committee concluded not to recommend evolocumab for primary heterozygous-familial hypercholesterolaemia.

Implementation of the patient access scheme in the NHS

4.25 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 noted the

company's sensitivity analyses to explore different assumptions about the implementation of the PAS (see section 3.52). It considered that most people would self-administer at home, with the repeat prescriptions being provided by primary care, although people are likely to continue to be followed up in secondary care. The Committee agreed that up to 90% of people may have evolocumab through FP10 prescriptions in primary care after 2 years. Because of this, it concluded that the ICERs for evolocumab in all 3 populations were more likely to be toward the top end of the ICER range reported by the company in its sensitivity analyses (see section 3.52).

Overall conclusion

4.26 The Committee acknowledged that evolocumab was a first-in-class 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. However, the Committee recalled its previous conclusion that the extent to which evolocumab could reduce CVD was a key area of uncertainty. So, it considered that equating the effect of evolocumab on CVD to that of statins, and assuming in the model that this effect would last indefinitely, was uncertain. The Committee was also concerned that the evidence informing the composite states in the model may not be robust. Furthermore, it considered that assuming that the risk of CVD was independent of whether or not the person can tolerate statins, or whether or not patients with heterozygous-familial hypercholesterolaemia have CVD, could be considered implausible. Importantly, the Committee was concerned about how

the company estimated the risks of CVD, particularly in relation to using the Framingham risk equations instead of the NICE-recommended and UK-validated QRISK2 assessment tool, and applying an unrealistically high factor to adjust the risk of CVD in people with heterozygous-familial hypercholesterolaemia. Finally, the Committee considered that the utility values in the model did not reflect the best available evidence. In summary, the Committee agreed that, although evolocumab might be cost effective in specific subgroups with CVD, the analyses presented by the company had several limitations, which made it unsure about the reliability of the results. The Committee considered that the degree of uncertainty in the cost-effectiveness evidence was too high for it to be able to make recommendations about evolocumab. It therefore concluded not to recommend evolocumab, alone or in combination with lipid-lowering therapies, for treating primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia in adults.

4.27 Overall, the Committee had concerns about the quality of the cost-effectiveness evidence presented. It would have preferred to have seen analyses that reflected the following:

- Considering alternative scenarios to reflect different assumptions about future treatment effects. These should include assuming that evolocumab does not give further benefit after a certain duration of treatment, or that its treatment effect tapers in the long term.
- Using the baseline characteristics of the population in GAUSS-2 to model patients who cannot tolerate statins.

- Modelling the heterozygous-familial hypercholesterolaemia population with or without CVD separately.
- Using the QRISK2 assessment tool to estimate the level of CVD risk in people without CVD (non-familial or heterozygous-familial hypercholesterolaemia). For the variables for which data were not collected, the average value for the specific UK population that reflects this variable could be used.
- Adjusting 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).
- Using the equation from the Health Survey for England to inform the relationship between age and background health-related quality of life.
- Modelling subgroups reflecting all the characteristics of the actual subgroup in clinical trials.
- Taking into account FP10 prescribing of evolocumab in primary care to reflect the true cost of evolocumab to the NHS.

Summary of Appraisal Committee's key conclusions

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

Evolocumab, alone or in combination with lipid-lowering therapies, is not recommended within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia in adults. The Committee agreed that the analyses presented by the company had several limitations, which made it unsure about the reliability of the results, and considered that the degree of uncertainty in the cost-effectiveness evidence was too high for it to be able to make recommendations about evolocumab.		1.1, 4.26
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard that the clinical unmet need is highest in certain subgroups of people who are considered to have a different prognosis from the typical person. It understood that for these people, the only option was apheresis, although this was not widely available, and so evolocumab would be a welcome alternative.	4.4
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 was a first-in-class therapy with a novel mechanism of action, which consistently reduced low-density lipoprotein cholesterol (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 evolocumab was likely to be reserved for people who are at a particularly high risk of cardiovascular disease (CVD), including people with heterozygous-familial hypercholesterolaemia, and those who cannot tolerate statins and in whom ezetimibe does not adequately control LDL-C.	4.3
Adverse reactions	The Committee noted that evolocumab was well tolerated by people.	4.8
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 but only for the	4.6, 4.9

	non-familial hypercholesterolaemia population, and 2 RCTs studied evolocumab in 2 subgroups defined in the scope. The Committee agreed that the RCTs were relevant, and of good quality. The Committee noted that the RCTs mainly gave data on 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.	4.7
Uncertainties generated by the evidence	The Committee concluded that the extent to which evolocumab could reduce CVD was still a key area of uncertainty, particularly with low concentrations of LDL-C at baseline.	4.9
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee noted that the effect of evolocumab was consistent across subgroups.	4.8

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.	4.8
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee noted that the model used a structure that differed from previous models for primary hypercholesterolaemia. The Committee expressed its concern about the internal validity of the model because the effect of using the composite states without robust evidence to model specific combinations of cardiovascular (CV) events was unclear.	4.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	The company assumed that people who could, and those who could not, tolerate statins have the same risks of CVD at baseline, although the risk of CVD was likely to be affected by whether or not the person can tolerate statins. The Committee noted that the company modelled the heterozygous-familial hypercholesterolaemia population with or	4.12, 4.15, 4.17, 4.18

	without CVD together, which did not reflect clinical practice. The Committee was aware that extensive validation studies on the Framingham risk equations used by the company to predict the risks of CVD for patients without CVD had shown that they systematically overestimated the risk of CVD. The Committee concluded that the relative risk from Benn et al. (2012) highly overestimated the risk of CVD among people with heterozygous-familial hypercholesterolaemia. The Committee noted that patients in the model had treatment continuously over their lifetime, and that the treatment effect lasted throughout the time horizon. The Committee agreed that the extent to which evolocumab could reduce CVD was uncertain. Also, it was unknown whether the effect of evolocumab would continue over time because long-term data were limited.	

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 heard from the Evidence Review Group (ERG) that some utility multipliers in the model were not based on the EQ-5D. Also, the utility multipliers in 3 states related to people who had had a myocardial infarction, and so may not be relevant. The Committee concluded that the equation from the Health Survey for England would better show the relationship between age and health-related quality of life than the study by Dolan et al. (1996) used in the model.	4.19
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee did not preclude that evolocumab might be cost effective in highly selected subgroups with CVD. However, given the limitations of the analyses, it was not satisfied that the ICERs were reliable enough for its decision-making, and concluded not to recommend evolocumab for any of the subgroups.	4.22

What are the key drivers of cost effectiveness?	The Committee noted that the model was highly sensitive to the relative risk used to adjust the predicted risks of CVD for the heterozygous-familial hypercholesterolaemia population.	4.17
Most likely cost-effectiveness estimate (given as an ICER)	The company estimated the following deterministic base-case incremental cost-effectiveness ratios (ICERs) with the patient access scheme: • Non-familial hypercholesterolaemia without CVD: £74,300 per quality-adjusted life year (QALY) gained for evolocumab plus statin compared with ezetimibe plus statin (statin-tolerant), and £78,800 per QALY gained for evolocumab compared with ezetimibe (statin-intolerant). • Non-familial hypercholesterolaemia with CVD: £46,000–50,900 per QALY gained for evolocumab plus statin with or without ezetimibe compared with ezetimibe plus statin (statin-tolerant), and from £49,300–52,800 per QALY gained for evolocumab with or without ezetimibe compared with ezetimibe (statin-intolerant). • Heterozygous-familial	4.20, 4.23

	hypercholesterolaemia: £22,900–24,800 per QALY gained for evolocumab plus statin with or without ezetimibe compared with ezetimibe plus statin (statin-tolerant), and £23,900–25,600 per QALY gained for evolocumab with or without ezetimibe compared with ezetimibe (statin-intolerant).	
Additional factors taken into account		
Patient access schemes (PPRS)	The company has agreed a simple discount patient access scheme with the Department of Health. The Committee agreed that up to 90% of people may have evolocumab through FP10 prescriptions in primary care after 2 years. Because simple discounts do not apply when drugs are prescribed through FP10 prescriptions, the Committee concluded that the ICERs for evolocumab in all 3 populations were more likely to be higher than base-case ICERs presented by the company, which assumed that the discount will be applied for all patients.	2.3, 4.25

End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	At the scoping stage, it was noted that certain ethnic minority groups do not accept having treatment by subcutaneous injection. 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.	

5 Implementation

5.1 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Proposed recommendations for further research

6.1 The Committee was aware that an ongoing RCT, FOURIER, would test whether or not 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
November 2015

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
Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Dr David Black

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 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

Project Manager

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