

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Technology appraisal guidance

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Your responsibility

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1 Recommendations

- 1.1 Alirocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:
- Low-density lipoprotein concentrations are persistently above the thresholds specified in table 1 despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached or further titration is limited by intolerance (as defined in [NICE's guideline on familial hypercholesterolaemia: identification and management](#)).
 - The company provides alirocumab with the discount agreed in the patient access scheme.

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

	Without CVD	With CVD: high risk of CVD	With CVD: very high risk of CVD
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l

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

Note: In this table a high risk of cardiovascular disease is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke, peripheral arterial disease; a very high risk of cardiovascular disease is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

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

2 The technology

2.1 Alirocumab (Praluent, Sanofi) is a monoclonal antibody that targets proprotein convertase subtilisin/kexin type 9 (PCSK9). It stops low-density lipoprotein receptors in the liver from degrading, helping to lower levels of low-density lipoprotein cholesterol (LDL-C) in the blood. Alirocumab has a marketing authorisation in the UK for '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.'

Alirocumab is given by subcutaneous injection. The recommended dose is either 75 mg or 150 mg every 2 weeks. In January 2021, the licensed dosage was updated to include another option of 300 mg every 4 weeks (monthly).

2.2 Common reported adverse reactions include local injection site reactions, upper respiratory tract signs and symptoms, and pruritus. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Alirocumab costs £168 for a 75 mg or 150 mg single-use prefilled pen (excluding VAT; MIMS, January 2016). The annual cost of treatment per patient is £4,383 for 75 mg or 150 mg every 2 weeks. The company has agreed a patient access scheme with the Department of Health that will provide a simple discount to the list price of alirocumab 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 Evidence

The [appraisal committee](#) considered evidence submitted by Sanofi and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Clinical effectiveness

- 3.1 The company presented evidence of the clinical effectiveness of alirocumab from 10 trials: ODYSSEY HIGH FH, FH I and II, LONG-TERM, COMBO I and II, OPTIONS I and II, MONO and ALTERNATIVE. The trials were from the ODYSSEY programme, which evaluated alirocumab as an add-on to maximally tolerated dose statins with or without other lipid-modifying therapies (LMT) including ezetimibe.

Clinical trials

- 3.2 ODYSSEY HIGH FH was a randomised, double-blind study in 107 people with heterozygous-familial hypercholesterolaemia whose LDL-C levels were not adequately controlled with a maximally tolerated, stable, daily dose of statin with or without other LMT. Patients were randomised in a 2:1 ratio to either alirocumab 150 mg or placebo. The difference in mean percent change from baseline in LDL-C level at 24 weeks was -39.1% ($p < 0.0001$) with alirocumab compared with placebo.
- 3.3 ODYSSEY FH I was a randomised, double-blind, study in 486 people with heterozygous-familial hypercholesterolaemia whose LDL-C levels were not adequately controlled with a maximally tolerated, stable, daily dose of statin with or without other LMT. Patients were randomised in a 2:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-C levels) or placebo. The difference in mean percent change from baseline in LDL-C level at 24 weeks (with possible up-titration) was -57.9% ($p < 0.0001$) with alirocumab compared with placebo.
- 3.4 ODYSSEY FH II was a randomised, double-blind study in 249 people with

heterozygous-familial hypercholesterolaemia whose LDL-C levels were not adequately controlled with a maximally tolerated, stable, daily dose of statin with or without other LMT. Patients were randomised in a 2:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-C levels) or placebo. The difference in mean percent change from baseline in LDL-C level at 24 weeks (with possible up-titration) was -51.4% ($p < 0.0001$) with alirocumab compared with placebo.

3.5 ODYSSEY COMBO I was a randomised, double-blind study in 316 people with hypercholesterolaemia and established coronary heart disease or coronary heart disease risk equivalents whose LDL-C levels were not adequately controlled with a maximally tolerated daily dose of statin with or without other LMT. Patients were randomised in a 2:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-C levels) or placebo. The difference in mean percent change from baseline in LDL-C level at 24 weeks was -45.9% ($p < 0.0001$) with alirocumab compared with placebo.

3.6 ODYSSEY COMBO II was a randomised, double-blind, ezetimibe-controlled, double-dummy study in 720 people with hypercholesterolaemia and established coronary heart disease or coronary heart disease risk equivalents whose LDL-C levels were not adequately controlled with a maximally tolerated daily dose of statin. Patients were randomised in a 2:1 ratio to either alirocumab (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-C levels) or ezetimibe 10 mg. The difference in mean percent change from baseline in LDL-C level at 24 weeks was -29.8% ($p < 0.0001$) with alirocumab compared with ezetimibe.

3.7 ODYSSEY LONG-TERM was a randomised, double-blind study in 2,341 people with non-familial hypercholesterolaemia or established coronary heart disease or coronary heart disease risk equivalent, or people with heterozygous-familial hypercholesterolaemia with or without coronary heart disease or coronary heart disease risk equivalents whose LDL-C levels were not adequately controlled with a maximally tolerated daily dose of statin with or without other LMT. Patients were randomised in a 2:1 ratio to either alirocumab 150 mg or placebo. The difference in mean percent change from baseline in LDL-C level at 24 weeks was -61.9% ($p < 0.0001$) with alirocumab compared with placebo.

- 3.8 ODYSSEY OPTIONS I was a randomised, double-blind study in 355 people with non-familial hypercholesterolaemia or heterozygous-familial hypercholesterolaemia and a history of coronary heart disease, risk of cardiovascular disease or diabetes with target organ damage, whose LDL-C levels were not adequately controlled with atorvastatin 20 mg to 40 mg. Patients on a baseline regimen of atorvastatin 20 mg were randomised in a 1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-C levels) with atorvastatin 20 mg, atorvastatin 40 mg, or atorvastatin 20 mg with ezetimibe 10 mg. Patients on a baseline regimen of atorvastatin 40 mg were randomised in a 1:1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-C levels) with atorvastatin 40 mg, atorvastatin 80 mg, atorvastatin 40 mg with ezetimibe 10 mg, or rosuvastatin 40 mg. For patients having atorvastatin 20 mg, the difference in mean percent change from baseline in LDL-C level at 24 weeks (with possible up-titration) was -39.1% ($p < 0.0001$) with alirocumab and statin (atorvastatin 20 mg) compared with statin (atorvastatin 40 mg) alone. The difference in mean percent change from baseline in LDL-C level was -23.6% ($p < 0.0001$) with alirocumab with statin (atorvastatin 20 mg) compared with ezetimibe with statin (atorvastatin 20 mg). For patients on atorvastatin 40 mg at baseline, the difference in mean percent change from baseline in LDL-C level at 24 weeks (with possible up-titration) was -49.2% ($p < 0.0001$) with alirocumab and statin (atorvastatin 40 mg) compared with statin (atorvastatin 80 mg) alone. The difference in mean percent change from baseline in LDL-C level was -32.6% ($p < 0.0001$) with alirocumab and statin (atorvastatin 40 mg) compared with statin alone (rosuvastatin 40 mg). The difference in mean percent change from baseline in LDL-C level was -31.4% ($p < 0.0001$) with alirocumab with statin (atorvastatin 40 mg) compared with ezetimibe with statin (atorvastatin 40 mg).
- 3.9 ODYSSEY OPTIONS II was a randomised, double-blind study in 305 people with non-familial hypercholesterolaemia or heterozygous-familial hypercholesterolaemia and a history of coronary heart disease, risk of cardiovascular disease, or diabetes with target organ damage whose LDL-C levels were not adequately controlled with rosuvastatin 10 mg to 20 mg. Patients on a baseline regimen of rosuvastatin 10 mg were randomised in a 1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-C levels) with rosuvastatin 10 mg, rosuvastatin 20 mg, or rosuvastatin 10 mg with ezetimibe 10 mg. Patients on a baseline regimen of

rosuvastatin 20 mg were randomised in a 1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-C levels) with rosuvastatin 20 mg, rosuvastatin 40 mg, or rosuvastatin 20 mg with ezetimibe 10 mg. For patients having rosuvastatin 10 mg at baseline, the difference in mean percent change from baseline in LDL-C level at 24 weeks (with possible up-titration) was -34.2% ($p<0.0001$) with alirocumab and statin (rosuvastatin 10 mg) compared with statin (rosuvastatin 20 mg) alone. The difference in mean percent change from baseline in LDL-C level (with possible up-titration) was -36.2% ($p<0.0001$) with alirocumab and statin (rosuvastatin 10 mg) compared with ezetimibe and statin (rosuvastatin 10 mg). For patients on rosuvastatin 20 mg at baseline, the difference in mean percent change from baseline in LDL-C level at 24 weeks (with possible up-titration) was -20.3% ($p=0.0453$) with alirocumab and statin (rosuvastatin 20 mg) compared with statin (rosuvastatin 40 mg) alone. The difference in mean percent change from baseline in LDL-C level was -25.3% ($p=0.0136$) with alirocumab with statin (rosuvastatin 20 mg) compared with ezetimibe with statin (rosuvastatin 20 mg).

- 3.10 ODYSSEY ALTERNATIVE was a randomised, double-blind, ezetimibe-controlled, double-dummy study in 361 people with people with non-familial hypercholesterolaemia or heterozygous-familial hypercholesterolaemia with a moderate, high or very high cardiovascular risk and a history of intolerance to statin. Patients were randomised in a 2:2:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-C levels), ezetimibe 10 mg or atorvastatin 20 mg. The difference in mean percent change from baseline in LDL-C level was -30.4% ($p<0.0001$) with alirocumab compared with ezetimibe.
- 3.11 ODYSSEY MONO was a randomised, ezetimibe-controlled, double-blind study in 103 people with hypercholesterolaemia with a moderate cardiovascular risk. Patients were randomised in a 1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-C levels) or ezetimibe 10 mg. The difference in mean percent change from baseline in LDL-C level at week 24 (with possible up-titration) was -31.6% ($p<0.0001$) with alirocumab compared with ezetimibe.

Meta-analyses

- 3.12 The company undertook meta-analyses of individual patient data for the mean percent change from baseline in calculated LDL-C levels (on-treatment) using a fixed-effects model. In these analyses, alirocumab (with or without statins) was compared with a statin or ezetimibe (with or without statin). The meta-analyses showed:
- The difference in mean percent change from baseline in LDL-C level at 12 weeks was approximately -49.3% with alirocumab 75 mg with statin compared with placebo with statin.
 - The difference in mean percent change from baseline in LDL-C level at 24 weeks ranged from -54.1% to -56.1% with alirocumab 75 mg (with possible up-titration to 150 mg) with statin compared with placebo with statin.
 - The difference in mean percent change from baseline in LDL-C level at 24 weeks was -62.5% with alirocumab 150 mg with statin compared with placebo with statin.
 - The difference in mean percent change from baseline in LDL-C level at 12 weeks ranged from -27.2% to -33.1% with alirocumab 75 mg with or without statin compared with ezetimibe with or without statin.
 - The difference in mean percent change from baseline in LDL-C level at 24 weeks ranged from -29.9% to -35.1% with alirocumab 75 mg (with possible up-titration to 150 mg) with or without statin compared with ezetimibe with or without statin.
- 3.13 The company also provided information from an independent meta-analysis of PCSK9 inhibitors (Navarese et al.). This showed a difference in mean percent change from baseline in LDL-C level of -47.49% (95% confidence interval [CI] -69.64 to -25.35) and reduced all-cause mortality and cardiovascular mortality with PCSK9 antibodies compared with control. The company stated that a large randomised controlled trial exploring the occurrence of cardiovascular events of alirocumab compared with placebo is expected to report in 2018.

Adverse effects of treatment

- 3.14 The company provided safety information based on combined phase 2 and phase 3 studies. The company stated that the rate of treatment-emergent adverse events (including serious adverse events) was similar between the alirocumab and control arms. It stated that there was no difference in the safety profile observed between alirocumab 75 mg and 150 mg. It also stated that discontinuation due to general allergic adverse events was infrequent but occurred in a higher percentage of the people having alirocumab.
- 3.15 The company estimated the risk of major adverse cardiovascular events (death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation) by pooling phase 3 ODYSSEY trial data. The analysis showed a lower risk of a major adverse cardiovascular event with alirocumab compared with control (hazard ratio [HR] 0.81; 95% CI 0.52 to 1.25), although this was not statistically significant. A post-hoc analysis from LONG-TERM also showed a lower risk of major adverse cardiac events with alirocumab compared with placebo (HR 0.52; 95% CI 0.31 to 0.90).

ERG's comments

- 3.16 The ERG noted that evolocumab was not considered to be a relevant comparator by the company because it was still under assessment by NICE. It noted that there were no head-to-head trials of alirocumab compared with evolocumab.
- 3.17 The ERG stated that although it had identified missing terms in the company's search strategy which may have affected its overall sensitivity, it generally considered the company's searches to be fit for purpose.
- 3.18 The ERG noted that the LDL-C reduction with alirocumab compared with control was rapid and persistent throughout follow-up.

Cost effectiveness

3.19 The company presented base-case cost-effectiveness analyses for alirocumab, either as an adjunct to statin with ezetimibe or with ezetimibe alone, in 4 populations:

- People with heterozygous-familial hypercholesterolaemia for primary prevention (referred to as the primary prevention [heterozygous-familial] population).
- People with heterozygous-familial hypercholesterolaemia for secondary prevention (referred to as the secondary prevention [heterozygous-familial] population).
- People with non-familial hypercholesterolaemia and high-risk cardiovascular disease (CVD). This includes people with a history of:
 - acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation)
 - coronary or other arterial revascularisation procedures
 - coronary heart disease
 - ischaemic stroke
 - peripheral arterial disease.
- People with non-familial hypercholesterolemia and a very high risk of CVD. These are people with recurrent cardiovascular events or polyvascular disease (referred to as the recurrent events/polyvascular disease [non-familial] population). This includes people with recurrent cardiovascular events, or cardiovascular events in more than 1 vascular bed.

Model structure

3.20 The company submitted a Markov model based on the modelling approaches developed for NICE's guidelines on lipid modification (now replaced by [NICE's guideline on cardiovascular disease: risk assessment and reduction, including](#)

lipid modification) and familial hypercholesterolaemia, and technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (now replaced by NICE's technology appraisal guidance on ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia), ticagrelor for the treatment of acute coronary syndromes and rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. The cycle length was 1 year and a half cycle correction was applied. An annual discount rate of 3.5% was applied to costs and health effects. The model had a lifetime time horizon and was conducted from a NHS and personal social services perspective.

3.21 The company's model consisted of 12 mutually exclusive health states:

- 3 initial health states: stable, 0 to 1 years following an acute coronary syndrome event, 1 to 2 years following an acute coronary syndrome event
- 3 types of events: non-fatal acute coronary syndrome including myocardial infarction and unstable angina requiring hospitalisation, non-fatal ischaemic stroke, and elective revascularisation
- 7 post-event health states: post non-fatal acute coronary syndrome (0 to 1 years, 1 to 2 years and stable coronary heart disease; that is, more than 2 years after an acute coronary syndrome event), post non-fatal ischaemic stroke (0 to 1 years, 1 to 2 years and stable ischaemic stroke; that is, more than 2 years following ischaemic stroke) and stable elective revascularisation.

The model also consisted of health states for cardiovascular death and non-cardiovascular death. Costs and outcomes were compared between identical cohorts of people on alirocumab and comparators.

3.22 The baseline characteristics (age, sex, percentage of patients with diabetes and minimum LDL-C level) for each population were informed by UK data from the Health Improvement Network (THIN) database, patient characteristics from ODYSSEY trials and the UK National Familial Hypercholesterolaemia audit.

- For heterozygous-familial hypercholesterolaemia, the starting age was 50 years for primary prevention and 60 years for secondary prevention. The baseline LDL-C level was 2.59 mmol/l, 50% of the cohort were men, 7% of the primary prevention cohort had diabetes and 26% of the secondary

prevention cohort had diabetes.

- For high-risk cardiovascular disease, the starting age was 65 years and the baseline LDL-C level was 3.36 mmol/l. Around 60% of the cohort were men and 23% had diabetes.
- For recurrent events/polyvascular disease, the starting age was 65 years and the baseline LDL-C level was 2.59 mmol/l. Around 60% of the cohort were men and 30% had diabetes.

3.23 The baseline probabilities of cardiovascular death in all post-acute coronary syndrome and post-ischaemic stroke health states were adjusted to account for the higher risk of future events associated with recurrence of cardiovascular events.

Treatment, clinical variables and parameters

3.24 Alirocumab was given in line with its marketing authorisation. The patient population was modelled according to severity of hypercholesterolaemia (by baseline LDL-C levels) before starting treatment. Baseline cardiovascular risk (calculated using THIN data) was adjusted by LDL-C level using a log-linear relationship between the absolute LDL-C observed in statin studies and cardiovascular events using the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of statins. The company used the difference in mean percent change of alirocumab compared with alternatives based on estimates from specific clinical trials and meta-analyses. The model assumed that the relative reduction in LDL-C for alirocumab was constant across all subgroups.

3.25 In the absence of cardiovascular events data from the clinical trials for alirocumab, the company used LDL-C reduction as a surrogate to link to cardiovascular events. In its base-case analysis, the company chose the Navarese meta-analysis of 24 randomised controlled trials (n=10,159) to provide the rate at which the risk of a cardiovascular event declines with a reduction in LDL-C levels. This was because it preferred estimates from PCSK9 inhibitor studies rather than estimates from statin studies (such as CTTC), because they better reflected the population who will have alirocumab. By assuming a

log-linear relationship between LDL-C levels and cardiovascular events, the company estimated the risk reduction for cardiovascular mortality as rate ratios (RRs): 0.64 per 1.0 mmol/l reduction in LDL-C rate (95% CI 0.40 to 1.04) and 0.64 for myocardial infarction (95% CI 0.43 to 0.96). The risk reduction for coronary revascularisation and ischaemic stroke was assumed to be the same as other non-fatal cardiovascular events.

Transition probabilities

- 3.26 Transition probabilities were based on Kaplan–Meier analyses from an observational retrospective cohort analysis using the THIN database of people with established cardiovascular disease, diabetes, familial hypercholesterolaemia or chronic kidney disease. This was used to calculate 1-year cardiovascular risk probabilities. Transition probabilities for the primary prevention (heterozygous-familial) population were based on the Dutch lipid criteria for people with heterozygous-familial hypercholesterolaemia, because the patient characteristics from THIN were not representative of this population. For the secondary prevention (heterozygous-familial) population (see section 3.19), some patient characteristics (such as rate of diabetes and age) were different from known prevalence. To address this, the company used data from Mohrschladt (2003) in its base-case analysis for this population.
- 3.27 Non-cardiovascular death probabilities in the model increased in accordance with age and sex using UK life tables. Probability of cardiovascular events also increased with age, in line with published data.

Utility values

- 3.28 Age-adjusted utility values for the primary prevention (heterozygous-familial) population were calculated using Health Survey for England (HSE) data for people with no history of cardiovascular disease, multiplied by the disutility associated with cardiovascular events taken from Ara and Brazier (2010). Baseline utilities in the model were as follows: non-fatal myocardial infarction 0.765, unstable angina 0.765, acute coronary syndrome 0.765, ischaemic stroke 0.775.

3.29 Age-adjusted utility values for the secondary prevention (heterozygous-familial), high-risk cardiovascular disease and recurrent events/polyvascular disease (non-familial) populations were calculated using HSE data for people with no history of cardiovascular disease, multiplied by the disutility values associated with a coronary cardiovascular health state (cardiovascular event more than 1 year ago) taken from Ara and Brazier 2010. Utility multipliers in the model were: primary prevention of heterozygous-familial hypercholesterolaemia 1 (assumed), secondary prevention of heterozygous-familial hypercholesterolaemia 0.924, acute coronary syndrome (0 to 12 months) 0.765, history of ischaemic stroke 0.822, acute coronary syndrome (13 to 24 months) 0.924, coronary heart disease 0.924, peripheral arterial disease 0.924, and polyvascular 0.854. Disutilities for further cardiovascular events in the model were applied to the secondary prevention (heterozygous-familial) population baseline utilities.

Costs

3.30 Initial costs of treatment for hypercholesterolaemia and cardiovascular events were based on the cost of hospitalisation, follow-up care and medication. Drug acquisition costs for the comparators were taken from the January 2015 edition of the BNF. The cost of the background therapy was weighted by the proportion of the cohort using the statin sources from market research data. The cost of alirocumab incorporated the patient access scheme.

3.31 Health state costs were based on the NICE guideline on lipid modification (now replaced by [NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification](#)) and costs for the first 3 years after a cardiovascular event were taken from the BNF, the NHS Drug Tariff, NHS reference costs, PSSRU unit costs, and NICE's previous guideline on stroke rehabilitation in adults (now replaced by [NICE's guideline on stroke rehabilitation in adults](#)). The costs for each health state were as follows:

- non-fatal myocardial infarction: £3,337 (incremental cost years 2 and 3: £788)
- unstable angina: £3,313 (incremental cost years 2 and 3: £385)
- acute coronary syndrome: £3,329 (incremental cost years 2 and 3: £654)

- revascularisation: £3,802
- ischaemic stroke: £4,092 (incremental cost years 2 and 3: £155)
- cardiovascular death: £1,174
- non-cardiovascular death: £0.

ERG comments

- 3.32 The ERG stated that in terms of face validity, the company's model structure and transition probabilities were plausible. However, the ERG noted that the company's model omitted the transient ischaemic attack and stable angina health states and that it had limited capacity to capture multiple cardiovascular event histories. It also stated that the company omitted treatment-emergent adverse events from the model. The ERG also noted that the secondary prevention (heterozygous-familial) population (see section 3.19) using Mohrschladt had a higher cardiovascular risk compared with data from THIN. It was unable to verify the most appropriate risk without another external data source. The ERG believed that the company's use of THIN for cardiovascular event and transition probabilities was appropriate because QRISK2 risk estimates were not valid for the high cardiovascular risk population.
- 3.33 Although the ERG accepted the company's decision to use an LDL-C threshold of 3.36 mmol/l for people with high-risk cardiovascular disease, it noted that Jameson et al. reported a mean LDL-C of 2.13 mmol/l in people with cardiovascular disease having atorvastatin in primary care in the UK. It also noted that a large proportion of people in THIN were having low-intensity statins and may not have been on optimal statin treatment. The ERG stated that the mean baseline LDL-C levels used by the company may not have been applicable to people having maximally tolerated statins and that it considered the company's mean LDL-C levels to be uncertain.
- 3.34 The ERG had several comments about the company's assumptions used to scale the estimated effect of alirocumab to cardiovascular events:
- It was satisfied with the company's approach to estimate the LDL-C

reduction with alirocumab compared with placebo.

- The ERG noted that the company assumed there is a linear/log-linear relationship between LDL-C and cardiovascular events as demonstrated by CTTC. It noted that the estimated relative reduction in cardiovascular events from Navarese was greater than estimates from CTTC. The ERG also noted that the estimates from Navarese were based on a smaller number of events reported in shorter trials with fewer patients compared with CTTC.
- The ERG noted that the company used all the trials used to estimate the mean reduction with LDL-C from the Navarese analysis, instead of only the trials used to estimate the HRs for specific cardiovascular events. In its response to clarification, the company provided estimates of LDL-C reduction using trials only informing the HRs for myocardial infarction and cardiovascular death; an LDL-C reduction of 1 mmol/l resulted in HRs of 0.58 for cardiovascular death and 0.68 for myocardial infarction. The ERG considered these values to be more relevant.
- The ERG noted that the company's estimated HR for myocardial infarction events was used for ischaemic stroke and coronary revascularisation events. The ERG stated this was a controversial assumption, because other studies (such as CTTC) show that a reduction in LDL-C levels may have less of an effect on ischaemic stroke risk than on acute coronary syndrome risk.

3.35 The ERG stated that the company assumed 100% treatment continuation and compliance over the entire time horizon. It noted that the high compliance was in line with ODYSSEY (approximately 98%) and that the assumption was consistent with NICE's guideline on lipid modification (now replaced by [NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification](#)) and NICE's technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (now replaced by [NICE's technology appraisal guidance on ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia](#)).

3.36 The ERG stated that the company's health state utility values were calculated and implemented appropriately. However, it had several comments on the costs used in the model:

- The company's model only captured costs for the first 6 months after a cardiovascular event in the first year, and so did not capture follow-up for the second half of the first year.
- Follow-up costs for cardiovascular events were incurred for up to 3 years after the event. The ERG considered this to be conservative and possibly unrealistic, considering the need for ongoing social care and medical attention.
- The costs for the stroke and post-stroke health states were low and inconsistent with costs applied in previous technology appraisals.
- The ERG was unclear how the cost of revascularisation was estimated.
- The company's submission mentioned that alirocumab will be continued in secondary care via a sponsored homecare service.

Company's results and sensitivity analysis

- 3.37 The company's incremental cost-effectiveness ratios (ICERs) for all comparisons, populations and sensitivity analyses incorporated the patient access scheme for alirocumab, as do all ICERs in this document (see tables 1 to 4).
- 3.38 In the primary prevention (heterozygous-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER was £36,793 per quality-adjusted life year (QALY) gained (incremental costs £52,256; incremental QALYs 1.42). For alirocumab and a statin compared with ezetimibe and a statin, the ICER was £48,193 per QALY gained (incremental costs £45,962; incremental QALYs 0.95).
- 3.39 In the secondary prevention (heterozygous-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER was £16,896 per QALY gained (incremental costs £39,306; incremental QALYs 2.33). For alirocumab and a statin compared with ezetimibe and a statin, the ICER was £20,352 per QALY gained (incremental costs £34,632; incremental QALYs 1.70). Using baseline risk data from THIN instead of Mohrschladt (2003) the ICER was £19,060 per QALY gained (incremental costs £40,733; incremental QALYs 2.14).

for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe.

- 3.40 In the high-risk cardiovascular disease (non-familial) population, for alirocumab and a statin compared with a statin alone, the ICER was £19,751 per QALY gained (incremental costs £34,684; incremental QALYs 1.76). For alirocumab and a statin compared with ezetimibe and a statin, the ICER was £24,175 per QALY gained (incremental costs £31,195; incremental QALYs 1.29). In the high-risk cardiovascular disease (non-familial) population who cannot have statins, the ICER for alirocumab and ezetimibe compared with ezetimibe alone was £17,256 per QALY gained (incremental costs £35,146; incremental QALYs 2.04). For alirocumab alone compared with ezetimibe alone the ICER was £17,295 per QALY gained (incremental costs £30,829; incremental QALYs 1.78).
- 3.41 In the recurrent events/polyvascular disease (non-familial) population, for alirocumab and a statin compared with a statin alone, the ICER was £19,447 per QALY gained (incremental costs £31,953; incremental QALYs 1.64). For alirocumab and a statin compared with ezetimibe and a statin, the ICER was £23,078 per QALY gained (incremental costs £28,781; incremental QALYs 1.25). For the recurrent events/polyvascular disease (non-familial) population who cannot have statins, the ICER for alirocumab and ezetimibe compared with ezetimibe alone was £13,669 per QALY gained (incremental costs £32,798; incremental QALYs 2.40). For alirocumab alone compared with ezetimibe alone, the ICER was 13,469 per QALY gained (incremental costs £28,820; incremental QALYs 2.14)

Sensitivity analyses

- 3.42 The company undertook a number of probabilistic sensitivity analyses, stating that the uncertainty in the results reflected the wide confidence intervals from preliminary PCSK9 inhibitor outcomes data.
- For the primary prevention (heterozygous-familial) population, the probability of alirocumab and a statin plus ezetimibe being cost effective compared with a statin and ezetimibe was between 15% and 36% (for a maximum ICER of £20,000 to £30,000 per QALY gained).
 - For the secondary prevention (heterozygous-familial) population, the

probability of alirocumab and a statin plus ezetimibe being cost effective compared with a statin and ezetimibe was between 56% and 79% (for a maximum ICER of £20,000 to £30,000 per QALY gained).

- For the high-risk cardiovascular disease (non-familial) population, the probability of alirocumab and a statin being cost effective compared with a statin alone was between 46% and 78% (for a maximum ICER of £20,000 to £30,000 per QALY gained).
- For the recurrent events/polyvascular disease (non-familial) population, the probability of alirocumab and a statin being cost effective compared with a statin alone was between 49% and 80% (for a maximum ICER of £20,000 to £30,000 per QALY gained).

3.43 The company also undertook deterministic sensitivity analyses to explore the upper and lower bounds of the confidence interval or by varying selected inputs by an arbitrary $\pm 20\%$. The ICERs for all populations were most sensitive to changes in the relationship of LDL-C level to cardiovascular events and annual cardiovascular risk.

Subgroup and scenario analyses

3.44 The company conducted subgroup analyses by LDL-C level:

- In the primary prevention (heterozygous-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER decreased from £36,793 per QALY gained at a threshold of 2.59 mmol/l to £28,923 per QALY gained at a threshold of 4.13 mmol/l.
- In the secondary prevention (heterozygous-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER decreased from £16,896 per QALY gained at a threshold of 2.59 mmol/l to £14,242 per QALY gained at a threshold of 4.13 mmol/l.
- In the high-risk cardiovascular disease (non-familial) population, for alirocumab and a statin compared with a statin alone, the ICER decreased from £25,287 per QALY gained at a threshold of 2.59 mmol/l to £16,043 per

QALY gained at a threshold of 4.13 mmol/l.

- In the recurrent events/polyvascular (non-familial) disease population, for alirocumab and a statin compared with a statin alone, the ICER decreased from £19,447 per QALY gained at a threshold of 2.59 mmol/l to £12,606 per QALY gained at a threshold of 4.13 mmol/l.

3.45 The company conducted a range of scenario analyses:

- Increasing the discontinuation rate from 0% to 3% and 8% led to a modest increase in the ICERs for all populations.
- Changing the cost and benefit discount rates from 3.5% to 0 or 5% substantially changed the ICERs in all populations.
- Reducing the treatment duration from lifetime to 1 to 5 years had a modest impact on the ICERs in all populations.
- Decreasing the time horizon from lifetime to 5 or 10 years substantially increased the ICERs in all populations.
- Using a different source to link LDL-C reduction to cardiovascular relative risk instead of Navarese changed the ICERs in all populations:
 - using relative risks from CTTC instead of Navarese increased the ICERs by approximately £16,000 to £24,700 per QALY gained
 - using relative risks from pooled phase 3 trials instead of Navarese increased the ICERs by approximately £8,800 to £15,700 per QALY gained
 - using relative risks from LONG-TERM instead of Navarese increased the ICERs by approximately £2,400 to £4,100 per QALY gained.
- Using a different adjustment to baseline cardiovascular risk had a modest impact on the ICERs in all populations.
- Using utility values from ODYSSEY instead of Ara 2010 significantly decreased ICERs in all populations.
- Changing the treatment strategy from up-titration to 100% use of alirocumab

75 mg or 150 mg had a modest impact on the ICERs in all populations.

ERG's exploratory analyses

3.46 The ERG undertook exploratory analyses for all comparators and populations, making 7 changes to the company's model. It presented ICERs for both Navarese and CTTC meta-analyses to show the uncertainty in the relationship between LDL-C reduction and cardiovascular events. In summary, the ERG's exploratory analyses:

- applied annual post-cardiovascular event costs (such as care for stroke) over the entire modelled time horizon (lifetime) instead of 3 years
- applied follow-up costs to the second half of first year costs following a cardiovascular event
- applied an updated cost of £8,618 for stroke and an annual care cost for stroke of £1,769
- used only trials informing the hazard ratios in Navarese instead of all trials, applying rate ratios of 0.67 per 1 mmol/l reduction for myocardial infarction and 0.58 per 1 mmol/l reduction in cardiovascular death
- applied a rate ratio of 0.79 per 1 mmol/l reduction in LDL-C for ischaemic stroke based on results from CTTC, instead of assuming the same rate ratio of 0.64 per 1 mmol/l reduction
- applied an annual discontinuation rate of 8% instead of 0% so that it is consistent with discontinuation observed in ODYSSEY and LONG-TERM
- applied the effects of ezetimibe on LDL-C reduction using rate ratios from CTTC.

3.47 In summary, the ERG's exploratory analyses showed only modest changes to the base-case ICERs for all comparisons in all populations using Navarese to estimate the relationship between LDL-C and cardiovascular events. Using CTTC to estimate the relationship between LDL-C and cardiovascular events substantially increased the ICERs for all comparisons in all populations. All these ICERs were in

excess of £20,000 per QALY gained.

Table 2 ERG exploratory analyses: deterministic base-case and additional comparison ICERs for the primary prevention (heterozygous-familial) population (cost per QALY), including patient access scheme

	Company's base case with rate ratios from Navarese	Company's scenario analysis with ratios from CTTC	ERG scenario with rate ratios from Navarese	ERG scenario with rate ratios from CTTC
Alirocumab + statins + ezetimibe vs statins + ezetimibe	£36,793	£60,736	£41,243	£67,215
People who cannot tolerate statins Alirocumab +ezetimibe vs ezetimibe	–	–	–	£45,786
Comparison with ezetimibe Alirocumab + statins vs ezetimibe + statins	£48,193	–	£52,363	£119,161

Table 3 ERG exploratory analyses: deterministic base-case and additional comparison ICERs for the secondary prevention (heterozygous-familial) population (cost per QALY) including patient access scheme

	Company's base case with rate ratios from Navarese	Company's scenario analysis with ratios from CTTC	ERG scenario with rate ratios from Navarese	ERG scenario with rate ratios from CTTC
Alirocumab + statins + ezetimibe vs statins + ezetimibe	£16,896	£32,937	£16,933	£33,339
People who cannot tolerate statins Alirocumab +ezetimibe vs ezetimibe	–	–	–	£22,042
Comparison with ezetimibe Alirocumab + statins vs ezetimibe + statins	£20,352	–	£19,437	£56,968

Table 4 ERG exploratory analyses: deterministic base-case and additional comparison ICERs for the high-risk CVD (non-familial) population (cost per QALY), including patient access scheme

	Company's base case with rate ratios from Navarese	Company's scenario analysis with ratios from CTTC	ERG scenario with rate ratios from Navarese	ERG scenario with rate ratios from CTTC
Alirocumab + statins vs statins	£19,751	£41,431	£19,432	£42,131
People who cannot tolerate statins Alirocumab + ezetimibe vs ezetimibe	£17,256	–	£17,130	£34,600
Comparison with ezetimibe Alirocumab + statins vs ezetimibe + statins	£24,175	–	£21,932	£70,081
People who cannot tolerate statins comparison with ezetimibe Alirocumab vs ezetimibe	£17,295	–	£16,487	£41,412

Table 5 ERG exploratory analyses: deterministic base-case and additional comparison ICERs for the recurrent events/polyvascular disease (non-familial) population (cost per QALY), including patient access scheme

	Company's base case with rate ratios from Navarese	Company's scenario analysis with ratios from CTTC	ERG scenario with rate ratios from Navarese	ERG scenario with rate ratios from CTTC
Alirocumab + statins vs statins	19,447	44,154	19,021	44,759
People who cannot tolerate statins Alirocumab + ezetimibe vs ezetimibe	13,669	–	15,791	33,519

	Company's base case with rate ratios from Navarese	Company's scenario analysis with ratios from CTTC	ERG scenario with rate ratios from Navarese	ERG scenario with rate ratios from CTTC
Comparison with ezetimibe Alirocumab + statins vs ezetimibe + statins	23,078	–	20,891	73,941
People who cannot tolerate statins comparison with ezetimibe alirocumab vs ezetimibe	13,469	–	13,342	32,742

Abbreviations: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Company's new evidence in response to consultation

- 3.48 In response to the appraisal consultation document, in which alirocumab was not recommended for primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia, the company was permitted to submit revised cost-effectiveness analyses which included a change to the patient access scheme for alirocumab. The company also incorporated the committee's preferred assumptions outlined in the appraisal consultation document and provided comparisons for alirocumab in combination with ezetimibe and statin compared with ezetimibe and statin.
- 3.49 In the primary prevention (heterozygous-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER was £45,004 per QALY gained (incremental costs £16,773; incremental QALYs 0.37) for people with an LDL-C above 3 mmol/l and £37,228 per QALY gained (incremental costs £16,531; incremental QALYs 0.44) for people with an LDL-C above 4 mmol/l.
- 3.50 In the secondary prevention (heterozygous-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER was

£22,600 per QALY gained (incremental costs £13,368; incremental QALYs 0.59) for people with an LDL-C above 3 mmol/l and £19,973 per QALY gained (incremental costs £13,092; incremental QALYs 0.66) for people with an LDL-C above 4 mmol/l.

- 3.51 In the high-risk CVD (non-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER was £35,899 per QALY gained (incremental costs £13,556; incremental QALYs 0.38) for people with an LDL-C above 3 mmol/l and £24,835 per QALY gained (incremental costs £13,012; incremental QALYs 0.52) for people with an LDL-C above 4 mmol/l.
- 3.52 In the recurrent events/polyvascular disease (non-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER was £27,644 per QALY gained (incremental costs £12,255; incremental QALYs 0.44) for people with an LDL-C above 3 mmol/l and £19,291 per QALY gained (incremental costs £11,588; incremental QALYs 0.60) for people with an LDL-C above 4 mmol/l.
- 3.53 The company conducted new subgroup analyses using different rate ratios from the CTTC meta-analysis for the relationship between LDL-C levels and cardiovascular outcomes:
- Using CTTC rate ratios as applied in [NICE's technology appraisal guidance on ezetimibe](#) reduced the ICERs by between £1,000 to £2,400 per QALY gained for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe.
 - Using CTTC rate ratios as applied in [NICE's technology appraisal guidance on evolocumab](#) reduced the ICERs by between £3,800 and £9,700 per QALY gained for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe.

ERG comments

- 3.54 The ERG stated that the company's new evidence was consistent with the committee's preferred modelling assumptions.

- 3.55 The ERG agreed with the company's assertion that the rate ratios used to estimate the relationship between LDL-C levels and cardiovascular outcomes for alirocumab were different from the rate ratios used in the NICE technology appraisals of ezetimibe and evolocumab. It noted that:
- The rate ratios used in the NICE technology appraisal of evolocumab were derived from 5 trials of more intensive statin treatment compared with less intensive statin treatment using the CTTC meta-analysis from 2010.
 - The rate ratios used in the NICE technology appraisal of ezetimibe were derived from trials of statins compared with control using the CTTC meta-analysis from 2010.
 - The rate ratios used in the NICE technology appraisal of alirocumab were derived from 27 trials of both more intensive statin treatment compared with less intensive statin treatment, and trials of statins compared with control using the CTTC meta-analysis from 2012.

ERG's revised exploratory analyses

- 3.56 The ERG undertook revised exploratory analyses to estimate the LDL-C level at which the ICER falls below a maximum acceptable ICER of £30,000 per QALY gained. In summary, the baseline LDL-C levels for an ICER below £30,000 per QALY gained ranged from approximately 3.5 mmol/l for the recurrent events/polyvascular (non-familial) disease population to approximately 6.1 mmol/l for the primary prevention (heterozygous-familial) population (see table 6).

Table 6 ERG's revised exploratory analysis: LDL-C level (mmol/l) when the ICER is below £30,000 per QALY gained for alirocumab with ezetimibe plus statin compared with ezetimibe with statin, including patient access scheme

Population	Mean baseline LDL-C (mmol/l) for ICER ≤£30,000 per QALY gained
Primary prevention (heterozygous-familial) population	~6.1
Secondary prevention (heterozygous-familial) population	~4.0

Population	Mean baseline LDL-C (mmol/l) for ICER ≤£30,000 per QALY gained
High-risk cardiovascular disease (non-familial)	~4.1
Recurrent events/polyvascular (non-familial) disease	~3.5

Abbreviations: ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of alirocumab, having considered evidence on the nature of primary hypercholesterolaemia and mixed dyslipidaemia and the value placed on the benefits of alirocumab 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 people with familial hypercholesterolaemia have a lifetime risk of cardiovascular events and their quality of life is adversely affected by the need to be on treatment throughout their life. The committee noted that some people taking statins for hypercholesterolaemia can experience side effects such as muscle and joint pain that can disrupt daily activities and reduce quality of life. It heard from the clinical and patient experts that although low-density lipoprotein (LDL) apheresis is an alternative treatment option for people with very severe hypercholesterolaemia, it is not available in all areas and is not a sustainable therapy because it requires lengthy attendance at a clinic every 2 weeks and time to recover from the procedure. The committee concluded that the current treatment options for hypercholesterolaemia or mixed dyslipidaemia may not be sufficient in all cases, and that alternative treatment options are desirable.
- 4.2 The committee discussed the marketing authorisation for alirocumab and how alirocumab might be used in practice. The committee was aware that alirocumab has a marketing authorisation for use in adults with primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia (see [section 2.1](#)), and understood that 5 clinical groups of people can be distinguished within the marketing authorisation for treating primary hypercholesterolaemia:
- A primary prevention non-familial hypercholesterolaemia group.
 - A secondary prevention non-familial group of people with established cardiovascular disease, who have previously had a cardiovascular event (the high-risk cardiovascular disease [non-familial] population). This group

included people with non-familial hypercholesterolaemia with a history of:

- acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation)
 - coronary or other arterial revascularisation procedures
 - coronary heart disease
 - ischaemic stroke
 - peripheral arterial disease.
- A subgroup of people from the high-risk group who have had more than 1 previous cardiovascular event or who have polyvascular disease (referred to as the recurrent events/polyvascular disease [non-familial] population). This group included people with non-familial hypercholesterolaemia with recurrent cardiovascular events, or cardiovascular events in more than 1 vascular bed.
 - A primary prevention heterozygous-familial hypercholesterolaemia group (the primary prevention [heterozygous-familial] population)
 - A secondary prevention heterozygous-familial hypercholesterolaemia group (the secondary prevention [heterozygous-familial] population). This group included people with heterozygous-familial hypercholesterolaemia with a history of:
 - acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation)
 - coronary or other arterial revascularisation procedures
 - coronary heart disease
 - ischaemic stroke
 - peripheral arterial disease.

The committee considered that these groups broadly corresponded to those defined in the company submission. It noted that the homozygous-familial hypercholesterolaemia population is not within the

marketing authorisation for alirocumab (see section 2.1). It also noted that the company did not present any evidence for people with non-familial hypercholesterolemia without a history of cardiovascular disease (primary prevention) and therefore, agreed that it could not make recommendations for this population. The committee noted that the 4 groups defined by the company were within the marketing authorisation, and concluded that the company's subgroups were appropriately defined and relevant for its decision-making.

- 4.3 The committee discussed whether alirocumab would be used for treating mixed dyslipidaemia. It noted that although the marketing authorisation and the final scope for alirocumab included people with mixed dyslipidaemia, the company did not present any separate evidence for this population. The committee was aware that people with mixed dyslipidaemia also have higher LDL-C levels, and heard from the clinical experts that treatment for mixed dyslipidaemia is partly determined by LDL-C level. The committee was aware that people with heterozygous-familial hypercholesterolaemia are considered to be at high risk of CVD not only because of the high LDL-C concentrations, but also because of the lifelong exposure to such concentrations. The committee understood from the clinical experts that although alirocumab was likely to mainly be used for primary hypercholesterolaemia in clinical practice, it may also be used for treating mixed dyslipidaemia when LDL-C levels remain persistently high.
- 4.4 The committee considered the current treatment options and comparators for people with hypercholesterolaemia. The committee heard from the clinical experts that a maximally tolerated dose of statins is the main treatment option for familial and non-familial hypercholesterolaemia (as described in NICE's guidelines on [familial hypercholesterolaemia](#) and NICE's guideline on lipid modification [now replaced by [NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification](#)]), but that a minority of people cannot have statins. It understood that common side effects such as fibromyalgia and headache contribute to intolerance and discontinuation of statin therapy. The committee was also aware that NICE's technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (now replaced by [NICE's technology appraisal guidance on ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia](#)) recommends ezetimibe monotherapy as an option to

treat primary hypercholesterolaemia when statin treatment is insufficient. The committee concluded that a maximally tolerated dose of statins with ezetimibe was the main treatment option and therefore was an appropriate comparator for alirocumab in this appraisal.

- 4.5 The committee discussed statin therapy for treating hypercholesterolaemia. It was aware that the marketing authorisation stated that alirocumab should be used in combination with a statin or with a statin and other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of statin, or alone or in combination with other lipid-lowering therapies in patients who cannot have a statin or for whom a statin is contraindicated (see [section 2.1](#)). The committee heard from the clinical expert that although up to approximately 23% of people with primary hypercholesterolemia were currently reported to be intolerant to statins, the true rate was likely to be between 0.5% to 3.0% of the population because there were no clear diagnostic criteria for statin intolerance. The committee acknowledged that there is no universally accepted definition of intolerance to statins, but was aware of the definition of intolerance used in [NICE's guideline on familial hypercholesterolaemia](#). It agreed that some people could be misidentified as intolerant to statins and that the true size of the population that cannot take statins was relatively small compared to the wider population covered by the marketing authorisation. The committee was aware that there may also be people in whom statins are contraindicated. It was aware that these people have the same unmet clinical need as those who cannot tolerate statins and that there is no biologically plausible reason for the alirocumab to work differently in these people. The committee was aware that the populations in the company's new evidence (see [section 3.48](#)) were defined by the LDL-C level at which treatment with alirocumab should be started. The committee was aware that people who cannot take statins have higher than average LDL-C levels, and would therefore meet the LDL-C levels needed to start treatment with alirocumab for people who can take statins. The committee concluded that it was not necessary to make separate recommendations for people who cannot take statins.
- 4.6 The committee discussed the place of lipoprotein apheresis in managing primary hypercholesterolaemia, noting that this was not included as a comparator in the final scope for this appraisal. The committee noted from consultation comments that apheresis is not only costly and onerous for the patient, but also difficult to

access because only a few centres offer it. The committee further heard from the clinical expert that lipoprotein apheresis would be considered for people with heterozygous-familial hypercholesterolaemia whose LDL-C level remains above 5.0 mmol/l or decreases by less than 40% when taking maximally tolerable doses of combined drug therapy. The committee concluded that treatments that avoid the need for apheresis would be welcomed.

- 4.7 The committee heard from the clinical expert that alirocumab should only be used when LDL-C levels are persistently high despite lipid-lowering therapy. The committee recalled that statins with or without ezetimibe are the main treatment for primary hypercholesterolaemia, but that some people may be misidentified as being unable to take statins (see section 4.5) which may make subsequent treatments less cost effective. Because of this, the committee emphasised that its recommendations for alirocumab should only apply when the maximum tolerated lipid-lowering therapy has failed. It clarified that this meant that either when the maximum dose has been reached or when further titration is limited by intolerance (as defined in [NICE's guideline on familial hypercholesterolaemia: identification and management](#)).

Clinical effectiveness

- 4.8 The committee considered the clinical-effectiveness evidence for alirocumab. It agreed that the trials included patients whose characteristics reflected those with hypercholesterolaemia seen in clinical practice in England, and that the results could be generalised to clinical practice. It noted that in people with hypercholesterolaemia, alirocumab statistically significantly reduced LDL-C levels from baseline at 24 weeks by 39% to 62% compared with placebo, 24% to 36% compared with ezetimibe, and 20% to 49% compared with a statin. The committee heard from the clinical expert that PCSK9 inhibitors could reduce LDL-C by up to 60% compared with placebo and that the treatment would have a sustained benefit, especially for people with familial hypercholesterolaemia. It also noted the ERG's comments that alirocumab was shown to have a similar safety profile to control groups. The committee concluded that alirocumab is clinically effective in reducing LDL-C levels when compared with placebo, ezetimibe or statins in people with hypercholesterolaemia.

- 4.9 The committee discussed the effect of alirocumab on cardiovascular events in people with hypercholesterolaemia. It noted that the trials mainly reported surrogate end points (especially 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 noted that the company provided information about the relationship between LDL-C and cardiovascular events from the Navarese meta-analyses of PCSK9 inhibitor trials. The committee heard from the clinical expert that the currently accepted relationship between LDL-C and cardiovascular events is based on a Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of statin trials. It understood that the CTTC meta-analysis included trials that had long follow-up periods, were designed to measure cardiovascular outcomes, had a large number of patients and many observed events. In contrast, the Navarese meta-analysis of PCSK9 inhibitors included trials with shorter follow-up periods, fewer patients and fewer events. The committee also discussed the company's new evidence submitted in response to the appraisal consultation document, which used the CTTC meta-analysis. The company stated that although NICE's technology appraisals for ezetimibe and evolocumab used the CTTC meta-analysis, it had used the most conservative estimate of the relationship between LDL-C and cardiovascular outcomes in its own modelling for alirocumab. The committee heard from the ERG that this estimate was taken from the most recent update of the CTTC meta-analysis, which included more trials and patients than the older meta-analysis used in the other NICE technology appraisals. Therefore, the committee concluded that the most appropriate evidence to assess this relationship was from the most recent update of the CTTC meta-analysis.

Cost effectiveness

- 4.10 The committee considered the structure of the company's model. It noted that the model was consistent with the approaches for hypercholesterolaemia developed for related NICE guidance. Although the structure omitted the transient ischaemic attack and stable angina health states, the ERG considered these limitations to be conservative assumptions and considered the model to be of good quality with an appropriate structure. The committee concluded that the company's approach to modelling and the model structure was a reasonable basis for its decision-making.

- 4.11 The committee considered the baseline characteristics, risks and the transition probabilities used by the company. The committee understood that they were based on relevant real-world data from the Health Improvement Network (THIN) database, and noted the ERG's comment that there was good agreement with medium-term survival for the high-risk cardiovascular disease and recurrent events/polyvascular disease (non-familial) populations. The committee therefore agreed that using data from THIN for these populations was appropriate. It understood that the company checked the face validity of baseline characteristics with known prevalence. It was aware that the company acknowledged that the baseline characteristics based on THIN were different from the known prevalence for the primary and secondary prevention (heterozygous-familial) populations. Therefore, the committee accepted the company's approach using the Dutch lipid criteria with THIN instead of THIN alone, to identify people for the primary prevention (heterozygous-familial) population because the baseline characteristics were considered more realistic. The committee noted the company's belief that the patient characteristics for the secondary prevention (heterozygous-familial) population using the Dutch lipid criteria with THIN still lacked face validity, because they were different from known prevalence. The committee noted that the company used an alternative source (Mohrschladt) for this population and that this resulted in a composite annual baseline cardiovascular risk twice as high when compared with data from THIN. Although the ERG was unable to verify whether this alternative source was appropriate, the committee agreed that on balance, given that the patient characteristics from a real-world dataset (THIN) were different from known prevalence, it was appropriate to use Mohrschladt for the secondary prevention (heterozygous-familial) population. The committee concluded that the baseline characteristics, risks and transition probabilities used in the company's model were acceptable for its decision-making.
- 4.12 The committee considered the incremental cost-effectiveness ratios (ICERs) per quality-adjusted life year (QALY) for each group separately (as defined in section 4.2). It considered the ICERs from the company's new evidence in response to the appraisal consultation document, and noted that they incorporated both a revised patient access scheme and the committee's preferred assumptions as outlined in the appraisal consultation document.
- 4.13 The committee discussed how the company defined subgroups by LDL-C level

for each population in its new evidence. The committee recognised that using subgroups based on LDL-C levels at which treatment should be started (that is, threshold LDL-C levels) was consistent with both suggestions from consultation comments received in response to the appraisal consultation document and the committee's approach in previous technology appraisals. However, the committee recognised that the threshold LDL-C levels were calculated as an average and would therefore include some people in whom alirocumab was most beneficial and cost effective (that is, people at relatively high baseline LDL-C levels) as well as people in whom alirocumab was less beneficial and cost effective (that is people, at relatively low baseline LDL-C levels). Therefore, the committee agreed that the LDL-C levels in the company's new evidence may not be representative of the threshold at which alirocumab would be cost effective for all patients in the subgroup. The committee then noted that the ERG's revised exploratory analysis identified the LDL-C level at which the ICER could be within the range normally considered to be a cost-effective use of NHS resources (using a maximum acceptable ICER of less than £30,000 per QALY gained). The committee concluded that the company's approach was clinically plausible and consistent with other NICE technology appraisals for hypercholesterolaemia, and that the ERG's revised exploratory analysis could be used to more accurately identify the LDL-C level at which the ICER would be within the range normally considered to be a cost-effective use of NHS resources.

Non-familial hypercholesterolaemia (primary prevention) population

- 4.14 The committee noted that the company did not submit evidence for people with non-familial hypercholesterolaemia without a history of cardiovascular disease (see section 4.2). Because of this, the committee concluded that alirocumab in combination with other lipid-lowering therapies had not been shown to be a cost-effective use of NHS resources for treating non-familial hypercholesterolaemia in adults without a history of cardiovascular disease and did not recommend alirocumab for this group.

Non-familial hypercholesterolaemia high-risk cardiovascular disease (secondary prevention) population

- 4.15 In this population, the ICERs to be considered for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe were between £24,800 and £44,300 per QALY gained. Applying the ERG's revised exploratory analysis showed that the ICER for alirocumab in combination with other lipid-lowering therapies compared with other lipid-lowering therapies alone would be below £30,000 per QALY gained at an LDL-C level of 4.1 mmol/l. The committee agreed that alirocumab in combination with other lipid-lowering therapies could be considered a cost-effective use of NHS resources compared with lipid-lowering therapies alone for treating primary non-familial hypercholesterolaemia in adults with a high risk of cardiovascular disease and persistent LDL-C levels of at least 4.0 mmol/l despite having the maximum tolerated lipid-lowering therapy, and recommended it for this group.

Non-familial hypercholesterolaemia recurrent events/polyvascular disease (secondary prevention) population

- 4.16 In this population, the ICERs to be considered for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe were between £19,300 and £34,000 per QALY gained. Applying the ERG's revised exploratory analysis showed that the ICER would be below £30,000 per QALY gained at an LDL-C level of 3.5 mmol/l. The committee agreed that alirocumab in combination with other lipid-lowering therapies could be considered a cost-effective use of NHS resources compared with lipid-lowering therapies alone for treating primary non-familial hypercholesterolaemia in adults with a very high risk of cardiovascular disease and persistent LDL-C levels of at least 3.5 mmol/l despite having the maximum tolerated lipid-lowering therapy, and recommended it for this group.

Heterozygous-familial hypercholesterolaemia (primary prevention)

- 4.17 In this population, the ICERs to be considered for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe were between £37,000 and £50,000 per QALY gained. The committee noted that all of these ICERs were above the maximum acceptable ICER normally considered to represent a cost-effective use of NHS resources (£20,000 to 30,000 per QALY gained). Although no ICERs were available for LDL-C levels above 4 mmol/l, the committee noted that, in general, the ICERs tended to decrease as the LDL-C level threshold for treatment increased. Therefore, it agreed that at higher LDL-C levels (above 4 mmol/l) the ICER for alirocumab could plausibly approach the range normally considered to be a cost-effective use of NHS resources. The committee also recalled that the ICERs for specific LDL-C level thresholds for treatment could include a cohort of people in whom alirocumab would not be cost effective (see section 4.13). The committee noted that the ERG's revised exploratory analysis showed the ICER would be below £30,000 per QALY gained at an LDL-C level of 6.1 mmol/l, and agreed that this was most likely the LDL-C level at which the ICER would be within the range normally considered to be a cost-effective use of NHS resources. The committee also noted that people with hypercholesterolaemia with an LDL-C level above 5.0 mmol/l would be eligible for apheresis; it recalled its conclusion that treatments that avoid the need for apheresis would be welcomed (see section 4.6), but was aware that the company's model did not incorporate the cost and disutility associated with apheresis, which could reduce the resulting ICER. The committee concluded that despite the high ICERs, alirocumab in combination with other lipid-lowering therapies could plausibly be considered a cost-effective use of NHS resources compared with other lipid-lowering therapies alone for treating heterozygous-familial hypercholesterolaemia in adults without a history of cardiovascular disease and persistent LDL-C levels of at least 5.0 mmol/l despite having the maximum tolerated lipid-lowering therapy, and recommended it for this group.

Heterozygous-familial hypercholesterolaemia (secondary prevention)

- 4.18 In this population, the ICERs to be considered for alirocumab and a statin plus

ezetimibe compared with a statin and ezetimibe were between £20,000 and £24,000 per QALY gained. Applying the ERG's revised exploratory analysis showed that the ICER for alirocumab in combination with other lipid-lowering therapies compared with other lipid-lowering therapies alone would be below £30,000 per QALY gained at an LDL-C level of 4.0 mmol/l. The committee considered consultation comments that indicated that people with heterozygous-familial hypercholesterolaemia with a history of cardiovascular disease had a lifelong risk of future cardiovascular events. It also noted consultation comments suggesting that treatment with alirocumab should be started at an LDL-C level of 3 mmol/l, or at 4.0 mmol/l pending further evidence from cardiovascular outcome studies. The committee accepted that alirocumab would be beneficial for people with a lifelong risk of cardiovascular events in this population group. The committee also considered consultation comments suggesting that an LDL-C level above 4 mmol/l to start treatment would exclude some people at high risk of cardiovascular disease. Having accepted that a minimum LDL-C level of 4 mmol/l may exclude a small group of people, the committee agreed that a lower LDL-C level of 3.5 mmol/l for starting treatment would be more appropriate than 4.0 mmol/l. On balance, the committee concluded that alirocumab in combination with other lipid-lowering therapies could be considered a cost-effective use of NHS resources compared with other lipid-lowering therapies for treating heterozygous-familial hypercholesterolaemia in adults with a history of cardiovascular disease and persistent LDL-C levels of at least 3.5 mmol/l despite having the maximum tolerated lipid-lowering therapy, and recommended it for this group.

Mixed dyslipidaemia

- 4.19 The committee was aware that the company's model did not include people with mixed dyslipidaemia. It discussed whether its recommendations for primary hypercholesterolaemia could be generalised to mixed dyslipidaemia. The committee recalled that people with mixed dyslipidaemia also have elevated LDL-C concentrations, and that treatment for mixed dyslipidaemia is partly determined by the LDL-C concentration (see section 4.3). The committee understood that unlike people with non-familial hypercholesterolemia, people with heterozygous-familial hypercholesterolaemia are at high risk of cardiovascular disease not only because of the high LDL-C concentrations, but

also because of the lifelong exposure to such concentrations. Therefore, the committee concluded that the recommendations for people with mixed dyslipidaemia should be the same as the recommendations for people with non-familial hypercholesterolaemia.

- 4.20 The committee discussed whether the ICERs presented accurately reflect the cost of alirocumab to the NHS. It understood that the actual discount received by the NHS may be less than the percentage discount offered in the patient access scheme. This is because people may move from secondary to primary care after several years, and simple discounts do not apply when drugs are prescribed through GP's FP10 prescriptions. The committee considered that the subgroups for which alirocumab is recommended have severe hypercholesterolaemia and a high risk of CVD, so treatment should continue in secondary care where simple patient access schemes apply. The committee concluded that the discounted patient access scheme price of alirocumab would be consistently applied for all people for whom alirocumab is recommended.
- 4.21 The committee discussed whether alirocumab could be considered innovative, and noted that clinical and patient experts thought it to be an innovative drug. The committee acknowledged that alirocumab was one of the first in a new class of drugs with a novel mechanism of action. Even so, it concluded that there was no evidence of additional gains in health-related quality of life over those already included in the QALY calculations, and that there was no need to change its conclusions on that basis.
- 4.22 The committee considered a potential equality issue raised by a patient and professional organisation that the incidence of familial hypercholesterolaemia could be higher in people of Ashkenazi Jewish origin. The committee concluded that its recommendations for alirocumab would apply to all patients and that the recommendation would not affect people protected by the equality legislation any differently.
- 4.23 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee

heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has primary hypercholesterolaemia or mixed dyslipidaemia and the healthcare professional responsible for their care thinks that alirocumab is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for research

- 6.1 The committee was aware that an ongoing randomised controlled trial exploring the occurrence of cardiovascular events of alirocumab compared with placebo are available is expected in 2018. The committee agreed that this trial would give useful data on the direct effect of alirocumab on cardiovascular disease.

7 Appraisal committee members, guideline representatives and NICE project team

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

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

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

NICE project team

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

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