NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (review of NICE technology appraisal guidance 132)

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ezetimibe 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 9) 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 ezetimibe 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: 5pm on 10 November 2015

Second Appraisal Committee meeting: 18 November 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

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 Ezetimibe monotherapy is recommended as an option for treating primary heterozygous-familial and non-familial hypercholesterolaemia in adults, when a statin is considered inappropriate or is not tolerated, only if:

- they need lipid modification therapy for the primary prevention of cardiovascular disease and have both:
  - type 2 diabetes and
  - a 20% or greater 10−year risk of developing cardiovascular disease according to the QRISK2 risk assessment tool or
- they need lipid-modification therapy for the secondary prevention of cardiovascular disease.

1.2 Adults whose treatment with ezetimibe is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Ezetimibe (Ezetrol, Merck Sharp & Dohme) is a cholesterol-absorption inhibitor that blocks the intestinal absorption of dietary and biliary cholesterol and related plant sterols, without affecting the uptake of triglycerides or fat-soluble vitamins. Because of this mechanism of action, ezetimibe can be combined with a statin to

provide either a complementary or an alternative mode of cholesterol reduction.

2.2 Ezetimibe, in combination with a statin or as monotherapy, has a marketing authorisation in the UK. It is licensed in combination with an HMG-CoA reductase inhibitor (statin) as an adjunctive therapy to diet for primary heterozygous-familial or non-familial hypercholesterolaemia that is not appropriately controlled with a statin alone. Ezetimibe monotherapy has a marketing authorisation as an adjunctive therapy to diet for primary heterozygous-familial or non-familial hypercholesterolaemia when a statin is considered inappropriate or is not tolerated.

2.3 Adverse reactions with ezetimibe as monotherapy or in combination with a statin are usually mild and transient. When given as monotherapy, they most commonly include abdominal pain, diarrhoea, flatulence and fatigue. When taken with a statin, the most common additional adverse reactions include increased alanine transaminase, aspartate transaminase or both, headache and myalgia. For full details of adverse effects and contraindications, see the summaries of product characteristics.

2.4 Ezetimibe is taken orally at a dose of 10 mg once daily. Ezetimibe is available in a dose of 10 mg (28-tablet pack) at a net price per pack of £26.31 (excluding VAT; 'British national formulary' [BNF]; accessed September 2015). A fixed-dose combination tablet (Inegy, Merck Sharp & Dohme) containing ezetimibe and simvastatin is available in doses of ezetimibe 10 mg and simvastatin 20 mg (28-tablet pack) at a net price per pack of £33.42, ezetimibe 10 mg and simvastatin 40 mg (28-tablet pack) at a net price per pack of £38.98, and ezetimibe 10 mg and simvastatin 80 mg (28-tablet pack) at a net price per pack of £41.21

(excluding VAT; BNF; accessed September 2015). Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 9) considered evidence submitted by Merck Sharp & Dohme and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical-effectiveness evidence

3.1 The company provided a narrative summary of 3 double-blind randomised clinical outcome trials (SHARP, IMPROVE-IT and SEAS), which examined the effectiveness of ezetimibe in reducing cardiovascular events. The company also did a systematic literature review to identify randomised controlled trials of ezetimibe (monotherapy and in combination with a statin) for treating primary hypercholesterolaemia that had a duration longer than 12 weeks. The company's meta-analyses included 24 randomised controlled trials plus the IMPROVE-IT clinical trial report.

Overview of clinical trials

3.2 SHARP was a randomised, double-blind, placebo-controlled study in 9270 patients with chronic kidney disease and unknown history of myocardial infarction or coronary revascularisation. Patients were randomised in a 4:4:1 ratio to either ezetimibe 10 mg plus simvastatin 20 mg once daily, placebo once daily, or simvastatin 20 mg for 1 year to assess the safety of ezetimibe. After 1 year, because no safety concerns were identified, the simvastatin arm was re-randomised to either ezetimibe 10 mg plus simvastatin 20 mg once daily or placebo once daily. At a median follow-up of 4.9 years, ezetimibe plus simvastatin produced a 17% proportional reduction in the primary composite efficacy endpoint of coronary heart disease, death, non-fatal myocardial infarction,

revascularisation, or non-fatal non-haemorrhagic stroke compared with placebo (relative risk [RR] 0.83, 95% confidence interval [CI] 0.74 to 0.94, p=0.0021). The reduction in non-fatal myocardial infarction or coronary death (RR 0.92, 95% CI 0.76 to 1.11) was not statistically significant, but the trial was not powered to assess the major atherosclerotic events separately. Mean reduction in low-density lipoprotein cholesterol (LDL-c) at 26–31 months was 0.85 mmol/litre with ezetimibe plus simvastatin compared with placebo (a relative reduction of 61%).

3.3 IMPROVE-IT was a randomised, double-blind, active-controlled study in 18,144 patients with stabilised acute coronary syndrome. Patients were randomised in a 1:1 ratio to either ezetimibe 10 mg plus simvastatin 40 mg once daily or simvastatin 40 mg once daily. At a median follow-up of 6 years, ezetimibe plus simvastatin produced a 6.4% RR reduction in the primary composite efficacy endpoint of cardiovascular death, major coronary event, or non-fatal stroke compared with treatment with simvastatin therapy alone (hazard ratio 0.936, 95% CI 0.89 to 0.99, p=0.016). There was a further reduction in LDL-c at 1 year of 0.43 mmol/litre with ezetimibe plus simvastatin compared with simvastatin therapy alone (a relative reduction of 24%).

3.4 SEAS was a randomised, double-blind, placebo-controlled study in 1873 patients with mild-to-moderate, asymptomatic aortic stenosis. Patients were randomised 1:1 to have either ezetimibe 10 mg plus simvastatin 40 mg once daily or placebo once daily. Median follow-up was 52.2 months. The primary composite efficacy endpoint outcome measured major cardiovascular events, including death from cardiovascular causes, aortic-valve replacement, non-fatal myocardial infarction, hospitalisation for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous

coronary intervention, and non-haemorrhagic stroke. The outcome occurred in 333 patients (35.3%) patients having ezetimibe plus simvastatin and in 355 patients (38.2%) having placebo (hazard ratio 0.96, 95% CI 0.83 to 1.12, p=0.59).

Meta-analyses

3.5 The company did meta-analyses for mean percent change from baseline in LDL-c and total cholesterol. The company compared ezetimibe 10-mg monotherapy with placebo and ezetimibe 10 mg as an add-on to a statin with a statin alone. For each outcome, pairwise meta-analysis was done using a random effects model. The company presented the relative treatment effect (mean difference and 95% CI) of ezetimibe compared with placebo for each study, pooled mean difference and 95% CI for each subgroup. There was a large degree of heterogeneity in all analyses.

3.6 In its response to clarification, the company's meta-analysis of 12 randomised controlled trials, showed that ezetimibe used as monotherapy provided a statistically significant reduction in LDL-c (−20.59%, 95% CI −22.13 to −19.05) and total cholesterol (−16.07%, 95% CI −17.01 to −15.13). When ezetimibe was used in combination with a statin, a meta-analysis of 17 randomised controlled trials showed that ezetimibe provided a further statistically significant lowering in LDL-c (−15.6%, 95% CI −17.05 to −14.13) and total cholesterol (−12.17%, 95% CI −12.90 to −11.45) combined with a statin compared with statin therapy alone.

3.7 The company also identified 3 pre-planned subgroups: adults with type 2 diabetes, adults with chronic kidney disease and adults with heterozygous familial hypercholesterolaemia. In adults with chronic kidney disease and adults with heterozygous familial

hypercholesterolaemia, no meta-analyses were done because only 1 trial was identified in each subgroup (both trials were in combination with a statin). In adults with type 2 diabetes, 1 trial using monotherapy and 3 trials in combination with a statin were identified. In patients with type 2 diabetes, the mean difference in LDL-c for ezetimibe as an add-on to a statin compared with statin therapy alone was −18.8% (95% CI −20.7 to −17.0). In patients without type 2 diabetes, the mean difference was −15.0% (95% CI −15.8 to −14.1). The estimated difference in treatment effect between patients with type 2 diabetes and those without was −3.87% (95% CI −5.85 to −1.90).

Adverse effects of treatment

3.8 The company reported that no new safety concerns related to ezetimibe were raised in SHARP or IMPROVE-IT. It said that, in both of these trials, the safety findings were consistent with those described in the current summary of product characteristics for ezetimibe and simvastatin. It further stated that there were no meaningful differences between the treatment groups in clinical adverse events, including those leading to discontinuation of study drug and those reported as serious.

Evidence Review Group comments

3.9 The Evidence Review Group (ERG) stated that the company's search strategy to identify relevant studies was broadly appropriate, but considered the search insufficiently sensitive. The ERG could not confirm that the company's approach was comprehensive in identifying relevant studies, and also noted that the company's submission did not provide any information on how ongoing studies were identified. The ERG commented that SEAS would not have been retrieved by the company's search strategy and noted that SEAS and SHARP did not meet the eligibility criteria because they

compare a combination of ezetimibe and simvastatin with placebo. The ERG also identified an additional randomised controlled trial that it considered should have been included in the systematic review.

3.10 The ERG identified several studies included in the meta-analyses that did not meet the eligibility criteria specified in the company's submission, because the patient population may not have had primary hypercholesterolaemia. In its response to clarification, the company justified the inclusion of these studies by suggesting that the patient populations were at high risk of cardiovascular disease and relevant to clinical practice. The ERG noted that the decision to exclude Asian studies may have been inconsistently applied in the company's submission.

3.11 The ERG noted that no attempt was made to consider revascularisation or quality-of-life outcomes in the company's systematic review even though these outcomes were specified in the final scope. The ERG noted that in the company's economic model, clinical outcomes were linked to the lowering of LDL-c levels through an external meta-analysis (Cholesterol Treatment Trialists' Collaboration; CTTC), which was similar to the approach used in NICE's technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. The ERG was of the opinion that the approach used by the company in this appraisal was not fully justified because at least 3 trials in the company's submission assessed clinical outcomes. The ERG believed that a direct meta-analysis of clinical outcomes would have provided more clinically relevant information. The ERG noted high levels of statistical heterogeneity in the meta-analyses and observed that no attempt had been made to investigate the reasons for this.

3.12 The ERG believed that the company could have done a network meta-analysis for LDL-c levels, and potentially included different statin doses as separate treatments within the network as well as other combinations of statins, placebo and lipid-regulating drugs.

3.13 The ERG stated that the adverse events in each trial were narratively summarised in the company's systematic review. The ERG also noted, when considering the rate of adverse events, that there were no clear differences between groups.

Cost-effectiveness evidence

3.14 The company's base-case cost-effectiveness analyses included patients with primary hypercholesterolaemia in a primary prevention (without established cardiovascular disease) or a secondary prevention population (with established cardiovascular disease), using ezetimibe either:

- as a monotherapy in patients where a statin is considered inappropriate or is contraindicated or not tolerated, or
- co-administered with a statin in adults whose condition is not appropriately controlled with a statin alone, either after appropriate dose titration of initial statin therapy or because dose titration is inappropriate or not tolerated.

The company also discussed 3 further subgroups: primary prevention for adults with type 2 diabetes, adults with chronic kidney disease and adults with heterozygous-familial hypercholesterolaemia.

Model structure

3.15 The company submitted a Markov model based on the modelling approaches previously developed for NICE technology appraisal guidance on statins for the prevention of cardiovascular events and

ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia). 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 an NHS and personal social services perspective.

3.16 For primary prevention, the baseline characteristics of the population in the model were informed by a Clinical Practice Research Datalink (CPRD) observational study, which investigated statin prescribing in the primary prevention population in the UK (n=300,914). The starting age was 60 years and 46.4% of the cohort was female. All patients started in the 'well' state and were assumed not to have previously had any cardiovascular event. Patients could remain in the 'well' state, or transition to 1 of 3 major cardiovascular events health states (unstable angina, myocardial infarction and stroke) or die. The effect of ezetimibe on stable angina and transient ischemic attack was explored in scenario analyses. Revascularisation was not modelled as a separate health state because it was captured in the cost data for the health states.

3.17 For secondary prevention, the baseline characteristics of the population in the model were taken from a UK retrospective observational study, in which the starting age was 69 years and 34.6% of the patients were female. People who had previously had a non-fatal cardiovascular event were categorised depending on whether they had unstable angina, myocardial infarction or a stroke. They could have any of the other cardiovascular events in the next cycle or die; patients who did not have any of these events moved into the respective post-event state.

3.18 For both primary and secondary prevention, the company modelled each non-fatal cardiovascular event in 2 stages. The first stage

captured costs and impact on health-related quality of life in the first year after the event, and the second stage captured the long-term post-event outcomes.

Model details

Treatment

3.19 Ezetimibe was given in line with its marketing authorisation in the model. The comparator for ezetimibe monotherapy was 'no treatment' and the comparator for ezetimibe plus a statin was the maximum tolerated dose of statin therapy alone. The company stated that using atorvastatin as the main statin in the base-case analyses reflected the NICE guideline on lipid modification and clinical practice:

- For primary prevention with ezetimibe plus a statin, atorvastatin 20 mg was used. The company explained that this was because the dose may not be up-titrated in the relevant population.
- For secondary prevention with ezetimibe plus a statin, atorvastatin 40 mg was used.
  - The company stated that although atorvastatin 80 mg is recommended in the NICE guideline on lipid modification and most patients in clinical practice start on this dose post-event, the dose is often later reduced by GPs because of tolerability issues.
  - The company also considered that patients who can tolerate atorvastatin 80 mg for primary or secondary prevention are likely to have their cholesterol appropriately controlled at this dose, and not need the ezetimibe to be added on.
- Lifetime treatment was assumed for both statins and ezetimibe (in line with each drug's summary of product characteristics).

Transition probabilities

3.20 The proportion of patients in each health state was determined by age-dependent, time-variant transition matrices. In the primary prevention base-case analyses, the 20% 10-year cardiovascular disease risk defined by QRISK2 was converted into 1-year probabilities (that is, per cycle). The distribution of patients to primary cardiovascular-disease-event health states and to initial health states in the secondary prevention analyses was based on Ward et al. (2007). Secondary event transition probabilities were sourced from the NICE guideline on lipid modification. Mortality was incorporated by transitioning to the cardiovascular and non-cardiovascular death health states, which could happen at the end of each model cycle. Non-cardiovascular-related death in the company's model was based on life tables from the Office of National Statistics.

Clinical variables and parameters

3.21 In the technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia, a CTTC meta-analysis was used to model the treatment effect of ezetimibe and the comparators, linking the absolute reduction in LDL-c to the proportional reduction of cardiovascular events. Although IMPROVE-IT and SHARP have subsequently investigated the effect of adding ezetimibe to statin therapy on reducing cardiovascular events, their patient populations were narrower than the population specified in ezetimibe's marketing authorisation. The company considered that baseline characteristics, cardiovascular risk and treatment pathway for the population in the clinical trials would be different from the other populations (for example, primary prevention, high-risk primary hypercholesterolaemia patients with type 2 diabetes and

those having ezetimibe monotherapy). Therefore, the company again chose to use the CTTC meta-analysis to model the effect of ezetimibe on cardiovascular outcomes linked to decreased LDL-c.

3.22 The CTTC has done meta-analyses of randomised controlled trials of statins to show the link between lowering LDL-c and reducing coronary events. The most recent CTTC meta-analysis from 2010 included 26 randomised controlled trials and showed that reducing LDL-c by 1.0 mmol/litre with statin treatment reduced the risk of non-fatal myocardial infarction (RR 0.74, 95% CI 0.69 to 0.78), stroke (RR 0.85, 95% CI 0.80 to 0.90), any cardiovascular death (RR 0.86, 95% CI 0.82 to 0.90) and all non-cardiovascular deaths (RR 0.97, 95% CI 0.91 to 1.03) compared to control.

3.23 For the comparator group in the ezetimibe monotherapy analyses, the baseline event rates were used for patients who had no treatment. For the comparator group in the ezetimibe plus add-on statin analyses, the baseline transition probabilities were adjusted to reflect the intensity of background statin therapy (that is, different maximum tolerated doses). The company then derived risk ratios to apply to the baseline risk data using randomised controlled trial data with cardiovascular endpoints for the comparator arm. The risk ratios used in the base case of the company's model comparator arm for each event, sourced from the NICE guideline on lipid modification, were: myocardial infarction (non-fatal) 0.46; stroke (non-fatal) 0.80; cardiovascular death 0.72; non-cardiovascular death 0.96; unstable angina (non-fatal) 0.46 (same as non-fatal myocardial infarction). Identical risk ratios were used for primary and secondary prevention populations.

3.24 The company did 2 meta-analyses to estimate the relative clinical effectiveness of ezetimibe in LDL-c change from baseline:

- ezetimibe 10-mg monotherapy compared with placebo, based on 12 RCTs (n=3094)
- ezetimibe 10 mg as an add-on to a statin compared with statin therapy alone, based on 17 RCTs (n=18,966).

3.25 The company incorporated the results of the meta-analyses into its economic model to estimate the LDL-c reduction with ezetimibe as monotherapy or in combination with a statin (see section 3.5). For the subgroup of patients with type 2 diabetes, the company also incorporated the results from the meta-analysis into its economic model (see section 3.7).

Utility values

3.26 The company derived utility values for each of the 9 health state from the literature, the following utility values were used: well 1.00; unstable angina 0.77; post-unstable angina 0.80; myocardial infarction 0.76; post-myocardial infarctions 0.80; stroke 0.50; post-stroke 0.63; cardiovascular and non-cardiovascular death 0. Baseline utility values were age-adjusted and time dependent and fell as the cohort aged. The company advised that it expected adverse reactions associated with ezetimibe to have minimal impact on patients' health-related quality of life and therefore did not apply any treatment-related utility decrements.

Costs

3.27 Drug acquisition costs were taken from the drug and pharmaceutical electronic market information tool (eMit) and the Monthly Index of Medical Specialities (MIMs). Monitoring costs were those used in the NICE guideline on lipid modification. Health-state costs were taken from published literature and inflated to 2013/2014 values. The costs used for each health state were: well £0; stable angina £242.38; post-stable angina £242.48; unstable

angina £575.21; post-unstable angina £245.06; myocardial infarction £6154.50; post-myocardial infarction £625.27; transient ischemic attack £3982.3; post-transient ischemic attack £1386.22; stroke £14,151.26; post-stroke £3927.73 and cardiovascular death £5536.52. Higher monitoring and appointment costs were applied during the first year of both primary and secondary treatment than in subsequent years.

Company's base-case results and sensitivity analyses

3.28 In its response to clarification, the company corrected an error in its model relating to the inflation of cardiovascular risk over time. This slightly increased the incremental cost-effectiveness ratios (ICERs) for the primary prevention population compared with the original submission (the error did not apply to the calculations for secondary prevention). For primary prevention, the corrected base-case ICERs were £30,129 per quality-adjusted life year (QALY) gained (incremental costs £5188; incremental QALYs 0.172) for ezetimibe monotherapy compared with no treatment and £58,473 per QALY gained (incremental costs £5437; incremental QALYs 0.093) for ezetimibe as an add-on to a statin compared with statin therapy alone. For secondary prevention, the base-case ICERs were £17,553 per QALY gained (incremental costs £3885; incremental QALYs 0.221) for ezetimibe monotherapy compared with no treatment and £30,940 per QALY (incremental costs £4113; incremental QALYs 0.133) gained for ezetimibe as an add-on to a statin compared with statin therapy alone.

3.29 The company explored parameter uncertainty in deterministic sensitivity analyses according to upper and lower bound values. For both primary and secondary prevention, the ICER was most sensitive to changes in risk ratios for non-cardiovascular death and

the discounting of costs and health benefits. The company also explored uncertainty using probabilistic sensitivity analyses.

Company's subgroup results

3.30 The company also conducted subgroup analyses in adults with type 2 diabetes, and adults with chronic kidney disease. For primary prevention in adults with type 2 diabetes, the corrected ICERs were £20,294 per QALY gained (incremental costs £4106; incremental QALYs 0.202) for ezetimibe monotherapy compared with no treatment and £31,352 per QALY gained (incremental costs £4360; incremental QALYs 0.139) for ezetimibe as an add-on to a statin compared with statin therapy alone. For secondary prevention in adults with chronic kidney disease, the ICER for ezetimibe plus a statin compared with statin therapy alone was £30,939 per QALY gained (incremental costs £4112; incremental QALYs 0.133).

3.31 The company noted that adults with heterozygous-familial hypercholesterolaemia have high LDL-c (at least 8 mmol/litre) and are at significantly elevated cardiovascular risk. However, the company was unable to do cost-effectiveness analyses because of limited data available on the group's baseline risks. It provided a scenario analysis using the base-case population with high levels of LDL-c.

Company scenarios

3.32 The company did a range of scenario analyses. In the primary prevention population having ezetimibe monotherapy, the scenarios that had the greatest impact on the ICER (base case: £30,129 per QALY gained) were:

- Shortening the time horizon from lifetime to 10 years, which increased to £101,898 per QALY gained (incremental costs and incremental QALYs not reported).
- Decreasing the 10-year cardiovascular risk to 10%, which increased the ICER to £47,067 per QALY gained (incremental costs and incremental QALYs not reported).
- Assuming a price reduction of 75% after ezetimibe's patent expires, which decreased the ICER to £10,146 per QALY gained (incremental costs and incremental QALYs not reported).

A similar pattern was seen in the scenario analyses in the primary prevention population having ezetimibe plus a statin, and in the secondary prevention populations having ezetimibe as monotherapy or in combination with a statin.

Evidence Review Group comments

3.33 The ERG considered the structure of the economic model to be largely appropriate and generally consistent with previous models used to inform the previous NICE technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. However, it noted that the stable angina and transient ischaemic attack health states had been excluded from the company's base-case analysis. The ERG was of the opinion that it was inappropriate to assume zero risk of these events because morbidity, costs and associated downstream risks may influence comparisons. It further noted that ezetimibe might reduce the risks of transient ischaemic attack and stable angina and influence the risk of other cardiovascular events in the model.

3.34 The ERG was concerned about the face validity of the cardiovascular risks increasing with age in the company's

submission for the base-case analysis of the primary prevention population, and suggested that the risk of primary cardiovascular events may not increase sharply enough with age. It stated that the modelled annual increases may have been over-adjusted to account for increases in the risk of transient ischaemic attack and stroke, which had not been included in the estimated annual risk increases. The ERG was not satisfied by the company's explanation of this in its response to clarification.

3.35 The ERG considered the approach to estimating treatment effect using reductions in LDL-c linked cardiovascular events for ezetimibe monotherapy and ezetimibe as an add-on to a statin in the primary prevention cohort. The ERG thought the approach was partially justified because no trials investigating cardiovascular events for ezetimibe compared with placebo had been done in the primary population or for ezetimibe monotherapy in the secondary prevention population. However, the ERG was not convinced by the company using this approach for ezetimibe as an add-on to a statin in the secondary prevention cohort. The ERG considered that IMPROVE-IT offers a more appropriate source of clinical-effectiveness data.

3.36 The ERG stated that the relationship of LDL-c reduction to non-cardiovascular events (sourced from the CTTC meta-analysis) suggested that the rate ratio was not statistically different from 1. The ERG stated that the relative effectiveness of ezetimibe compared with no treatment or statin therapy alone for the non-cardiovascular events, included in the company's base case, was inconsistent with previous modelling carried out in NICE's technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia.

3.37 The ERG stated that the treatment effect of ezetimibe as an add-on to a statin compared with statin therapy alone was additive rather than multiplicative in the company's base-case analysis. To estimate the absolute further reduction in LDL-c associated with ezetimibe as an add-on to a statin in its base case, the company had estimated the additive percentage reduction in LDL-c levels for a statin plus ezetimibe compared with statin therapy alone and had applied this to the modelled baseline (pre-treatment) LDL-c value. When considering ezetimibe as an add-on treatment to a statin, the ERG noted that applying the weighted average multiplicative percentage reduction to typical LDL-c levels gave a smaller absolute further reduction than applying the additive effect to the baseline (pre-treatment) LDL-c level.

3.38 The ERG considered the selection of utility values for most health states to be reasonably well justified and that the approach was generally consistent with that in the original NICE technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. However, it had some concerns about how the company combined the age- and sex-specific baseline utility data with the health-state utility data. Furthermore, the ERG identified more up-to-date utility values from Ara and Brazier (2010) and alternatives for the unstable angina, post unstable angina, myocardial infarction and post-myocardial infarction health states that it considered to be more representative and suitable.

3.39 The ERG noted that the company had sourced drug intervention and comparator costs from eMit or MIMS, and noted that the Guide to the methods of technology appraisal states that the preferred source for drugs prescribed predominantly in primary care is the NHS Drug Tariff. The ERG generally found the monitoring

assumptions and costs to be appropriate. For health-state costs, the ERG noted that costs associated with stroke and myocardial infarction were based on old estimates inflated to the current cost year, which may lead to inaccuracy and fail to account for changes in clinical practice.

3.40 The ERG was aware that the company had done both deterministic and probabilistic sensitivity analyses to evaluate the uncertainty around different parameters in the model. It noted several issues relating to the parameter distribution used for the probabilistic sensitivity analysis, which resulted in a significant underestimation of uncertainty around the ICERS. The ERG noted that the company tried to validate the model using data from IMPROVE-IT and stated that the company's model under predicted the incidence of events such as myocardial, stroke and non-cardiovascular death compared with the trial. The ERG noted that no attempt was made to assess external validity of primary prevention model.

Evidence Review Group's exploratory analyses

3.41 The ERG carried out additional exploratory analyses (see Table 1). These were broadly done in 4 steps:

- Step 1: Correction of apparent bugs in the model relating to the different half-cycle correction, the annual age-related increase in the risk of cardiovascular events, the proportional distribution of first cardiovascular event by age and sex, and several distributions used in the probabilistic sensitivity analyses. The ICERs calculated by the ERG's exploratory analyses for primary and secondary prevention, monotherapy and as an add-on were modestly lower than the company's base-case ICERs.
- Step 2: Including the transient ischaemic attack and stable angina states in the model with the relative treatment effects (for

statins and ezetimibe) for these events switched off. The ERG's exploratory analysis (after making the changes outlined in steps 1 and 2) had limited impact on the ICERs.

- Step 3: Applying age adjustments to alternative and newer health-state utilities. The ERG's exploratory analysis (after the changes outlined in steps 1, 2, 3) had a limited impact on the ICERs.
- Step 4: Assigning no effect of LDL-c reductions on non-cardiovascular related deaths, but applying relative treatment effects of ezetimibe and statins for transient ischaemic attack and stable angina. The ERG's preferred exploratory analysis (after the changes outlined in steps 1, 2, 3 and 4) showed that, for primary prevention, the ICER for ezetimibe compared with no treatment was £31,939 per QALY gained (incremental costs £4770; incremental QALYs 0.149) and the ICER for ezetimibe as an add-on to a statin compared with statin therapy alone was £75,950 per QALY gained (incremental costs £5064; incremental QALYs 0.067). In the secondary prevention population, the ICER for ezetimibe compared with no treatment was £17,279 per QALY gained (incremental costs £3505; incremental QALYs 0.203) and the ICER for ezetimibe as an add-on to a statin compared with a statin therapy alone was £36,042 per QALY gained (incremental costs £3783; incremental QALYs 0.105).

3.42 The ERG also conducted 2 additional scenarios:

- Scenario A: Using multiplicative effects of ezetimibe (as an add-on) on post-statin LDL-c levels instead of an additive treatment effect. This models reduction in LDL-c associated with statin therapy, and then applies the estimated further multiplicative proportional reduction in LDL-c with ezetimibe from post-statin

LDL-c levels. The ERG's exploratory analysis results outlined in steps 1, 2 ,3 and 4 and scenario A showed that the ICERs for ezetimibe as an add-on to a statin compared with statin therapy alone in the primary prevention population ranged from £43,230 per QALY gained (incremental costs £4,865; incremental QALYs 0.113) for a post-statin LDL-c attainment of 3.5 mmol/litre to £116,243 per QALY gained (incremental costs £5196; incremental QALYs 0.045) for a post-statin LDL-c attainment of 2 mmol/litre. The ICERs for ezetimibe as an add-on to a statin compared with statin therapy alone in the secondary prevention population ranged from £22,056 per QALY gained (incremental costs £3629; incremental QALYs 0.165) for a post-statin LDL-c attainment of 3.5 mmol/litre to £51,975 per QALY gained (incremental costs £3801; incremental QALYs 0.073) for a post-statin LDL-c attainment of 2 mmol/litre.

- Scenario B: Using the ezetimibe add-on to a statin treatment effect on cardiovascular outcomes from the IMPROVE-IT trial instead of using LDL-c reduction to link to cardiovascular outcomes (which used the CTTC meta-analysis). The ERG exploratory analysis results outlined in steps 1, 2 ,3 and 4 and scenario B showed the ICER for ezetimibe as an add-on to a statin (using simvastatin) compared with statin therapy alone in the secondary prevention population was £115,354 per QALY gained (incremental costs £3335; incremental QALYs 0.029).

Table 1 ERG exploratory analyses: deterministic base-case ICERS (cost per QALY)

Scenario	Primary prevention		Secondary prevention	
	Monotherapy ezetimibe 10 mg compared with no treatment (£)	With statin atorvastatin 20 mg compared with ezetimibe 10 mg + atorvastatin 20 mg (£)	Monotherapy ezetimibe 10 mg compared with no treatment (£)	With statin atorvastatin 40 mg compared with ezetimibe 10 mg + atorvastatin 40 mg (£)
Company's base case[a]	30,129[a]	58,473[a]	17,553	30,940
Step 1 (as calculated by ERG)	26,253	48,886	16,563	29,351
Steps 1+2 (as calculated by ERG)	25,274	46,479	17,871	32,970
Steps 1+2+3 (as calculated by ERG)	25,479	47,045	14,988	27,937
Steps 1+2+3+4 (as calculated by ERG)	31,939	75,950	17,279	36,042

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

[a] Includes age-adjusted risk fix provided in response to clarification for the primary prevention population.

3.43 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 ezetimibe, having considered evidence on the nature of primary heterozygous-familial and non-familial hypercholesterolaemia and the value placed on the benefits of ezetimibe by people with the conditions, those who represent

them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.1 The Committee was aware that the appraisal was a review of NICE's technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia, primarily to take into account the cardiovascular outcome data from IMPROVE-IT. It noted that ezetimibe monotherapy is recommended as an option for the treatment of adults with primary hypercholesterolaemia who:

- would otherwise start statin therapy but who are unable to do so because of contraindications to initial statin therapy
- are intolerant to statin therapy.

It noted that ezetimibe, co-administered with initial statin therapy is recommended as an option for the treatment of adults with primary hypercholesterolaemia who:

- have started statin therapy when LDL-c is not appropriately controlled either after dose titration of initial statin therapy or because dose titration is limited by intolerance to statin therapy and
- when consideration is given to change from initial statin therapy to an alternative statin.

The Committee was aware that the NICE guideline on lipid modification cross-referred to NICE's technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia.

4.2 The Committee considered the current practice for treating primary hypercholesterolaemia. The Committee observed that the patient population in the company's submission was different to the

marketing authorisation and the NICE final scope for ezetimibe (see section 2.2) because it considered the prevention of cardiovascular disease. The Committee heard from the clinical experts that the way cardiovascular risk is assessed and managed has changed since the original NICE technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia was published, because of the recommendations in the updated NICE guideline on lipid modification. It heard that there is now a greater emphasis on managing cardiovascular risk rather than meeting target cholesterol levels. The Committee was aware that the NICE guideline on lipid modification recommended offering statins for treating hypercholesterolaemia for primary prevention of cardiovascular disease in people with a 10% or more 10−year risk of developing cardiovascular disease for many clinical scenarios. The Committee heard from the clinical experts that despite the NICE guideline on lipid modification, the decision to treat hypercholesterolaemia for the primary prevention of cardiovascular disease sometimes occurs when the 10-year risk of developing cardiovascular disease is higher than 10%. The Committee concluded that, in clinical practice in the NHS in England, treatment of hypercholesterolaemia for the prevention of cardiovascular disease sometimes starts when a person's 10-year risk of developing cardiovascular disease is higher than 10%

4.3 The Committee considered the current treatment pathway for people with primary hypercholesterolaemia. The Committee heard from the clinical experts that statins are the mainstay of treatment for familial and non-familial hypercholesterolaemia (as described in NICE's guideline on familial hypercholesterolaemia and on lipid modification). It heard that although the NICE guideline on lipid modification recommends atorvastatin at doses up to 80 mg, higher

doses are often not tolerated in clinical practice. It further heard from the clinical experts that that fibrates, nicotinic acid and bile acid sequestrants (anion exchange resins) are not routinely used to treat non-familial hypercholesterolaemia (in line with the NICE guideline on lipid modification). The Committee then heard that, although recommended in the NICE guideline on familial hypercholesterolaemia, these treatments are not commonly used to treat familial hypercholesterolaemia because they are poorly tolerated. It heard from the clinical experts 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, despite increasing the dose of the statin, or if a person is unable to try higher doses of the statin because it is likely to cause side effects. The Committee concluded that atorvastatin is the main option for treating primary hypercholesterolaemia (when a statin is considered appropriate), and that no treatments apart from ezetimibe monotherapy are routinely used to treat non-familial hypercholesterolaemia in adults who are unable to take a statin.

4.4 The Committee considered the completeness of the clinical evidence provided by the company. It discussed the company's methods for identifying studies and the way in which decisions were made to include evidence in the meta-analysis. The Committee heard from the ERG that the search strategy could not be reproduced, and the eligibility criteria for inclusion had been applied inconsistently. Although the Committee had concerns about the company's approach, it heard from clinical experts that they were not aware of any other evidence that had not been identified. The Committee concluded that the evidence retrieved by the company's searches was acceptable for its decision-making.

4.5 The Committee discussed the relevance of the available clinical evidence for ezetimibe in reducing cardiovascular events for people with primary hypercholesterolaemia. It noted that, of the 3 trials, only IMPROVE-IT was relevant to the final NICE scope (because SHARP and SEAS compared ezetimibe as an add-on to a statin plus placebo). The Committee heard from the clinical experts that the trial population in IMPROVE-IT represented only part of the eligible population that could have statins or ezetimibe because the patients had acute coronary syndrome (that is, they were having treatment for secondary prevention, and not primary prevention of cardiovascular disease). The Committee concluded although there were 3 trials that had results for the effect of ezetimibe on cardiovascular outcomes, only 1 provided data that was relevant to the final NICE scope and that it was not generalisable to the full population covered by ezetimibe's marketing authorisation in the UK.

4.6 The Committee discussed the use of cholesterol levels (such as LDL-c) to link to cardiovascular outcomes. The Committee noted the findings from the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis, which showed a statistically significant association between LDL-c levels and cardiovascular outcomes. It was aware that LDL-c levels had been used to link to outcomes in the absence of clinical outcome data in NICE's technology appraisal guidance on ezetimibe for primary hypercholesterolaemia. It heard from the clinical and patient experts that although cholesterol levels are considered important by patients, they would prefer the certainty of hard clinical outcomes. The Committee considered that using direct trial evidence of a cardiovascular outcome, where available, is preferred to using a surrogate outcome. Although the true extent of the relationship between LDL-c and cardiovascular outcomes is

uncertain, the Committee accepted that there is likely to be a relationship between LDL-c and cardiovascular outcomes based on the CTTC meta-analysis. It concluded that although it preferred clinical outcomes, LDL-c could be used as a link for cardiovascular outcomes in the absence of trial evidence.

4.7 The Committee discussed whether the company's approach to data synthesis was appropriate. The Committee noted the ERG's comment that a network meta-analysis of different statin doses as separate treatments within the network as well as other combinations of statins, placebo and lipid-regulating drugs could be done. It further noted the requirement of the final scope to consider other lipid-regulating drugs, but acknowledged their limited use in clinical practice (see section 4.3). The Committee heard from the clinical experts that high-intensity treatment with atorvastatin was the main statin treatment used in current practice and considered that data for other statins would be of limited relevance. Because of the limited number of treatments used in current practice, the Committee concluded that although the network meta-analyses could have been useful, the company's pairwise meta-analyses for ezetimibe with or without a statin compared with no treatment or statin therapy alone was acceptable for its decision-making.

4.8 The Committee discussed the clinical-effectiveness results for ezetimibe monotherapy. In the absence of clinical outcome data, the Committee accepted the finding of the meta-analysis that there was a statistically significant decrease in LDL-c levels for adults treated with ezetimibe compared with placebo. It concluded that, compared with placebo, ezetimibe monotherapy is clinically effective in adults for whom a statin is considered inappropriate or is not tolerated.

4.9 The Committee discussed the clinical-effectiveness results for clinical outcomes of ezetimibe in combination with a statin. The Committee noted that SHARP and IMPROVE-IT showed statistically significant improvement in clinical outcomes and reduction in LDL-c, but SEAS showed no statistical improvement in clinical outcomes for ezetimibe and simvastatin compared with placebo. The Committee accepted the clinical experts' explanation that the asymptomatic aortic stenosis population was less likely to respond to ezetimibe and statins compared with the general population eligible for treatment, and noted that the primary composite endpoint included aortic valve disease-related outcomes. The Committee concluded that ezetimibe in combination with a statin had some effect on clinical outcomes compared with placebo or statin therapy alone in adults for whom a statin is considered inappropriate or is not tolerated.

4.10 The Committee discussed the clinical-effectiveness results from the meta-analysis of ezetimibe in combination with a statin. The Committee noted that SHARP and SEAS compared ezetimibe as an add-on to a statin with placebo, instead of only comparing it with a statin. It accepted this as a valid reason not to include these trials in the meta-analysis. The Committee heard from the company that many of the trials in the meta-analysis did not examine ezetimibe with atorvastatin on a maximum tolerated dose as recommended by the NICE guideline on lipid modification. The Committee understood that this could have resulted in inaccurate relative estimates of LDL-c reduction. Despite this uncertainty, the Committee accepted that the results of meta-analysis were unlikely to be significantly biased. The Committee accepted the finding of the meta-analysis that there was a statistically significant decrease in LDL-c levels for adults treated with ezetimibe as an add-on to a statin compared with statin therapy alone. The Committee

concluded from the meta-analysis and the findings of IMPROVE-IT that, compared with statin therapy alone, ezetimibe with a statin is clinically effective in adults who have primary hypercholesterolaemia that is not appropriately controlled with statin therapy.

Cost effectiveness

4.11 The Committee considered the company's modelling approach of analysing the primary and secondary prevention of cardiovascular disease separately. It noted that this differed from the approach taken in the NICE technology appraisal guidance on ezetimibe for hypercholesterolaemia but was consistent with the NICE guideline on lipid modification. The Committee heard from the clinical experts that current practice for primary hypercholesterolaemia was based on primary and secondary prevention of cardiovascular disease. The Committee concluded that the approach in the company's model of separately analysing the groups who needed treatment for the primary and secondary prevention of cardiovascular disease was acceptable for its decision-making.

4.12 The Committee discussed the structure of the company's economic model. It found this to be generally acceptable but noted the company's base-case model excluded the stable angina and transient ischaemic attack health states. The Committee agreed with the ERG's view that it was inappropriate to assume zero risk of these events, because downstream costs and risks associated with the occurrence of stable angina and transient ischaemic attack may still influence comparisons. The Committee concluded that the stable angina and transient ischaemic attack health states should be included in the analyses to capture the broader consequences of primary hypercholesterolaemia.

4.13 The Committee considered the approach in the model for the primary prevention population to incorporate cardiovascular risk. The Committee noted the company's base-case analysis modelled a 10-year cardiovascular risk of 20% using the QRISK2 risk assessment tool. Although the NICE guideline on lipid modification recommended consideration of primary prevention of cardiovascular disease at a 10-year cardiovascular risk of 10%, the Committee recalled that the clinical experts had said that in clinical practice, treatment was not always offered unless the 10-year cardiovascular risk was higher than this (see section 4.2). The Committee concluded that it was not unreasonable to assume that treatment for primary hypercholesterolaemia for the primary prevention of cardiovascular disease would start at a 10-year cardiovascular risk of 20% and that the company's modelling assumption used in the base case was acceptable for decision-making.

4.14 The Committee discussed whether the company's model accurately captured the costs and health benefits associated with treating primary hypercholesterolaemia. It noted the ERG's comments that newer utility values were available and agreed that those used in the ERG's exploratory analyses were more appropriate than those used in the company's base case. The Committee debated whether using newer costs rather than using older, inflated, costs was appropriate. The Committee heard from the company that it used older, inflated, cost-data sources so that the approach was consistent with NICE's technology appraisal guidance on ezetimibe for hypercholesterolaemia. The Committee noted that this meant the costs for each health state did not reflect any changes in costs as a result of evolving clinical practice. The Committee heard from the ERG that updating the data could either increase or decrease costs, making it difficult to predict the

implications for cost effectiveness, but that a high impact on the ICERs was not expected. The Committee concluded that the costs in the company's model were acceptable, but that it preferred the more up-to-date utility values used in the ERG's exploratory analyses.

4.15 The Committee discussed how the company applied the treatment effect of ezetimibe in model:

- It noted the assumption of no effect of dietary control when used with ezetimibe.
- It accepted the company's assumption of a constant treatment effect because it heard from the clinical experts that the effect of treatment did not wane over time.
- It noted the ERG's comment that there was no statistical association between LDL-c and non-cardiovascular related deaths in the CTTC meta-analysis, and concluded it was unreasonable to assume that the treatment effect of ezetimibe should apply to non-cardiovascular related deaths.
- The Committee recognised that there was no robust evidence supporting any particular approach (additive or multiplicative) to estimate the treatment effect of ezetimibe as an add-on to a statin. It noted that a multiplicative approach had been used in NICE's technology appraisal guidance on ezetimibe for hypercholesterolaemia, but concluded that the additive approach, which was used to estimate the treatment effect of ezetimibe as an add-on to a statin in the company's base case and many of the ERG's exploratory analyses, was acceptable.
- The Committee concluded that it was appropriate to use an LDL-c to link to cardiovascular outcomes in the absence of clinical data (see section 4.6), but that clinical outcome data from IMPROVE-IT should have been used to estimate treatment

effect in the secondary prevention analysis of ezetimibe as an add-on to a statin compared with statin therapy alone. The Committee noted the effect of the ERG's exploratory analysis (scenario B), which estimated the effect of IMPROVE-IT outcome data, was to substantially raise the incremental cost-effectiveness ratio (ICER) for an additive approach in secondary prevention suggesting, in this situation at least, that LDL-c when used as a proxy may overstate the clinical impact of ezetimibe.

The Committee concluded the modelled treatment effect of ezetimibe with the modifications described above was acceptable for its decision-making.

4.16 The Committee discussed the cost-effectiveness estimates for ezetimibe in the primary prevention population. Taking the issues noted in sections 4.12, 4.14 and 4.15 into account, and accepting the ERG's corrections of apparent bugs in the company's model, it decided that the most plausible ICERs were from the ERG's preferred exploratory analysis (see section 3.41) as follows:

- in excess of £31,900 per quality-adjusted life year (QALY) gained for ezetimibe monotherapy compared with no therapy
- in excess of £76,000 per QALY gained for ezetimibe as an add-on to a statin compared with statin therapy alone.

The Committee noted that these ICERs exceeded the range normally considered to be a cost‑effective use of NHS resources (up to £20,000–30,000 per QALY gained). The Committee concluded that ezetimibe, as monotherapy or in combination with a statin, is not a cost‑effective use of NHS resources for treating primary hypercholesterolaemia in adults when a statin is considered inappropriate or is not tolerated and who need lipid-modification therapy for the primary prevention of cardiovascular

disease. The Committee did not recommend ezetimibe as monotherapy or in combination with a statin for this group.

4.17 The Committee discussed the cost-effectiveness estimates in the secondary prevention population. Taking the issues noted in sections 4.12, 4.14 and 4.15 into account, the Committee concluded that the most plausible ICERs were from the ERG's preferred exploratory analysis for ezetimibe monotherapy (see section 3.41), and the ERG's exploratory analysis that used the risk ratios for clinical outcomes from IMPROVE-IT (see section 3.42) for ezetimibe as an add-on to a statin as follows:

- in excess of £17,300 per QALY gained for ezetimibe monotherapy compared with no therapy
- £115,400 per QALY gained for ezetimibe as an add-on to a statin compared with a statin alone.

The Committee noted the ICER for ezetimibe monotherapy plausibly fell within the range normally considered to be a cost‑effective use of NHS resources (up to £20,000–30,000 per QALY gained). It also noted the ICER for ezetimibe as an add-on to a statin greatly exceeded the range normally considered to be a cost-effective use of NHS resources (up to £20,000–30,000 per QALY gained). The Committee concluded that ezetimibe monotherapy could be considered a cost‑effective use of NHS resources compared with no treatment for treating primary hypercholesterolaemia in adults when a statin is considered inappropriate or is not tolerated and who need lipid-modification therapy for the secondary prevention of cardiovascular disease and, therefore, recommended it for this group. The Committee concluded that ezetimibe as an add-on to a statin was not a cost-effective use of NHS resources compared with a statin alone for

treating primary hypercholesterolaemia in adults who need lipid-modification therapy for the secondary prevention of cardiovascular disease, and did not recommend it for this group.

4.18 The Committee considered the cost-effectiveness estimates for the different subgroups presented by the company. The Committee noted the subgroups were adults with type 2 diabetes needing lipid-modification therapy for the primary prevention of cardiovascular disease and adults with chronic kidney disease needing lipid-modification therapy for the secondary prevention of cardiovascular disease. The Committee was aware that the company presented no evidence for adults with type 1 diabetes needing lipid-modification therapy. The Committee noted that the ERG had not conducted exploratory analyses in adults with type 2 diabetes and adults with chronic kidney disease; however, the Committee observed that the ERG's preferred exploratory analyses increased the ICERs compared with the company's base-case analyses in other groups. The Committee therefore concluded that the company's ICERs in these subgroups were likely to overestimate ezetimibe's cost effectiveness.

4.19 The Committee considered the most plausible ICER for ezetimibe monotherapy in adults with type 2 diabetes compared with no treatment to be at least £20,300 per QALY gained. The Committee noted that this ICER would plausibly fall within the range normally considered to be a cost-effective use of NHS resources (up to £20,000–30,000 per QALY gained). The Committee concluded that ezetimibe monotherapy could be considered a cost‑effective use of NHS resources compared with no treatment for treating primary hypercholesterolaemia in adults when a statin is considered inappropriate or is not tolerated only if they need lipid-modification therapy for the primary prevention of cardiovascular disease, and

have both type 2 diabetes and a 20% or greater 10−year risk of developing cardiovascular disease, and recommended it for this group.

4.20 The Committee considered the most plausible ICER for ezetimibe as an add-on to a statin for adults with type 2 diabetes compared with statin therapy alone to be at least £31,400 per QALY gained. The Committee noted that the ICER exceeded the range normally considered to be a cost-effective use of NHS resources (up to £20,000–30,000 per QALY gained). The Committee concluded that ezetimibe as an add-on to a statin was not a cost-effective use of NHS resources compared with a statin alone for the treatment of primary hypercholesterolaemia for adults who need lipid-modification therapy for the primary prevention of cardiovascular disease and have type 2 diabetes, and did not recommend ezetimibe for this group.

4.21 The Committee considered the most plausible ICER for ezetimibe as an add-on to a statin compared with a statin alone in adults with chronic kidney disease needing lipid-modification therapy for the secondary prevention of cardiovascular disease to be at least £31,000 per QALY gained. The Committee noted that the ICER exceeded the range normally considered to be a cost-effective use of NHS resources (up to £20,000–30,000 per QALY gained). The Committee concluded that ezetimibe as an add-on to a statin compared with a statin alone for the treatment of primary hypercholesterolaemia in adults who need lipid-modification therapy of for the secondary prevention of cardiovascular disease, and have chronic kidney disease was not a cost-effective use of NHS resources and did not recommend ezetimibe for this group.

4.22 The Committee discussed other factors that could influence the range of plausible ICERs for each population group:

- It was aware of the company's scenario analyses, and in particular, the hypothetical price reduction after ezetimibe's patent expiry. The Committee was unable to consider this scenario because a specified price has to be available and guaranteed across the NHS (see the Guide to the methods of technology appraisal).
- It did not identify evidence to show that health-related quality of life was inadequately captured by the QALY. It concluded that health-related quality of life was adequately captured in the model.
- It noted that clinical experts thought that ezetimibe was a unique drug, but was no longer considered innovative or a step change in management. The Committee concluded that ezetimibe was not considered innovative.

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

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (review of NICE technology appraisal guidance 132)	Section
Key conclusion		
Ezetimibe monotherapy is recommended as an option for treating primary heterozygous-familial and non-familial hypercholesterolaemia in adults, when a statin is considered inappropriate or is not tolerated, only if: • they need lipid modification therapy for the primary prevention of cardiovascular disease and have both: – type 2 diabetes and – a 20% or greater 10 year risk of developing cardiovascular disease according to the QRISK2 risk assessment tool or • they need lipid-modification therapy for the secondary prevention of cardiovascular disease. Adults whose treatment with ezetimibe is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop. The Committee concluded that the in the primary prevention population the most plausible incremental cost-effectiveness ratios (ICERs) were as follows: • in excess of £31,900 per quality-adjusted life year (QALY) gained for ezetimibe monotherapy compared with no therapy • in excess of £76,000 per QALY gained for ezetimibe as an add-on		1.1, 4.16,4.17, 4.19

to a statin compared with statin therapy alone. • at least £20,300 per QALY gained for ezetimibe monotherapy compared with no treatment in adults with type 2 diabetes The Committee concluded that in the secondary prevention population that the most plausible ICERs were as follows: • in excess of £17,300 per QALY gained for ezetimibe monotherapy compared with no therapy • £115,400 per QALY gained for ezetimibe as an add-on to a statin compared with a statin alone.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee concluded that atorvastatin is the main treatment option for treating primary hypercholesterolaemia, and that no treatments apart from ezetimibe are routinely used to treat non-familial hypercholesterolaemia in adults who are unable to take a statin.	4.2, 4.3
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?	Ezetimibe is a cholesterol-absorption inhibitor that blocks the intestinal absorption of dietary and biliary cholesterol and related plant sterols, without affecting the uptake of triglycerides or fat-soluble vitamins. The Committee concluded that ezetimibe was not innovative because it heard from clinical experts that ezetimibe was no longer considered innovative or a step change in management.	2.1, 4.22
What is the position of the treatment in the pathway of care for the condition?	The Committee noted that the NICE technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia had recommended ezetimibe monotherapy for the treatment of adults with primary hypercholesterolaemia for whom initial statin therapy was contra-indicated or who were intolerant to statin therapy. It noted that ezetimibe, co-administered with initial statin therapy was recommended for people who started statin therapy when low-density lipoprotein cholesterol LDL-c is not appropriately controlled either after dose titration of initial statin therapy or because dose titration was limited by intolerance to statin therapy. The Committee noted that the mainstay of treatment for hypercholesterolaemia is based	4.1, 4.2, 4.3

	on NICE's guideline on familial hypercholesterolaemia and on lipid modification. It heard from clinical experts 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, despite increasing the dose of the statin, or if a person is unable to try higher doses of the statin because it is likely to cause side effects.	
Adverse reactions	Ezetimibe's summary of product characteristics lists abdominal pain, diarrhoea, flatulence and fatigue as adverse reactions for ezetimibe. The company stated that there were no clear differences between the treatment groups in clinical adverse events.	2.3, 3.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee observed that the company's submission included 3 clinical trials (IMPROVE-IT, SHARP and SEAS), which presented evidence on cardiovascular outcomes. The Committee also observed that the company's systematic review and meta-analysis on LDL-c levels included	3.11, 4.4, 4.5, 4.7

	24 randomised trials plus the IMPROVE-IT clinical trial report. It noted the Evidence Review Group (ERG) could not confirm that the company's approach was comprehensive in identifying relevant studies, but it heard from clinical experts that they were not aware of any other unidentified evidence. The Committee concluded that the company's pairwise meta-analyses for ezetimibe with or without a statin compared with no treatment or statin therapy alone was acceptable.	

Relevance to general clinical practice in the NHS	The Committee was aware that there is greater emphasis on managing cardiovascular risk rather than meeting target cholesterol levels for the treatment of hypercholesterolaemia. It heard that the prevention of cardiovascular disease sometimes starts when a person's 10-year risk of developing cardiovascular disease is higher than 10%. The Committee observed that the patient population in the company's submission was different to the marketing authorisation and the NICE final scope for ezetimibe because it considered the prevention of cardiovascular disease. The Committee concluded that although the 3 trials (IMPROVE-IT, SHARP, SEAS) had results for the effect of ezetimibe on cardiovascular outcomes, only 1 provided data that was relevant to the final NICE scope.	4.2, 4.5
Uncertainties generated by the evidence	The Committee concluded that there is likely to be a relationship between LDL-c and cardiovascular outcomes. It also concluded that although it preferred cardiovascular outcomes, LDL-c could be used as a link for cardiovascular outcomes in the absence of trial evidence.	4.6

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee was aware of evidence from 4 clinical trials in adults with type 2 diabetes, a trial in patients with chronic kidney disease and a trial in patients with heterozygous familial hypercholesterolaemia. The Committee considered the cost-effectiveness estimates for the subgroups presented by the company.	3.7, 4.18
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that compared with placebo, ezetimibe monotherapy is clinically effective in reducing LDL-c levels in adults for whom a statin is considered inappropriate or is not tolerated. The Committee concluded from the meta-analysis and the findings of IMPROVE-IT that compared with statin therapy alone, ezetimibe with a statin reduced LDL-c levels in adults who have primary hypercholesterolaemia that is not appropriately controlled with statin therapy. The Committee concluded that ezetimibe in combination with a statin had some effect on clinical outcomes compared with placebo or statin therapy alone in adults for whom a statin is considered inappropriate or is not tolerated.	4.8, 4.9,4.10

How has the new clinical evidence that has emerged since the original appraisal (TA132) influenced the current (preliminary) recommendations?	The Committee noted the ezetimibe had been recommended in the original NICE technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. The Committee heard from the clinical and patient experts that although cholesterol levels are considered important by patients, they would prefer the certainty of hard clinical outcomes. The Committee considered that using direct trial evidence of a cardiovascular outcome, such as IMPROVE-IT, is preferred to using a surrogate outcome, such as LDL-c levels. It concluded that although it preferred cardiovascular outcomes, LDL-c could be used as a link for cardiovascular outcomes in the absence of trial evidence.	4.1, 4.5, 4.6, 4.15

Evidence for cost effectiveness		
Availability and nature of evidence	The Committee concluded that the approach in the company's model of separately analysing the groups who needed treatment for the primary and secondary prevention of cardiovascular disease was acceptable for its decision-making. The Committee thought the company's base-case model was generally acceptable but agreed with the ERG's view that it was inappropriate to assume zero risk of stable angina and transient ischaemic attack events in the model and preferred the ERG's exploratory analyses.	4.11, 4.12

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee concluded that the costs in the company's model were acceptable, but that it preferred the more up-to-date utility values used in the ERG's exploratory analyses. The Committee accepted the company's assumption of a constant treatment effect for its decision making, but concluded it was unreasonable to assume that the treatment effect of ezetimibe should apply to non-cardiovascular related deaths. The Committee also concluded that it was appropriate to use an LDL-c to link to cardiovascular outcomes in the absence of cardiovascular data but that cardiovascular outcome data from IMPROVE-IT should have been used to estimate treatment effect in the secondary prevention analysis of ezetimibe as an add-on to a statin compared with statin therapy alone.	4.14, 4.15

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 noted the ERG's comments that newer utility values were available and agreed that those used in the ERG's exploratory analyses were more appropriate than those used in the company's base case. The Committee concluded that health-related quality of life was adequately captured in the QALY.	4.14, 4.22

Are there specific groups of people for whom the technology is particularly cost effective?	The Committee considered the most plausible ICER for ezetimibe monotherapy in adults with type 2 diabetes compared with no treatment to be at least £20,300 per QALY gained. The Committee concluded that ezetimibe monotherapy could be considered a cost-effective use of NHS resources compared with no treatment for treating primary hypercholesterolaemia in adults when a statin is considered inappropriate or is not tolerated only if they need lipid-modification therapy for the primary prevention of cardiovascular disease, they have both type 2 diabetes and a 20% or greater 10 year risk of developing cardiovascular disease, and recommended it for this group.	4.19
What are the key drivers of cost effectiveness?	The Committee noted that the ERG's exploratory analysis, which estimated the effect of IMPROVE-IT outcome data substantially raised the ICER in the secondary prevention population.	4.15

Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that in the primary prevention population that the most plausible ICERs were from the ERG's preferred exploratory analysis as follows: • in excess of £31,900 per QALY gained for ezetimibe monotherapy compared with no therapy • in excess of £76,000 per QALY gained for ezetimibe as an add-on to a statin compared with statin therapy alone. The Committee concluded that in the secondary prevention population that the most plausible ICERs were from the ERG's preferred exploratory analysis for monotherapy, and the ERG's exploratory analysis that used the risk ratios for clinical outcomes from IMPROVE IT as follows: • in excess of £17,300 per QALY gained for ezetimibe monotherapy compared with no therapy • £115,400 per QALY gained for ezetimibe as an add-on to a statin compared with a statin alone.	4.16, 4.17

How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA132) influenced the current (preliminary) recommendations?	The Committee noted that ezetimibe had been recommended in the original NICE technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. The Committee accepted the approach in the company's model of separately analysing the groups who needed treatment for the primary and secondary prevention of cardiovascular disease. However, it preferred the ERG's exploratory analyses, which included the transient ischaemic attack and stable angina states, applied age adjustments to alternative and newer health-state utilities, and assigned no effect of LDL-c reductions on non-cardiovascular related deaths in the model. It also preferred the ERG exploratory analysis when the treatment effects on cardiovascular outcomes was used instead of using LDL-c as a surrogate outcome. The Committee recommended ezetimibe monotherapy for treating primary hypercholesterolaemia in adults when a statin is considered inappropriate or is not tolerated only if they need lipid-modification therapy for the primary prevention of cardiovascular disease, and have both type 2 diabetes and a 20% or greater 10 year risk of developing cardiovascular disease according to the QRISK2 risk assessment tool. It also	4.1, 4.11, 4.12, 4.14, 4.15, 4.16, 4.17

	recommended ezetimibe monotherapy for treating primary hypercholesterolaemia in adults when a statin is considered inappropriate or is not tolerated only if they need lipid-modification therapy for the secondary prevention of cardiovascular disease.	
Additional factors taken into account		
Patient access schemes (PPRS)	The Committee concluded that the PPRS Payment Mechanism was irrelevant for the consideration of cost effectiveness of ezetimibe.	4.23
End-of-life considerations	Not applicable	n/a
Equalities considerations and social value judgements	No potential equality issues were identified during the scoping process, in any of the submissions or during the Committee meeting. None had been previously identified in NICE technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia.	n/a

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires

clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

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

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

5.4 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 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 prevention. NICE pathway (2015).
- Familial hypercholesterolaemia. NICE pathway (2015).
- Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 181 (2014).
- Identification and management of familial hypercholesterolaemia NICE clinical guideline 71 (2008).
- Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. NICE technology appraisal guidance 132 (2007).

Under development

- Hypercholesterolaemia (primary), dyslipidaemia (mixed) – evolocumab. NICE technology appraisal guidance, publication expected April 2016.
- Hypercholesterolaemia (primary) and dyslipidaemia (mixed) – alirocumab NICE technology appraisal guidance, publication expected June 2016.
- Familial hypercholesterolaemia (standing committee update). NICE clinical guideline, publication date to be confirmed.

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. 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.

Eugene Milne

Vice-Chair, Appraisal Committee C

November 2015

8 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

Professor Kathryn Abel
Institute of Brain and Behaviour Mental Health, University of Manchester

Mr David Chandler
Lay Member

Mrs Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

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

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Nigel Langford

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

Dr 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

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson

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

Dr Paul Tappenden

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine & Dentistry

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.

Jasdeep Hayre

Technical Lead

Linda Landells

Technical Adviser

Lori Farrar

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen Health Technology Assessment (HTA) Group:

Scotland G, Javanbakht M, Scott N, Cruickshank M, Sharma P, Fraser C, Simpson W, Brazzelli M. Ezetimibe for treating primary (heterozygous-familial and non-familial) hypercholesterolaemia. Aberdeen HTA Group, 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:

- Merck Sharp & Dohme Ltd

II. Professional/expert and patient/carer groups:

- HEART UK
- British Heart Foundation
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- NHS Oxfordshire Clinical Commissioning Group
- NHS West Essex 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
- Aberdeen Health Technology Assessment Group
- National Institute for Health Research Health Technology Assessment Programme

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 ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (review of TA132) by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Dr Adie Viljoen, Chemical Pathologist, nominated by Merck Sharp & Dohme Ltd – clinical expert
- Professor Anne-Marie Kelly, Consultant Chemical Pathologist, nominated by the Royal College of Pathologists – clinical expert
- Stephen Boley, 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.

- Merck Sharp & Dohme Ltd