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Ezetimibe for the treatment of primary (heterozygous- familial and non-familial) hypercholesterolaemia

NICE technology appraisal guidance 132

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia

Ordering information

You can download the following documents from www.nice.org.uk/TA132

- The full guidance (this document).
- A quick reference guide for healthcare professionals.
- Information for people with primary (heterozygous-familial and non-familial) hypercholesterolaemia and their carers ('Understanding NICE guidance').
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone the NHS Response Line on 0870 1555 455 and quote:

- N1402 (quick reference guide)
- N1403 ('Understanding NICE guidance').

This guidance is written in the following context

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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1 Guidance

This guidance should be read in conjunction with NICE guidance on the initiation of statin therapy (NICE technology appraisal guidance 94). NICE has published clinical guidelines on the management of blood pressure and blood lipids in people with type 2 diabetes (Inherited clinical guideline H) and secondary prevention for patients following a myocardial infarction (NICE clinical guideline 48). The following clinical guidelines are under development: lipid modification; familial hypercholesterolaemia; type 2 diabetes (update). This guidance should be read in the context of the relevant clinical guideline, when available.

- 1.1 Ezetimibe monotherapy is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who would otherwise be initiated on statin therapy (as per NICE guidance TA 94 in adults with non-familial hypercholesterolaemia) but who are unable to do so because of contraindications to initial statin therapy.
- 1.2 Ezetimibe monotherapy is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who are intolerant to statin therapy (as defined in section 1.6).
- 1.3 Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who have been initiated on statin therapy (as per NICE guidance TA 94 in adults with non-familial hypercholesterolaemia) when:
 - serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled (as defined in section 1.5) either after appropriate dose titration of initial statin therapy or because dose titration

is limited by intolerance to the initial statin therapy (as defined in section 1.6)

and

- consideration is being given to changing from initial statin therapy to an alternative statin.

1.4 When the decision has been made to treat with ezetimibe coadministered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.

1.5 For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk assessment in accordance with national guidance on the management of cardiovascular disease for the relevant populations.

1.6 For the purposes of this guidance, intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests.

2 Clinical need and practice

2.1 Hypercholesterolaemia is defined as the presence of high concentrations of cholesterol in the blood. Primary hypercholesterolaemia is associated with an underlying genetic cause; this may be a specific genetic defect, as in the autosomal dominant disorder familial hypercholesterolaemia (FH). In heterozygous-familial hypercholesterolaemia (He-FH) one of the pair of low-density lipoprotein (LDL) cholesterol receptor genes is defective or mutated and impairs the LDL cholesterol receptor activity. The result being that LDL cholesterol levels are markedly elevated, with other forms of cholesterol

remaining normal. Non-familial hypercholesterolaemia is the more common form of primary hypercholesterolaemia where a number of genes interact with dietary and other factors such as smoking and physical inactivity.

- 2.2 Individuals with hypercholesterolaemia are at increased risk of cardiovascular disease (CVD) because long-term elevations of cholesterol accelerate the build up of fatty deposits in the arteries, a process known as atherosclerosis. The narrowing of the arteries can cause cardiovascular problems such as angina (pain or discomfort in the chest or neighbouring parts of the body because of insufficient oxygen reaching the heart), myocardial infarction (MI [heart attack]) and stroke. CVD is the most common cause of death in the UK, accounting for approximately 216,000 deaths in 2004, and it is a major cause of illness, disability and reduced quality of life.
- 2.3 People with FH have marked elevations in cholesterol and are at particular risk of developing premature CVD. For example, untreated people with HeFH are likely to develop cardiovascular symptoms by the fourth or fifth decade of life. HeFH affects around 1 in every 500 adults in Europe.
- 2.4 Total cholesterol concentration is comprised of LDL cholesterol, high-density lipoprotein [HDL] cholesterol and triglycerides (TGs). The increased risk of CVD in people with hypercholesterolaemia is highly correlated with raised LDL cholesterol concentrations. By contrast, HDL cholesterol is inversely associated with the risk of developing CVD. Elevated concentrations of TGs are also associated with higher cardiovascular risk but usually to a lesser extent than raised LDL cholesterol concentrations. In addition to cholesterol concentrations, a person's risk of developing CVD increases with age, smoking, lack of physical activity, obesity, high blood pressure and diabetes.
- 2.5 In England, the average total cholesterol concentration in adults is approximately 5.6 mmol/litre, of which LDL cholesterol comprises an average of 3.6 mmol/litre. The UK population has one of the highest average cholesterol concentrations in the world.

- 2.6 The current management of primary hypercholesterolaemia includes dietary and lifestyle changes such as smoking cessation, weight loss and increased physical activity. The decision to initiate therapy with a lipid-regulating drug is generally based on an assessment of a person's overall cardiovascular risk. Statins are the first-choice drugs (usually non-proprietary simvastatin), but other lipid-regulating drugs (such as fibrates, nicotinic acid derivatives or anion exchange resins) may also be used.
- 2.7 In 2006, NICE published guidance on the initiation of statin therapy (TA 94). This recommends initiation of statin therapy for adults with clinical evidence of CVD, or as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. The guidance also recommends that statin therapy should usually be initiated with a drug with a low acquisition cost (taking into account the required daily dose and price per dose).

3 The technology

- 3.1 Ezetimibe (Ezetrol, Merck Sharp and Dohme Limited and Schering-Plough Limited) is a cholesterol absorption inhibitor that blocks the intestinal absorption of dietary and biliary cholesterol and related plant sterols, without affecting the uptake of TGs or fat-soluble vitamins. Because ezetimibe uses this mechanism to lower cholesterol, it can be combined with a statin to provide complementary cholesterol reduction.
- 3.2 Ezetimibe, coadministered with a statin, is licensed as an adjunctive therapy to dietary manipulation in people with primary (heterozygous-familial or non-familial) hypercholesterolaemia that is not appropriately controlled with a statin alone, or as a monotherapy when a statin is inappropriate or not tolerated. Ezetimibe is also licensed as an adjunct to dietary manipulation for use in people with homozygous familial sitosterolaemia, and in combination with a statin in people with homozygous FH. These latter indications are not covered by this appraisal.

- 3.3 A fixed-dose combination tablet containing ezetimibe and simvastatin is available (Inegy, Merck Sharp and Dohme Limited and Schering-Plough Limited). It is licensed as an adjunctive therapy to dietary manipulation in people with primary (heterozygous-familial or non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate (that is, hypercholesterolaemia or hyperlipidaemia that is not appropriately controlled with a statin alone or people who have already been treated with a statin and ezetimibe). It is also licensed as an adjunctive therapy to dietary manipulation for use in people with homozygous FH.
- 3.4 The adverse effects of ezetimibe monotherapy are usually mild and transient and most commonly include headache, abdominal pain and diarrhoea. When coadministered with a statin, the most common adverse effects include gastrointestinal disturbances, headache, fatigue and myalgia (muscle pain). For full details of adverse effects and contraindications, see the summaries of product characteristics.
- 3.5 The recommended dosage of ezetimibe is 10 mg/day, which may be administered at any time of the day, with or without food. The recommended dosage of the ezetimibe plus simvastatin in combination is ezetimibe 10 mg plus simvastatin 20 mg (10/20 mg) or 10/40 mg, once in the evening. A 10/80-mg dose is recommended only in people with severe hypercholesterolaemia and a high risk for cardiovascular complications.
- 3.6 The cost of ezetimibe is £26.31 for 28 × 10-mg tablets (excluding VAT; 'British national formulary' [BNF] 53rd edition). The cost of the ezetimibe and simvastatin combination tablet is £33.42 for 28 × 10/20-mg tablets, £38.98 for 28 × 10/40-mg tablets and £41.21 for 28 × 10/80-mg tablets (excluding VAT; BNF 53rd edition). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 *Clinical effectiveness*

- 4.1.1 Thirteen randomised controlled trials (RCTs) were identified by the Assessment Group as meeting the inclusion criteria of their review. Overall, all trials were considered to be well designed and conducted. The trials varied in duration from 12 to 48 weeks. The Assessment Group, in their primary analysis, excluded studies of less than 12 weeks. All trials included people with primary hypercholesterolaemia with average baseline LDL cholesterol concentrations ranging from 3.4 mmol/litre to 6.5 mmol/litre and included mixed populations of people with and without a history of CVD. No studies reported health-related quality of life or clinical endpoints such as cardiovascular morbidity and mortality; in the trials identified, surrogate outcomes such as total cholesterol, LDL cholesterol, HDL cholesterol and TG concentrations were used as indicators of clinical outcomes.
- 4.1.2 The Assessment Group noted that it is not clear whether the participants in the studies represent the populations defined in the scope of the appraisal, that is, people with primary hypercholesterolaemia that has not been adequately controlled with a statin alone or people in whom statin therapy is considered inappropriate or is not tolerated. The majority of studies required washout or discontinuation of ongoing lipid-regulating drug treatments for up to 12 weeks before randomisation, and no information was available on pre-trial treatment history.
- 4.1.3 To represent the population of people with hypercholesterolaemia that is not appropriately controlled with statin therapy, six 12-week, fixed-dose RCTs (n = 3610) were identified that compared ezetimibe plus statin therapy with statin therapy alone. The statin under investigation was simvastatin in four RCTs and atorvastatin and pravastatin, respectively, in the remaining two

RCTs. The Assessment Group carried out a meta-analysis on the RCTs, which reported the mean percentage change in lipid profiles from pre-statin baseline, expressed as a proportion of pre-statin cholesterol concentrations, and compared the overall change in each lipid profile between the two therapies. Ezetimibe plus statin therapy was associated with an additional mean reduction in total and LDL cholesterol concentrations of 10.4% (95% confidence interval [CI], 11.1 to 9.6) and 13.9% (95% CI, 14.9 to 13.0), respectively, of pre-statin treatment concentrations compared with statin therapy alone. This equated to a 22.4% reduction achieved by the combination of ezetimibe plus statin compared to an on-statin baseline LDL cholesterol concentration.

- 4.1.4 In addition to the fixed-dose studies, the Assessment Group identified four extension studies (n = 1800) that compared ezetimibe plus statin therapy with a titrated statin dose. It was not considered possible to meta-analyse the statin titration studies because of a high degree of heterogeneity. Two studies demonstrated that ezetimibe coadministered with atorvastatin has a significantly greater LDL cholesterol-lowering effect compared with atorvastatin alone (additional mean reduction: -9.8%, $p < 0.05$ and -12.9%, $p < 0.05$). One study found that ezetimibe coadministered with simvastatin led to a significantly greater LDL cholesterol reduction compared with atorvastatin monotherapy (additional mean reduction: -6.9%, $p < 0.05$). A further study compared the LDL cholesterol-lowering effect of ezetimibe coadministered with simvastatin compared with simvastatin monotherapy and found the additional mean reduction to be -27% ($p < 0.05$). A similar pattern of efficacy was observed in plasma total cholesterol concentration. One study included an HeFH subgroup; in the ezetimibe plus statin arm 17% reached the LDL cholesterol target (2.6 mmol/litre or less) compared to 4% in the statin monotherapy arm. It was not possible to differentiate the effectiveness between different doses of alternative statins on the basis of the evidence in any of the fixed-dose or statin titration studies.

- 4.1.5 The Assessment Group carried out an additional meta-analysis of shorter-term studies (less than 12 weeks in duration) comparing ezetimibe coadministered with statin therapy with statin therapy alone. In the shorter-term studies, ezetimibe was given to participants in addition to their ongoing statin therapy. The Assessment Group conducted a meta-analysis of the five studies identified (6 to 8 weeks in duration) and reported the mean percentage change in lipid profiles from the time ezetimibe was added to the statin, expressed as a proportion of post-statin cholesterol concentrations. The results showed that the addition of ezetimibe to statin therapy reduced LDL cholesterol concentrations by 23.2% (95% CI, 24.3 to 22.1) more than statin therapy alone.
- 4.1.6 One statin titration study, available as a conference abstract only, was identified that compared ezetimibe coadministered with a statin versus other lipid-lowering drugs coadministered with a statin (ezetimibe plus simvastatin versus niacin plus atorvastatin or rosuvastatin). Low-to-moderate doses of niacin plus atorvastatin/rosuvastatin achieved similar LDL cholesterol reductions and greater HDL cholesterol increases in this study compared with the highest doses of rosuvastatin monotherapy or ezetimibe coadministered with simvastatin. No further details on clinical effectiveness were given.
- 4.1.7 Seven RCTs (n = 2577) comparing ezetimibe monotherapy with placebo represented the population in which statin therapy is considered inappropriate or is not tolerated. All were 12-week studies and were included in a meta-analysis performed by the Assessment Group. Ezetimibe monotherapy was associated with a statistically significant mean reduction in total cholesterol concentrations (13.4%, 95% CI, 14.2 to 12.6) and LDL cholesterol concentrations (18.6%, 95% CI, 19.7 to 17.4) compared with placebo.
- 4.1.8 No RCTs were identified that directly compared the efficacy and safety of ezetimibe monotherapy with lipid-lowering drugs other than a statin.

Subgroups

4.1.9 Four studies demonstrated LDL cholesterol-lowering effects of ezetimibe treatment across subgroups, including different ethnic groups and people with or without conditions such as CVD, diabetes and HeFH. None of the subgroup comparisons showed statistically significant differences between subgroups. All other trials reported that the effect of ezetimibe therapy on LDL cholesterol concentrations was generally consistent across all subgroups. The Assessment Group carried out an additional subgroup analysis of the effect of ezetimibe therapy in people with or without HeFH. The greater reductions in LDL and total cholesterol concentrations in the HeFH group were not found to be statistically significant.

Adverse events

4.1.10 Adverse events reported in each of the included studies were summarised by the Assessment Group. Meta-analyses were considered inappropriate because of insufficient data and low occurrences of adverse events.

4.1.11 Therapy with ezetimibe coadministered with a statin was found to have a similar adverse event profile to that of statin therapy alone. It was found that treatment-related adverse events ranged from 14% to 23% in the ezetimibe plus statin arm and from 13% to 27% in the statin-only arm. The number of people that discontinued treatment because of treatment-related adverse events was similar across both treatment groups (1% to 6% in the ezetimibe plus statin arm and 1% to 7% in the statin-only arm). Ezetimibe monotherapy was found to have a similar adverse event profile to placebo. The most commonly reported adverse events were musculoskeletal disorders (2–5%) and upper respiratory infections (7–11%). It was found that treatment-related adverse events ranged from 9% to 18% in the ezetimibe monotherapy arm and from 9% to 24% in the placebo arm.

Evidence on the relationship between changes in lipid concentrations and clinical outcomes

4.1.12 The Assessment Group reported that some meta-analyses of clinical studies have established that lowering LDL cholesterol concentrations is associated with a reduced risk of cardiovascular events in people with, or at high risk of, CVD. The results of a meta-analysis of data from 14 RCTs of statins including 90,056 participants, published in 2005 by the Cholesterol Treatment Trialists' Collaborators (CTTC), demonstrated that a 1.0 mmol/litre reduction in LDL cholesterol was associated with a 23% reduction in the 5-year incidence of a coronary event (non-fatal MI or death from coronary heart disease [CHD]) and a 21% reduction in major coronary events, coronary revascularisation and stroke. A meta-analysis of data from nine trials of non-statin treatments (bile acid sequestrants, surgery and diet) and 10 trials of statin treatments, including a total of 81,859 participants, was also published in 2005. When the relationship between LDL cholesterol concentrations and CHD risk was assessed, larger reductions in LDL cholesterol were shown to be associated with greater reductions in CHD, with no difference between the statin and non-statin trials.

4.2 Cost effectiveness

Published economic evaluations

4.2.1 The Assessment Group identified two published papers and one abstract that assessed the cost effectiveness of ezetimibe. The three analyses were country-specific evaluations using an economic model known as the Cook model. The first published cost-effectiveness study reported results from Germany, Spain and Norway. The model compared ezetimibe plus statin with three statin-only strategies, using simvastatin and atorvastatin. The incremental cost per life-year gained ranged from £8000 to £50,000 depending on the treatment strategy used and whether or not the person had a history of CHD or diabetes. The second published cost-effectiveness study reported results from Canada and estimated the cost effectiveness of adding

ezetimibe to statin therapy (atorvastatin) in people whose cholesterol levels had not reached the treatment goal of LDL cholesterol levels lower than 2.5 mmol/litre. The incremental cost per quality-adjusted life year (QALY) gained ranged from £26,000 to £46,000. The abstract reported a UK-based model of ezetimibe plus statin therapy with statin titration and statin therapy without titration in people whose total cholesterol concentrations had not reached their goal of 5.0 mmol/litre or less. The incremental cost per QALY gained for ezetimibe plus statin therapy versus statin monotherapy was £8000, whereas for ezetimibe plus statin therapy versus statin titration the incremental cost per QALY gained was £9000.

Manufacturer's analyses

- 4.2.2 Merck Sharp and Dohme Limited and Schering-Plough Limited submitted two models: the 'Cook' model, an adaptation of the model used in the published economic evaluations described in section 4.2.1, and the 'Basic' model.
- 4.2.3 The Cook model evaluated the cost effectiveness of ezetimibe plus statin therapy in people whose cholesterol concentrations are not appropriately controlled by current statin therapy alone. In the base-case scenarios, ezetimibe plus current statin therapy was compared with current statin therapy alone, and also with double the dose of the current statin. Ezetimibe monotherapy was compared with no treatment in people who are intolerant to statin therapy or in whom statins are contraindicated.
- 4.2.4 The Cook model is a Markov model and includes nine health states. Benefits of treatment were modelled using changes in total and HDL cholesterol concentrations derived from a meta-analysis of short-term RCTs. Algorithms from the Framingham study were used to predict future cardiovascular events. For people with diabetes who have a history of CVD, algorithms from the 'UK Prospective Diabetes Study' were used to calculate probabilities of events. The cost of CHD events (angina, MI and fatal CHD) and health-related utilities were based on those reported in the 2004 statins assessment report. Drug

costs were generally based on the July 2006 NHS drug tariff. A UK NHS perspective was used and costs and benefits were discounted at 3.5%.

- 4.2.5 For the base-case scenarios, the incremental cost per QALY gained of ezetimibe plus current statin therapy ranged from just under £8000 to just under £122,000. For ezetimibe monotherapy versus no treatment, the incremental cost per QALY gained ranged from just under £10,000 to just over £131,000.
- 4.2.6 The Basic model was developed to validate the results of the Cook model. The structure of the model is that of a simple decision tree. One treatment comparison considered ezetimibe plus a weighted average dose of non-proprietary and proprietary statins versus a weighted average dose of non-proprietary and proprietary statins alone. Another treatment comparison considered ezetimibe plus simvastatin versus atorvastatin.
- 4.2.7 In contrast to the Cook model, the Basic model used published evidence from a meta-analysis conducted by the CTTC on the relationship between reductions in LDL cholesterol and the corresponding reduction in the incidence of cardiovascular events. The Basic model gave similar results to those calculated using the Cook model.

Assessment Group's model

- 4.2.8 The Assessment Group developed a Markov model to estimate the cost effectiveness of ezetimibe in five different scenarios. Scenario 2 represents people in whom statins are contraindicated or not tolerated. All other scenarios were designed to represent people whose cholesterol concentrations are not appropriately controlled with their current statin therapy.
- Scenario 1 – ezetimibe coadministered with current statin therapy versus current statin therapy titrated to the next dose.
 - Scenario 2 – ezetimibe monotherapy versus no treatment.

- Scenario 3 – ezetimibe coadministered with non-proprietary simvastatin versus atorvastatin.
- Scenario 4 – ezetimibe coadministered with current statin therapy versus current statin therapy alone.
- Scenario 5 – ezetimibe coadministered with rosuvastatin versus rosuvastatin monotherapy.

4.2.9 Framingham risk equations were used to derive baseline risks in the model. The effectiveness of treatments was modelled using the reported link between chemically induced changes in lipids and reductions in cardiovascular risk from the CTTC meta-analysis. The distribution across event types was based on UK-specific incidence and prevalence rates. Data from the published ezetimibe 12-week studies were used to inform efficacies of treatments in lowering LDL cholesterol concentrations. Statin titration of one dose was assumed to provide an additional 6% reduction in pre-statin baseline LDL cholesterol concentrations, based on a published meta-analysis of RCT evidence. The model incorporated percentage changes in LDL cholesterol concentrations as a proportion of post-statin LDL cholesterol concentrations.

4.2.10 The Assessment Group reported that there is a lack of published evidence on costs for some of the health states modelled, and assumptions based on expert opinion were used where published evidence was not available. Expert opinions were used to inform the levels and types of monitoring required, and published UK costs were applied to these estimates. Drug costs were taken from the BNF 53rd edition. The cost of current statin therapy for scenarios 1 and 4 is a weighted cost based on published data on prescribing rates in England in 2005. The costs of treatment-related adverse events were not included. Where necessary, costs used in the economic analysis were adjusted to 2006 prices. The analysis was conducted from a UK NHS perspective, and a discount rate of 3.5% on costs and benefits was applied.

- 4.2.11 Health-related utility data were obtained from published studies supported by clinical advice and were adjusted for age using data from a large UK-population-based survey using the EQ-5D. No reduction in utility for adverse effects of treatment was modelled.
- 4.2.12 Results were estimated for people with CVD and for people who have a 20% or greater 10-year risk of developing CVD. Results were presented by age (45, 55, 65 and 75 years), sex and baseline LDL cholesterol concentrations, and for 20-year and lifetime time horizons. The results presented below are based on a baseline LDL cholesterol concentration of 3.5 mmol/litre and a lifetime horizon.
- 4.2.13 For scenario 1, the incremental costs per QALY gained ranged from £24,000 to £43,000. The results were generally higher in women, older age groups and people without CVD. The incremental costs per QALY gained were between £24,000 and £31,000 for people aged 45 to 65 years, and between £29,000 and £43,000 for people aged 75 years.
- 4.2.14 For scenario 2, the incremental costs per QALY gained ranged from £24,000 to £42,000 and were generally higher in women, older age groups and people without CVD. The incremental costs per QALY gained were between £24,000 and £30,000 for people aged 45 to 65 years, and between £33,000 and £42,000 for people aged 75 years.
- 4.2.15 For scenario 3, the incremental costs per QALY gained ranged from £1500 to £4600, with only small variations between different groups.
- 4.2.16 For scenarios 4 and 5, the incremental costs per QALY gained ranged from £19,000 to £33,000. The results were generally higher in women, older age groups and people without CVD. The incremental costs per QALY gained were between £19,000 and £24,000 for people aged 45 to 65 years, and between £26,000 and £33,000 for people aged 75 years.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of ezetimibe for primary hypercholesterolaemia, having considered evidence on the nature of the condition and the value placed on the benefits of ezetimibe by people with primary hypercholesterolaemia, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The Committee considered the evidence on the clinical effectiveness of ezetimibe coadministered with statin therapy in adults whose cholesterol concentrations have not been appropriately controlled with statin therapy alone. The Committee heard from the clinical specialists that, because of its different mode of action, ezetimibe has an additive effect on the reduction of LDL and total cholesterol concentrations when combined with statin therapy. Thus, whereas doubling the dose of statin therapy or switching to an alternative statin generally leads to a further reduction in baseline LDL cholesterol concentrations of approximately 6% and 8%, respectively, the Committee concluded that the addition of ezetimibe to statin therapy is likely to lead to greater incremental reductions in LDL cholesterol concentrations.
- 4.3.3 The Committee noted the results of a meta-analysis performed by the Assessment Group which showed that ezetimibe plus statin therapy reduces LDL cholesterol concentrations by an additional 13.9% compared with statin therapy alone. The Committee was aware that the Assessment Group's meta-analysis was based on 12-week studies that required discontinuation of ongoing lipid-regulating treatments, which calculated the change as a proportion of the baseline LDL cholesterol concentration. It also noted this absolute change was approximately 22% when calculated as a proportion of the post-statin LDL cholesterol concentrations. The Committee concluded that this was consistent with the evidence from the 6- to 8-week studies in which ezetimibe was given to people in addition to their ongoing statin therapy.

- 4.3.4 Consideration was given to the evidence on the clinical effectiveness of ezetimibe monotherapy in adults who have contraindications to, or are intolerant of, statin therapy. The Committee heard from the clinical specialists and patient experts that some people are intolerant of statin therapy because of severe adverse effects such as severe muscle or gastrointestinal effects and altered liver function. The Committee noted that the results of a meta-analysis performed by the Assessment Group showed that ezetimibe monotherapy leads to statistically significant improvements in LDL and total cholesterol concentrations compared with placebo. The Committee further noted that the trials were generally conducted among people who were tolerant to statin therapy. However, it agreed that there appeared to be no biologically plausible reason why the results could not be generalised to statin-contraindicated or intolerant populations.
- 4.3.5 The Committee was aware of the absence of clinical outcomes recorded in all of the ezetimibe trials, and it considered the published evidence on the correlation between changes in lipid concentrations to reductions in cardiovascular events. It noted the views of the clinical specialists and the results of published meta-analyses that treatment which lowers LDL cholesterol concentrations is associated with cardiovascular outcome benefits independent of the treatment used. The Committee agreed that there is sufficient evidence to link reductions in LDL cholesterol concentrations induced by treatment with ezetimibe with future reductions in cardiovascular events. The Committee concluded that ezetimibe coadministered with a statin is clinically effective in adults who have primary hypercholesterolaemia that is not appropriately controlled with statin therapy, compared with statin therapy alone. It further concluded that ezetimibe monotherapy is clinically effective in people who have contraindications to, or are intolerant of, statin therapy, compared with placebo.
- 4.3.6 The Committee observed that the study populations in the clinical trials of ezetimibe were mainly white and that equivalent data for other ethnic groups are limited. However, it accepted the views of the clinical specialists that the

clinical effectiveness of ezetimibe, based on its mode of action, is unlikely to differ markedly between different ethnic groups, therefore separate recommendations are not required. It also agreed that the evidence did not suggest a difference in the effectiveness of ezetimibe in any other subgroup, including people with HeFH or diabetes, or people with or without a history of CVD.

- 4.3.7 The Committee also took into consideration the risks of adverse events associated with ezetimibe. It was aware of the limited long-term data on adverse events relative to the use of statins, but was reassured by the safety profile of ezetimibe observed in the clinical trials and by the views of the clinical specialists that no significant adverse events had emerged outside of the trials. In addition, the clinical specialists reported that they did not know of any existing increase in all-cause mortality, or of specific mortality, as a result of treatment with ezetimibe.
- 4.3.8 The Committee discussed the results of the economic analyses from the manufacturer's models and the Assessment Group's model. It concluded that the Assessment Group's model represented the most appropriate analysis on which to base its decision regarding the use of ezetimibe. This was because the Assessment Group's model was based on the effect on cardiovascular risk of reductions in cholesterol concentrations as a result of drug treatment. By contrast, the algorithms from the Framingham study, used in the main model submitted by the manufacturer, were based on the cardiovascular risk associated with a particular cholesterol concentration. The Committee also considered which time horizon was the most appropriate for the economic analysis. It agreed that a time horizon based on the costs and health outcomes associated with a lifetime of treatment should be assumed, given that ezetimibe is a lifelong treatment and benefits may occur well into the future.
- 4.3.9 The Committee considered the cost effectiveness of ezetimibe in various scenarios presented by the Assessment Group. The Committee was mindful

that all the cost-effectiveness estimates were associated with uncertainty. It was aware of the lack of data for ezetimibe on cardiovascular outcomes and the possibility that future adverse events relating to ezetimibe might become apparent with extended use over time. Therefore, the Committee agreed that it should take these uncertainties into consideration when making its recommendations.

4.3.10 The Committee considered the cost effectiveness of ezetimibe coadministered with statin therapy in adults whose cholesterol concentrations have not been appropriately controlled with statin therapy alone. The Committee noted that the incremental costs per QALY gained of ezetimibe, coadministered with current statin therapy versus current statin therapy titrated to the next dose, ranged from £24,000 to £43,000 (scenario 1 for people with baseline LDL cholesterol concentrations of 3.5 mmol/litre). Given the uncertainty around the range of incremental cost-effectiveness ratios (ICERs) for this scenario, in addition to the concerns heard by the Committee regarding the lack of long-term clinical effectiveness evidence for ezetimibe, the Committee agreed that ezetimibe coadministered with a statin should not be recommended as an alternative to dose titration of the initiated statin where dose titration is possible and not prevented by the emergence of adverse effects.

4.3.11 The Committee noted that the incremental costs per QALY gained of ezetimibe plus simvastatin compared with atorvastatin were all below £4600 regardless of age, sex and CVD history (scenario 3 for people with baseline LDL cholesterol concentrations of 3.5 mmol/litre). The Committee agreed therefore that adding ezetimibe to initial statin therapy as a treatment option is a cost-effective use of NHS resources when compared with switching to an alternative statin.

4.3.12 In addition, the Committee heard from the clinical and patient experts that the addition of ezetimibe to initial statin therapy, titrated to a dose considered appropriate for an individual, is a useful alternative to switching to an

alternative statin. The Committee concluded that ezetimibe, coadministered with initial statin therapy which has been titrated appropriately (statin therapy initiated as per NICE guidance TA 94 in adults with non-familial hypercholesterolaemia), should be recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia when consideration is being given to changing from initial statin therapy to an alternative statin in the following circumstances: when serum total or LDL cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy.

4.3.13 The Committee agreed that appropriate control of cholesterol concentrations should be based on individualised risk assessments in accordance with national guidance on the management of cardiovascular disease for the relevant population. To ensure the most cost-effective use of ezetimibe when coadministered with a statin, the Committee also agreed that its recommendations should be read in conjunction with the published NICE guidance on the initiation of statin therapy (TA 94).

4.3.14 The Committee was aware of the availability of a combination tablet of ezetimibe and simvastatin (Inegy). It considered the potential benefits of prescribing one tablet compared with two, but was mindful that it had not been demonstrated that the combination tablet gives a greater cholesterol-lowering effect than separately prescribing ezetimibe and a statin therapy. Given the absence of such data the Committee concluded that when the decision has been made to treat with ezetimibe coadministered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.

4.3.15 The Committee considered the cost effectiveness of ezetimibe monotherapy compared with no treatment in adults who are intolerant to statin therapy, estimated in scenario 2 of the Assessment Group's model. The Committee noted the limited treatment alternatives for this group of patients and accepted the views of the clinical specialists and patient experts that ezetimibe

monotherapy is a useful treatment option for people who are contraindicated to, or intolerant of, initial statin therapy, particularly among those who have high LDL cholesterol concentrations. It further noted that the incremental costs per QALY gained for ezetimibe monotherapy versus no treatment, assuming a baseline LDL cholesterol concentration of 3.5 mmol/litre, ranged from £24,000 to £30,000 between the ages of 45 and 65 years and from £33,000 to £42,000 at age 75 years. Owing to the limited treatment alternatives for this group of patients and the importance of ensuring equity across all age groups, the Committee concluded that ezetimibe monotherapy should be an option for the treatment of all adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who would otherwise be initiated on statin therapy (as per NICE guidance TA 94 in adults with non-familial hypercholesterolaemia) but who are unable to do so because of contraindications. In addition, the Committee concluded that ezetimibe monotherapy is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who are intolerant to statin therapy.

4.3.16 Finally, the Committee considered the definition of statin intolerance. It agreed that for the purposes of this guidance, intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines

and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

- 5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TA132).
- Audit criteria to monitor local practice.
 - A costing statement explaining the resource impact of this guidance.

6 Recommendations for further research

- 6.1 Collection of further data is needed to establish the long-term effectiveness of ezetimibe and whether there are any long-term adverse effects.

7 Related NICE guidance

- Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from: www.nice.org.uk/CG048

- Hypertension: management of hypertension in adults in primary care. NICE clinical guideline 34 (2006). Available from: www.nice.org.uk/CG034
- Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006). Available from: www.nice.org.uk/TA094

NICE is developing the following guidance (details available from www.nice.org.uk).

- Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline (publication expected January 2008).
- Type 2 diabetes: the management of type 2 diabetes (update). NICE clinical guideline (publication expected March 2008).
- Familial hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia. NICE clinical guideline (publication expected August 2008).

8 Date for review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in August 2010.

Andrew Dillon
Chief Executive
November 2007

Appendix A. Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is a standing advisory committee of the Institute. Its 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. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

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.

Dr Jane Adam

Radiologist, St George's Hospital, London

Professor A E Ades

MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Amanda Adler

Consultant Physician, Addenbrooke's Hospital, Cambridge

Anne Allison

Nurse Clinical Adviser, Healthcare Commission

Dr Tom Aslan

General Practitioner, Stockwell, London

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain

Lay Member

Professor John Cairns (Committee B)

Public Health and Policy, London School of Hygiene and Tropical Medicine

Professor Karl Claxton

Professor of Health Economics, University of York

Dr Richard Cookson

Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice, University of East Anglia

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Professor Christopher Eccleston

Director, Pain Management Unit, University of Bath

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin

Health Outcomes Manager, Johnson & Johnson Medical Ltd

Ms Linda Hands

Consultant Surgeon, John Radcliffe Hospital

Dr Rowan Hillson

Consultant Physician, Diabeticare, The Hillingdon Hospital

Professor Philip Home (Vice Chair)

Professor of Diabetes Medicine, University of Newcastle upon Tyne

Dr Terry John

General Practitioner, The Firs, London

Professor Richard Lilford

Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham

Dr Simon Maxwell

Senior Lecturer in Clinical Pharmacology and Honorary Consultant Physician, Queens Medical Research Institute, University of Edinburgh

Ms Judith Paget

Chief Executive, Caerphilly Local Health Board, Wales

Dr Ann Richardson

Lay Member

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Simon Thomas

Consultant Physician, General Medicine and Clinical Pharmacology, Newcastle Hospitals NHS Trust

Mr David Thomson

Lay Member

Dr Luke Twelves

General Practitioner, Ramsey Health Centre, North Huntingdon

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Dr Paul Watson

Director of Commissioning, East of England Strategic Health Authority

B Guideline representatives

The following individuals, representing the National Collaborating Centre responsible for developing the Institute's clinical guideline related to this topic, attended the meeting to observe and to contribute as advisors to the Committee.

- Beth Shaw, Technical Lead, National Collaborating Centre for Primary Care
- Dr Rubin Minhas, General Practitioner, Primary Care Cardiovascular Society
- Dr Jonathan Mant, Clinical Reader in Stroke Epidemiology, National Collaborating Centre for Chronic Conditions
- Mrs Nancy Turnbull, Chief Executive, National Collaborating Centre for Primary Care

C ***NICE project team***

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

Zoe Charles and Emma Pugh

Technical Leads

Louise Longworth

Technical Adviser

Alana Miller

Project Manager

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by the University of Sheffield, School of Health and Related Research (SchARR).

- Ara R, Tumor I, Pandor A, et al. Ezetimibe for the treatment of hypercholesterolaemia, December 2006
- Ara R, Tumor I, Pandor A, et al. Amendments to methodologies and revised results for the SchARR economic model, February 2007
- Ara R, Tumor I, Pandor A, et al. Amendments to methodologies and revised results for the SchARR economic model, April 2007

B The following organisations accepted the invitation to participate in this appraisal. They were also invited to make comment on the appraisal consultation document (ACD). Organisations listed in I and II were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsors:

- Merck Sharpe and Dohme Limited and Schering-Plough Limited

II Professional/specialist and patient/carer groups:

- Action Heart
- British Cardiac Society
- British Heart Foundation
- Department of Health
- Diabetes UK
- Heart UK
- Primary Care Cardiovascular Society
- Royal College of General Practitioners
- Royal College of Nursing

- Royal College of Physicians' Cardiology Committee
- Royal Pharmaceutical Society
- South Asian Health Foundation
- The Stroke Association
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- AstraZeneca UK Ltd
- British National Formulary
- Department of Health, Social Services and Public Safety for Northern Ireland
- Medicines and Healthcare products Regulatory Agency (MHRA)
- Merck Pharmaceuticals Ltd
- Merck Sharp & Dohme Ltd
- National Collaborating Centre for Chronic Conditions
- National Collaborating Centre for Primary Care
- National Coordinating Centre for Health Technology Assessment
- NHS Quality Improvement Scotland
- Novartis Pharmaceuticals UK Ltd
- Pfizer Ltd (Pharmacia)
- Sanofi Aventis Ltd
- School of Health & Related Research Sheffield

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commenators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on ezetimibe by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr David Monkman, General Practitioner, nominated by the Primary Care Cardiovascular Society – clinical specialist
- Dr Richard Wray, Consultant Cardiologist, nominated by the British Cardiovascular Society – clinical specialist
- Dr Anthony S Weirzbicki, Consultant Chemical Pathologist, nominated by South Asian Health Foundation – clinical specialist
- Mr Bruce Mayo, nominated by HEART UK – patient expert
- Mr Raymond Edwards, nominated by HEART UK – patient expert