NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

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

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the first Appraisal Committee meeting, it is prepared before the Institute receives consultees' comments on the Assessment Report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in Appendix A.

1 Background

1.1 The condition

Hypercholesterolaemia is defined as the presence of high levels of cholesterol in the blood. Primary hypercholesterolaemia is associated with an underlying genetic defect; this is due to either a single genetic defect, or more commonly, to the interaction of a number of genes with dietary and other factors such as smoking and physical inactivity. Secondary hypercholesterolaemia is caused by another disease state or by drug therapy and is not covered by this appraisal.

The majority of people with primary hypercholesterolaemia have mildly or moderately elevated cholesterol levels and exhibit no clinical symptoms. Severe hypercholesterolaemia can cause xanthomas (lesions on the skin

containing cholesterol and fats) and arcus corneae (cholesterol deposits in the eyes). However, the increased risk of cardiovascular disease (CVD) is the most significant problem associated with hypercholesterolaemia. Elevated cholesterol levels over a long period of time accelerate the build-up of fatty deposits in the arteries, a process known as atherosclerosis. The resulting narrowing of the arteries and impaired blood flow can lead to cardiovascular (CV) events such as angina (chest pain), 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 is a major cause of illness, disability and reduced quality of life.

People with very severe forms of primary hypercholesterolaemia, such as the genetic disorder heterozygous familial hypercholesterolaemia (HeFH), are at particular risk of developing premature CVD. This condition occurs in around 1 in every 500 people.

The increased risk of CVD in people with hypercholesterolaemia is mainly due to raised low-density lipoprotein cholesterol (LDL-c) levels. By contrast, high-density lipoprotein cholesterol (HDL-c) is inversely associated with CVD. Triglycerides (TGs) also raise CV risk but this is lower than the risk posed by raised LDL-c levels. In addition to cholesterol levels, a person's absolute risk of developing CVD depends on additional factors, including smoking, high blood pressure and diabetes.

Lipid levels vary in a person from day to day and can vary across different populations; consequently there are no fixed 'normal ranges' for blood lipids. In England, the average total cholesterol (Total-c) level in adults is approximately 5.6 mmol/litre, of which LDL-c comprises an average of 3.6 mmol/litre. The UK population has one of the highest average serum cholesterol levels in the world. In 2003, approximately 27% and 70% of people had Total-c levels greater than 6.5 mmol/litre and 5.0 mmol/litre, respectively. Total-c levels are similar in men and women, with small regional and socio-economic variations. However, the prevalence of low HDL-c levels (less than 1.0 mmol/litre) varies substantially by income, with high-level earners having higher levels of HDL-c (most notably in women). HDL-c levels do not vary

substantially by region. Among minority ethnic groups in England, Black Caribbean, Indian, Pakistani, Chinese and Irish populations have marginally lower mean Total-c and LDL-c levels than the general population. Variations in the prevalence of low HDL-c among ethnic groups are considerable, with the highest rates of low HDL-c for both sexes found in the Pakistani and Bangladeshi communities. By contrast, Black Caribbean people have a relatively low prevalence of low HDL-c.

1.2 Current management

The current management of primary (heterozygous familial and non-familial) hypercholesterolaemia includes dietary and lifestyle changes such as smoking cessation, weight loss and increased physical activity. Statins are the first-choice drugs in treating primary hypercholesterolaemia (that is, atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin), but other lipid-regulating drugs may also be used. Statins lower LDL-c levels by slowing down the production of cholesterol in the liver and increasing the liver's ability to remove the LDL-c already in the blood.

There are some additional strategies available to people whose lipid levels do not reduce appropriately with treatment or who are intolerant to statins. These are increasing the dose of the statin, changing to a more potent statin, switching to combination therapy with a statin and another lipid-regulating drug such as a fibrate, nicotinic acid or an anion exchange resin, or switching to monotherapy with another lipid-regulating drug.

The decision to initiate therapy with a lipid-regulating drug in people with hypercholesterolaemia is generally based on an assessment of a person's overall CV risk. In 2006, the NICE guidance on statins recommended statin therapy for all adults with clinical evidence of CVD (that is, for secondary CVD prevention). It also recommended statins should be administered for the primary prevention of CVD (that is, prevention in people without established CVD) in adults who have a 20% or greater 10-year risk of developing CVD. The NICE guidance does not include specific advice for people with familial hypercholesterolaemia.

The most recent guidance on lipid targets, published by six Joint British Societies (known as JBS2), recommends the following treatment thresholds in people with CVD or who have a 10-year CV risk of 20% or greater: Total-c less than 4.0 mmol/litre and LDL-c below 2.0 mmol/litre. There are no defined targets for HDL-c or TGs.

2 The technology

Table 1 Summary description of technology

Generic name	Ezetimibe	Ezetimibe and simvastatin
Proprietary name	Ezetrol	Inegy
Manufacturer	Merck Sharp and Dohme Limited and Schering-Plough Limited (MSD-SP)	Merck Sharp and Dohme Limited and Schering-Plough Limited (MSD-SP)
Dose	10 mg once daily	Fixed-dose combination tablet (ezetimibe 10 mg with simvastatin 20, 40 or 80 mg) once daily
Acquisition cost excluding VAT (*BNF* 52, September 2006)	28-tablet pack = £26.31	28 x 10 mg/20 mg = £33.42 28 x 10 mg/40 mg = £38.98 28 x 10 mg/80 mg = £41.21

Ezetimibe is a unique 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 is the first product on the market that uses this mechanism to lower cholesterol, it can be combined with a statin to provide complementary cholesterol reduction.

Ezetimibe, coadministered with a statin (or alone if a statin is inappropriate or not tolerated), is licensed as an adjunctive therapy to dietary manipulation in people with primary (heterozygous familial and non-familial) hypercholesterolaemia that is not appropriately controlled with a statin alone (see table 1). Ezetimibe is also licensed as an adjunct to dietary manipulation for use in people with homozygous familial hypercholesterolaemia in combination with a statin, and in people with homozygous familial sitosterolaemia. These indications are not covered by this appraisal.

A fixed-dose combination tablet containing ezetimibe and simvastatin is also available (see table 1). This is licensed as an adjunctive therapy to diet for use in people with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate (that is, hypercholesterolaemia or hyperlipidaemia 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 adjunctive therapy to diet for use in people with homozygous familial hypercholesterolaemia.

The side effects of ezetimibe monotherapy are usually mild and transient and include headache, abdominal pain and diarrhoea. When coadministered with a statin, side effects include gastro-intestinal disturbances, headache, fatigue and myalgia (muscle pain).

2.1 Current service provision

Ezetimibe has been available in England and Wales since April 2003 and prescribing rates have increased every year. The number of people who will be prescribed ezetimibe in 2007 is predicted to be approximately 157,000, based on an annual growth rate of 55% (the growth in 2005 compared with 2004). It is estimated that 20% of these people will be prescribed ezetimibe monotherapy and 80% will be prescribed ezetimibe coadministered with a statin. The total gross cost of ezetimibe in England and Wales in 2007 is estimated to be £54.3 million.

3 The evidence

3.1 Clinical effectiveness

Thirteen randomised controlled trials (RCTs) that met the inclusion criteria of the review were identified by the Assessment Group (see page 51 of the assessment report). These RCTs varied in duration (from 12 to 48 weeks) and in sample size (from 246 to 1528 participants). Studies of less than 12 weeks were not included on the grounds that they are unlikely to inform on survival, CV events, adverse events or health-related quality of life. All trials involved

people with primary hypercholesterolaemia with average baseline LDL-c levels ranging from 3.36 mmol/litre to 6.5 mmol/litre and included mixed populations of people with and without a history of CVD.

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 (heterozygous familial and non-familial) 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 there was no information on pre-trial treatment history or previous treatment success.

No studies reported clinical endpoints such as CV morbidity and mortality; in the trials identified, surrogate outcomes such as Total-c, LDL-c, HDL-c and TG levels were used as indicators of clinical outcomes.

Overall, all trials were considered to be well designed and conducted and included relatively balanced populations.

3.1.1 Ezetimibe coadministered with a statin versus a statin alone

To represent the population of people with hypercholesterolaemia that is not adequately controlled with statin therapy, 10 studies were identified that compared ezetimibe plus statin therapy with statin therapy alone. The statin dose was fixed in six studies and titrated in four.

Four of the fixed-dose statin RCTs used simvastatin as the statin under investigation, whereas the remaining two used atorvastatin and pravastatin. All were 12-week studies. A meta-analysis of the fixed-dose statin studies demonstrated that ezetimibe plus statin therapy is associated with a statistically significant reduction in LDL-c and Total-c levels compared with statin therapy alone, as shown in table 2. This trend was consistent across all studies and low heterogeneity was identified. Ezetimibe plus statin therapy also increased HDL-c levels and reduced TGs more than statin therapy alone. It was not possible to differentiate the effectiveness between varying doses of different statins on the basis of the evidence.

Table 2 Summary of the results of the meta-analysis performed by the Assessment Group

	Mean % change in lipid profile (95% confidence intervals)			
	Total-c	LDL-c	HDL-c	TGs
Ezetimibe plus statin (vs fixed-dose statin) Six RCTs, (N=3610)	-10.36% (-11.09 to -9.63)	-13.94% (-14.90 to -12.98)	1.29%[a] (0.46 to 2.12)	-8.27%[b] (-11.50 to -5.04)
Ezetimibe monotherapy (vs placebo) Seven RCTs, (N=2577)	-13.41% (-14.20 to -12.62)	-18.56% (-19.68 to -17.44)	3.00% (2.01 to 4.00)	-8.20%[c] (-11.25 to -5.16)

[a] Based on five RCTs, N = 3363.
[b] Based on two RCTs, N = 946.
[c] Based on four RCTs, N = 1977.
Total-c, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; TG, triglyceride; RCTs, randomised controlled trials.

In the statin titration RCTs, two studies compared ezetimibe plus atorvastatin with atorvastatin alone (one 24-week and one 14-week study), one study compared ezetimibe plus simvastatin with atorvastatin (a 24-week study) and one study compared ezetimibe plus simvastatin with simvastatin plus placebo (a 48-week study). In three of the RCTs, if target LDL-c levels were not reached, the statin was titrated up to the next dose until the person's lipid-level goal or maximum dose of statin was reached. The remaining RCT used a forced titration method, where the next dose of the statin was given every 6 weeks regardless of whether the target LDL-c level had been achieved. All four studies used the NCEP ATP II/III target levels from the USA (see pages 26 to 27 of the assessment report for details of these target levels).

Owing to a high degree of heterogeneity across the statin titration studies, meta-analysis was not considered to be appropriate and the results were presented individually. The source of heterogeneity is probably due to differences in the type of statin, dose titration and the duration of the studies. Because of incomplete and missing data, it was not considered possible to analyse the interaction of each statin dose during the titration process. Consequently, the data were pooled across all doses.

In all of the statin titration studies, ezetimibe plus statin therapy was associated with a statistically significant reduction in LDL-c and Total-c, as shown in table 3. Ezetimibe plus statin therapy also increased HDL-c levels and reduced TGs more than statin therapy alone, although the difference was not always statistically significant.

Table 3 Summary of results from statin titration studies*

	Mean % change in lipid profile			
	LDL-c	Total-c	HDL-c	TGs
Ezetimibe plus atorvastatin vs atorvastatin	-9.8	-7.9	0.9 (NS)	-12.7
	-12.9	-10.1	5.8	-0.5 (NS)
Ezetimibe plus simvastatin vs atorvastatin	-6.9	-3.1	2.6	-13.6
Ezetimibe plus simvastatin vs simvastatin plus placebo	-27	-18.4	0.8 (NS)	-5.4

* $p<0.05$ in all comparisons unless otherwise stated, 95% confidence intervals not given.
LDL-c, low-density lipoprotein cholesterol; Total-c, total cholesterol; HDL-c, high-density lipoprotein cholesterol; TG, triglyceride; NS, not statistically significant.

3.1.2 Results from shorter-term studies of ezetimibe coadministered with a statin versus a statin alone

The Assessment Group carried out a meta-analysis of shorter-term studies (less than 12 weeks in duration) comparing ezetimibe coadministered with statin therapy with statin therapy alone. Meta-analysis of the five studies identified (6 to 8 weeks in duration) showed that the addition of ezetimibe to statin therapy reduced LDL-c by 23% more than statin therapy alone. It should be noted that the 12-week studies (table 2) included a washout period of ongoing lipid-regulating drugs, whereas in the shorter-term studies, ezetimibe was given to people in addition to their ongoing statin therapy. The manufacturer also conducted a meta-analysis of five 6 to 8-week studies which found that ezetimibe coadministered with statin therapy reduced LDL-c by 23% more than statin therapy coadministered with placebo.

3.1.3 Ezetimibe coadministered with a statin versus other lipid-lowering drugs coadministered with a statin

One statin titration study, available as a conference abstract only, was identified that compared ezetimibe plus simvastatin with niacin plus atorvastatin or rosuvastatin. Low-to-moderate doses of atorvastatin/rosuvastatin plus niacin achieved similar LDL-c reductions and greater HDL-c increases in this study compared with the highest doses of rosuvastatin monotherapy or ezetimibe coadministered with simvastatin. No further details on clinical effect were given.

3.1.4 Ezetimibe monotherapy versus placebo

Seven studies that compared ezetimibe monotherapy with placebo were used to represent the population of people in the scope 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 reduction in LDL-c and Total-c levels compared with placebo, as shown in table 2. This trend of therapy effect was consistent across all studies and moderate heterogeneity was identified. The meta-analysis also showed that ezetimibe was associated with a statistically significant improvement in HDL-c and TGs compared with placebo.

3.1.5 Ezetimibe monotherapy versus other lipid-lowering drugs other than a statin

No RCTs were identified that directly compared the efficacy and safety of ezetimibe monotherapy with other lipid-lowering drugs.

3.1.6 Subgroups

Four studies demonstrated LDL-c lowering effects of treatment across subgroups such as different ethnic groups and people with or without conditions such as CVD, diabetes and HeFH. None of the subgroup comparisons was statistically significant. All other trials reported that the effect of ezetimibe on LDL-c was generally consistent across all subgroups without any further discussion.

The Assessment Group carried out an additional subgroup analysis of the effect of ezetimibe in people with or without HeFH. This analysis was based on one study that included data on these subgroups and some additional unpublished data obtained from the authors of the study. Ezetimibe coadministered with atorvastatin was compared with atorvastatin alone, and statin doses were titrated. The study found that, after 14 weeks, treatment with ezetimibe plus atorvastatin was associated with significant changes in both groups: LDL-c levels decreased by 34.6% in the HeFH group and by 31.1% in the non-HeFH group, and Total-c decreased by 27.0% in the HeFH group and by 24.7% in the non-HeFH group. The Assessment Group concluded that the greater reductions in LDL-c and Total-c levels in the HeFH group were not statistically significant. It further concluded that the trial was probably powered to only detect a difference between the treatment strategies rather than differences in the treatment effect between the two groups.

3.1.7 Health-related quality of life

The Assessment Group did not identify any studies that directly reported effects on the health-related quality of life of people receiving ezetimibe monotherapy or coadministered with a statin.

3.1.8 Adverse events

Ezetimibe coadministered with a statin was found to have a similar adverse event profile to statin therapy alone, with 63% and 65% of study participants, respectively, reporting adverse events. Of these, 18.5% of people in the ezetimibe plus statin arm and 17.5% in the statin-only arm were considered to have experienced a treatment-related adverse event. The number of people that discontinued treatment because of adverse events was similar across both treatment groups (5.9% in the ezetimibe plus statin arm and 4.9% in the statin-only arm).

Ezetimibe monotherapy was found to have a similar adverse event profile to placebo, with 63% and 61% of study participants, respectively, reporting adverse events. The most commonly reported adverse events were musculoskeletal disorders (2–5%) and upper respiratory infections (7–11%).

Of all adverse events, 9–20% were considered treatment-related. However, no trials reported any serious treatment-related adverse events.

The Assessment Group suggests that the low frequency of adverse events observed could be due to the relatively short time periods of the studies. The long-term adverse effects of ezetimibe are not known.

3.1.9 Evidence on linking changes in lipids to clinical outcomes

Given that none of the studies of ezetimibe reports clinical endpoints, the Assessment Group summarised the evidence on linking changes in lipids to clinical outcomes. Numerous clinical outcome trials have established that lowering LDL-c is associated with a reduced risk of CV events in people with or at high risk of CVD, the strongest evidence coming from systematic reviews and meta-analyses of clinical studies.

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-c was associated with a 23% reduction in the 5-year incidence of a coronary event (non-fatal MI or death from CHD) and a 21% reduction in major coronary events, coronary revascularisation and stroke. An earlier meta-analysis of statins, published in 2003, which investigated the relationship between LDL-c reduction and the risk of CHD events in 58 trials covering 148,321 participants, found that a reduction in LDL-c of 1.0 mmol/litre reduced the risk of CHD events by up to 36% over a treatment course of 6 years or more, regardless of initial risk.

Although the majority of evidence for the benefits of lowering LDL-c is derived from RCTs of statins, treatment to lower LDL-c levels is associated with CV outcome benefits independent of the treatment used. A meta-analysis of data from nine trials of non-statin treatments (bile acid sequestrants, surgery and diet) and ten trials of statin treatments, including a total of 81,859 participants, was published in 2005. When the relationship between LDL-c levels and CHD risk was assessed it was found that larger reductions in LDL-c are associated with greater reductions in CHD, with no difference between the statin and non-

statin trials. These results are consistent with an earlier meta-analysis, published in 1998, that assessed non-statin cholesterol-lowering therapies (including bile acid sequestrants, fibrates, nicotinic acid, surgery and diet), and with the results of the CTTC analysis.

3.2 Cost effectiveness

3.2.1 Published economic evaluations

The Assessment Group identified two published papers and one abstract that assessed the cost effectiveness of ezetimibe. Of these, only the study detailed in the abstract was based in the UK. One of the papers expressed outcomes in terms of life-years gained (LYG), whereas the other paper and the abstract reported outcomes in terms of quality-adjusted life years (QALYs). The three analyses are country-specific evaluations using a core economic model known as the Cook model.

The first published cost-effectiveness study was based in Germany, Spain and Norway. The model compared ezetimibe coadministered with three statin-only strategies using simvastatin and atorvastatin. The first treatment strategy looked at ezetimibe coadministered with current statin therapy versus current statin therapy with no titration. In the second strategy, for people whose lipid levels did not reach their goals, the statin dose was titrated up to the maximum dose recommended per country. The third strategy compared ezetimibe plus statin therapy with a 'titrate to goal' where all people received treatment that was titrated up to the highest daily dose approved. In Germany and Spain the treatment goal was LDL-c of 2.59 mmol/litre and in Norway the treatment goal was Total-c of 5.0 mmol/litre. Costs and benefits were discounted annually at 3%. The incremental cost per LYG ranged from £7.6K to £49.9K depending upon treatment strategy used and whether the patient had a history of CHD or diabetes.

The second published cost-effectiveness study was based in Canada and looked at the cost effectiveness of adding ezetimibe to statin therapy (atorvastatin) in patients whose cholesterol levels had not reached the treatment goal. Treatment strategies included ezetimibe plus fixed-dose statin

therapy versus fixed-dose statin monotherapy, and ezetimibe plus fixed-dose statin therapy versus statin titration. The primary analysis focused on people aged 65 years at very high risk of CHD with baseline LDL-c levels of 3.1 or 3.6 mmol/litre. The treatment goal was LDL-c levels lower than 2.5 mmol/litre. All costs were adjusted to 2002 prices, and cost and benefits were discounted annually at 5%. The incremental cost per QALY ranged from £26.2K to £45.9K.

The third cost-effectiveness study, published in abstract form only, was based in Scotland. The model compared ezetimibe plus statin therapy with statin titration and statin therapy without titration in people whose Total-c levels had not reached their goal of 5.0 mmol/litre or less. The people in this study were an average age of 65 years, had a history of CVD and had an average Total-c of 6.1 mmol/litre. The discounted incremental cost per QALY for ezetimibe plus statin therapy versus statin monotherapy was £8.3K, whereas for ezetimibe plus statin therapy versus statin titration the discounted cost per QALY was £8.9K.

3.2.2 Economic evaluations submitted by the manufacturer

Merck Sharp and Dohme Limited and Schering-Plough Limited (MSD-SP) submitted two models: the 'Cook' model, an adaptation of the model used in the published economic evaluations above, and the 'Basic' model.

In the Cook model, several scenarios have been used to evaluate the cost effectiveness of ezetimibe plus statin therapy in people currently taking statins whose lipid levels are not adequately controlled. 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. Alternative scenarios compared ezetimibe plus a low-cost statin with a more potent, high-cost statin. Ezetimibe monotherapy was also compared with no treatment in people who do not tolerate statin therapy or in whom statins are contraindicated.

The Cook model uses Markov processes to model nine discrete health states. Benefits of treatment were modelled using changes in Total-c and HDL-c

levels derived from previously published meta-analyses. Algorithms from the Framingham study were used to predict future CV 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 costs of CHD events (angina, MI and fatal CHD) and monitoring were based on values used in the 2004 statins assessment report with the costs of CHD events inflated to 2006. Treatment costs were generally based on drug tariffs, and sales figures representing the type and dose of statin used in practice were used to derive a weighted average cost of statin treatment for the base-case analysis. The health-related utilities for the various health states and utilities by age were also based on the 2004 statins assessment report.

In this model, a 1-year cycle was used and probabilities were recalculated each year based on changes in age, CVD history and lipids. No limit has been placed on the number of events a person can have. Costs and benefits accrue over a maximum period of 50 years, with analyses terminating when people reach 99 years of age. A UK NHS perspective was used and costs and benefits have been discounted at 3.5%. Further information on the model structure and inputs is given on pages 77 to 82 of the assessment report.

The results from the Cook model are summarised on page 84 of the assessment report. For the base-case scenarios, the costs per QALY of ezetimibe plus current statin therapy range from just under £8K to just under £122K. For ezetimibe monotherapy versus no treatment, the costs per QALY range from just under £10K to just over £131K. The highest incremental cost-effectiveness ratios (ICERs) are for South Asian men, aged 60 years, at a high risk of an event, with a baseline Total-c of 6.5 mmol/litre. By contrast, the lowest ICERs are for women aged 80 years, with no history of CVD, and with a baseline Total-c of 4.5 mmol/litre.

The probabilistic results suggest that, using a threshold of £20K per QALY, ezetimibe coadministered with weighted statin therapy compared with titrated statin therapy is cost effective for men with a history of CVD. The exception to

this is men aged 80 years with a Total-c of 4.5 or 5.5 mmol/litre. For women, the probabilistic results suggest that none of the treatment regimens is cost effective using a £20K per QALY threshold, with the exception of women with diabetes.

The second model submitted by MSD-SP, known as 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 and the key methods and assumptions used in the model are listed on page 83 of the assessment report.

The model evaluated two treatment comparisons using baseline LDL-c levels of 3.0, 3.5, 4.0 and 4.5 mmol/litre. The first treatment comparison considered ezetimibe plus a weighted average dose of generic and branded statins versus a weighted average dose of generic and branded statins alone. The second treatment comparison considered ezetimibe plus simvastatin versus atorvastatin.

In contrast to the Cook model, the Basic model uses published evidence from a meta-analysis conducted by the CTTC on the link between chemically induced reductions in LDL-c and corresponding reductions in CV events.

The authors of the model conclude that the Basic model gives similar results to those calculated using the Cook model. For further details, see page 84 of the assessment report.

3.2.3 The Assessment Group's critique of the manufacturer's economic evaluations

The Assessment Group considered the Cook model to have a reasonable and flexible structure but identified a number of major errors that creates uncertainties around the robustness of the results.

For example, the calculations and assumptions used to predict risks in the Cook model were considered by the Assessment Group to be inaccurate. Some of the errors were found to under-predict risk and benefits from treatment, whereas others were found to over-predict risk and benefits. In addition, the Assessment Group considered that the methods used to

distribute predicted risks to event type were inappropriate, overestimating benefits of treatment. The Assessment Group also noted that there were errors in the health state, monitoring and treatment costs, some of which were found to underestimate costs whereas others overestimated costs.

A further limitation of the Cook model was its use of algorithms from the Framingham study to predict CV events when only surrogate outcome measures are available. The Assessment Group's main criticism of this methodology is that the algorithms were not formulated to predict and continually re-evaluate risks based on chemically induced changes in cholesterol. Furthermore, the Assessment Group argued that this methodology has now been superseded because of evidence published by the CTTC that enables chemically induced changes in lipids, based on a meta-analysis of statins, to be linked to reductions in CV risk.

The Basic model uses the preferred methodology of linking chemically induced lipid changes to reductions in CV risk but it was designed to give approximate results only. Again, the Assessment Group considered the treatment and health state costs to be incorrect in this model.

The Assessment Group did not attempt to correct the errors detected or to modify the methods used in the models and it concluded that the results were not robust. Because the errors found were often conflicting (some overestimating and others underestimating effects), the Assessment Group considered that it was not possible to quantify the magnitude or the direction of impact on the ICERs.

3.2.4 The Assessment Group's economic analysis: methods

The Assessment Group developed a probabilistic Markov model to estimate the cost effectiveness of ezetimibe in four different scenarios.

- Scenario 1 – people who are tolerant to statins, and whose lipid levels have not achieved the UK target on current statin therapy, are treated with ezetimibe coadministered with current statin therapy or with current statin therapy titrated to the next dose.

- Scenario 2 – people in whom statins are contraindicated or not tolerated are treated with ezetimibe monotherapy or with no treatment.

- Scenario 3 – people who are tolerant to statins, and whose lipid levels have not achieved the UK target on current statin therapy, are treated with ezetimibe coadministered with generic simvastatin (that is, simvastatin marketed under its generic [chemical] name rather than a brand name) or are switched to atorvastatin.

- Scenario 4 – people who are tolerant to statins and require more potent treatments to achieve UK lipid targets, such as people with HeFH, are treated with ezetimibe coadministered with atorvastatin, or with rosuvastatin as monotherapy.

Framingham risk equations were used to derive baseline risks in the model. Effectiveness of treatments was modelled using a reported link between chemically induced changes in lipids and reductions in CV risk from the CTTC meta-analysis. Distribution across event types was based on UK-specific incidence and prevalence rates. The Assessment Group's meta-analysis of data from published ezetimibe 12-week studies was used to inform efficacy of treatments in lowering LDL-c levels. Lipid-regulating drugs other than statins, such as nicotinic acid, bile acid resin and fibrates, were not included in the model as comparators owing to a lack of robust evidence on effectiveness rates (for statin-tolerant people) or expert opinion (for people intolerant or contraindicated to statins).

Given the dependence on short-term surrogate outcomes, a 20-year time horizon was considered to be appropriate. However, additional results are reported that assess the costs and benefits accrued when using a 5-year or a lifetime horizon and truncating treatment at 2, 5 or 10 years but accruing costs and benefits associated with events avoided over 20 years.

For the main analysis, three different baseline LDL-c measurements were assumed: mild (3.0 mmol/litre), moderate (3.5 mmol/litre) and high (4.0 mmol/litre). Results are reported as incremental cost per QALYs gained and presented by age (45, 55, 65 and 75 years), sex, and whether they are for

primary or secondary prevention populations. The analysis was conducted from a UK NHS perspective and a discount rate of 3.5% on costs and benefits was applied.

Two subgroup analyses were carried out by the Assessment Group. The first analysis was conducted in people with diabetes and the second in people with HeFH. The evidence available on ezetimibe effectiveness in people with and without diabetes is not reported in sufficient detail to establish whether there is a significant difference in the effectiveness of ezetimibe in these populations. However, people with diabetes are at an increased risk of CVD and it was therefore assumed in the model that primary event rates are twice as high in this population than in people without diabetes.

For people with HeFH, the baseline risk of a primary event in the model was assumed to be twice that of those without HeFH. Baseline LDL-c measurements modelled for people with HeFH were 4.0, 5.0, 6.0 and 7.0 mmol/litre. It was assumed that people with HeFH require more potent statin treatment; consequently the treatment regimen described in scenario 4 was used for this subgroup. The analysis was based on a non-statistically significant difference in effectiveness rates from the one study that presented results for people with HeFH, and on baseline LDL-c values that are outside the range of values used to establish the link between LDL-c and reductions in CV events.

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 British national formulary (BNF, August 2006). The cost of current statin therapy for scenario 1 is a weighted cost based on published data on prescribing rates in England in 2005. (Note: these data were collected prior to publication of NICE guidance on the initiation of statin therapy). For scenario 3, statin costs were based on 50% of people being treated receiving a 20-mg dose of simvastatin/atorvastatin and the remaining 50% receiving 40 mg. The fixed-

dose combination tablet containing ezetimibe and simvastatin (20 mg or 40 mg) was not considered because it costs more than ezetimibe plus a generic statin (20 mg or 40 mg). In scenario 4, it was assumed that 75% of people being treated with statins receive atorvastatin/rosuvastatin 20 mg and 25% receive the 40-mg dose of the respective drug. The costs of treatment-related adverse events were not included. Where necessary, costs used in the economic analysis were adjusted to 2006 prices. Further details of the estimates of resources and costs used in the economic analysis are provided on pages 105 to 107 of the assessment report.

Health-related utility data were obtained from published studies where available and were adjusted for age using data from a large UK-population-based survey using the EQ-5D (Note: this may lead to some double-counting of disutility as the reduction in utility associated with increased age will be in some part due to coronary-related comorbidities). It is assumed that the side effects of the treatment regimens will be small in comparison to the potential benefits and no reduction in utility has therefore been modelled. Further details on health-related utility are given on pages 107 to 110 of the assessment report.

The Assessment Group's model is based on the following key assumptions.

- There are no treatment benefits during the first year.
- Treatment with ezetimibe plus a statin has a compliance rate comparable to statin monotherapy. Compliance rates are therefore not modelled.
- Statin titration of one dose provides an additional reduction in LDL-c of 6%, based on a published meta-analysis of RCT evidence.
- Short-term lipid changes will be maintained over long time periods and changes in lipids levels will translate into reductions in CV events.
- The relationship between statin-induced changes in LDL-c and reductions in CV events is generalisable to ezetimibe-induced changes in LDL-c.
- There are no serious long-term effects of ezetimibe.

Full details of the methods used are provided in pages 91 to 111 of the assessment report.

3.2.5 The Assessment Group's economic analysis: results

A summary of the ICERs for scenarios 1 to 4 are presented in table 4.

Table 4 Summary of ICERS for scenarios 1 to 4

	Primary prevention (£)	Secondary prevention (£)
Scenario 1[a] Ezetimibe coadministered with current statin therapy vs titration of current statin therapy to next dose	48K to 144K	104K to 299K
Scenario 2[a] Ezetimibe monotherapy vs no treatment	26K to 361K	57K to 810K
Scenario 3[a] Ezetimibe coadministered with generic simvastatin vs atorvastatin	4K to 93K	8K to 201K
Scenario 4[b] Ezetimibe coadministered with atorvastatin vs rosuvastatin	14K to 43K	38K to 128K

[a] Scenarios 1 to 3: incremental cost-effectiveness ratios (ICERs) vary by age, sex, baseline low-density lipoprotein cholesterol (LDL-c) levels (3.0, 3.5, 4.0 mmol/litre) and time horizon (5 years, 20 years, lifetime, truncating treatment at 2, 5 or 10 years but accruing costs and benefits associated with events avoided over 20 years).
[b] Scenario 4: ICERs are estimated for a 20-year time horizon and vary by age, sex and baseline LDL-c (4.0, 5.0, 6.0, 7.0 mmol/litre).

Key patterns in the ICERs are as follows.

- The ICERs decrease as the time horizon increases.
- If the base-case 20-year time horizon is used, the results are generally of a similar magnitude across all ages.
- If a lifetime horizon is used, the ICERs increase by age and are slightly higher for women than men of the same age. The lifetime results suggest that it is more cost effective to commence treatment at a younger age.

- The results are more cost effective for cohorts with higher baseline LDL-c levels.

- The results are less cost effective for people with a history of CVD. The Assessment Group state this is because they commence the analysis in a health state that incurs ongoing costs and disutilities, whereas people with no history of CVD are in an event-free health state and only incur treatment costs.

- Univariate sensitivity analysis (using a baseline LDL-c of 3.5 mmol/litre and a 20-year time horizon) revealed that the results for scenarios 1 to 3 are most sensitive to the effectiveness rates used, to the values used to translate reductions in LDL-c levels to CV events avoided, to the health-related quality of life utilities, and to the time lag used for applying effectiveness. Sensitivity analyses were not presented for scenario 4.

3.2.5.1 Scenario 1

Table 4 shows that, irrespective of age, sex, baseline LDL-c and the time horizon used, all the ICERs estimated by the Assessment Group for scenario 1 are at least £48K for people without a history of CVD and at least £104K for people with CVD.

The results of the probabilistic sensitivity analysis for scenario 1 demonstrate that, using a threshold of £30K per QALY, ezetimibe plus current statin treatment versus current statin treatment titrated by one dose is not cost effective. Key results of the univariate analysis are summarised in table 5.

A separate analysis was conducted for people with diabetes using a 20-year time horizon and varying baseline LDL-c levels. This resulted in ICERs of at least £38K for people without a history of CVD and of at least £110K for people with CVD. Probabilistic sensitivity analysis was not conducted for people with diabetes.

Table 5 Results of univariate sensitivity analyses for scenarios 1 to 3: variables with the largest impact on the results

	Effect on ICERs		
	Scenario 1	**Scenario 2**	**Scenario 3**
Using effectiveness rates from shorter-term studies where people received ezetimibe without a washout period	Almost 50% reduction	Not applicable	75% reduction
RR on events corresponding to reduction in LDL-c	20% reduction using lower 95% CI and 30% increase using upper 95% CI	As scenario 1	40–45% reduction using lower 95% CI and 30% increase using upper 95% CI
Constant utility by age	20% reduction at 45 years of age and 30% reduction at 75 years of age	As scenario 1	As scenario 1
Health-related utility values associated with CV events decreased by 10%	12% increase for people with CVD and a 13% reduction for people without CVD	12% increase for people with CVD and a 14% reduction for people without CVD	As scenario 2
Health-related utility values associated with CV events increased by 10%	10% reduction for people with CVD and a 19% increase for people without CVD	As scenario 1	10% reduction for people with CVD and an 18% increase for people without CVD
Varying the time lag for applying effectiveness (0 or 2 years)	20% increase/reduction at 75 years of age and 10% increase/reduction at 45 years of age	20% increase/reduction at 75 years of age and 12% increase/reduction at 45 years of age	28% increase or reduction at 75 years of age and 15% increase/reduction for people aged 45 years

ICERs, incremental cost-effectiveness ratios; RR, relative risk; LDL-c, low-density lipoprotein cholesterol; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease.

3.2.5.2 Scenario 2

Table 4 shows that the ICERs in scenario 2 range from £26K to £361K for primary prevention cohorts and from £57K to £810K for secondary prevention cohorts. The lowest ICERs are based on a lifetime horizon, as summarised in table 6.

Table 6 Summary of incremental cost-effectiveness ratios (ICERs) by time horizon for scenario 2[a]

	Primary prevention (£)	**Secondary prevention (£)**
5 years	242K to 361K	384K to 810K
20 years	43K to 64K	70K to 129K
Lifetime	26K to 61K	57K to 118K
Truncating treatment at 2, 5 or 10 years but accruing costs and benefits associated with events avoided over 20 years	60K to 82K (2 years)	89K to 170K (2 years)
	38K to 55K (5 years)	57K to 110K (5 years)
	33K to 54K (10 years)	53K to 105K (10 years)
[a] A baseline low-density lipoprotein cholesterol (LDL-c) level of 3.5 mmol/litre is assumed.		

The results of the probabilistic sensitivity analysis suggest that, assuming a threshold of £30K per QALY, ezetimibe monotherapy versus no treatment is not cost effective. Key results of the univariate analysis are summarised in table 5.

A separate analysis for people with diabetes using a 20-year time horizon and varying baseline LDL-c levels resulted in ICERs of at least £58K for people with a history of CVD. For people with diabetes but without a history of CVD, ICERs range from £19K to £42K. ICERs are below £30K in men and women in all age groups where the baseline LDL-c was 4.0 mmol/litre, and in men in all age groups where the baseline LDL-c was 3.5 mmol/litre. Probabilistic sensitivity analysis was not conducted for people with diabetes.

3.2.5.3 Scenario 3

Table 4 shows that the ICERs in scenario 3 range from £4K to £93K for primary prevention cohorts and from £8K to £201K for secondary prevention cohorts.

At a baseline LDL-c of 3.5 mmol/litre, ICERs are below £30K in men and women in all age groups with or without a history of CVD where the time horizon used was 20 years or a lifetime.

Additional results were presented using a 20-year time horizon and varying the baseline LDL-c level. At a baseline LDL-c of 3.0 mmol/litre, ICERs are below £18K in men and women in all age groups without a history of CVD and below £29K for men of all ages with a history of CVD. For women with a history of CVD, ICERs range from £27K to £36K, being higher among older cohorts. For more details, see table 47 on page 131 of the assessment report.

Assuming treatment stops at 2, 5 or 10 years (but measuring the costs and benefits of events avoided over a 20-year period) results in ICERs below £20K for all cohorts without a history of CVD. For cohorts with CVD, ICERs are below £26K when treatment is truncated at 5 or 10 years and between £18K and £42K when treatment is truncated at 2 years.

The results of the probabilistic sensitivity analysis suggest that, assuming a threshold of 30K per QALY, ezetimibe plus generic simvastatin versus atorvastatin monotherapy is cost effective for all cohorts irrespective of age, sex or CVD history. The majority of results are also cost effective assuming a threshold of £20K per QALY. Key results of the univariate analysis are summarised in table 5. Separate results for people with diabetes were not presented.

3.2.5.4 Scenario 4

ICERs were estimated for a 20-year time horizon only and presented by age, sex and baseline LDL-c levels of 4.0, 5.0, 6.0 and 7.0 mmol/litre. For primary prevention cohorts at baseline LDL-c levels of 4.0, 5.0, 6.0 and 7.0 mmol/litre, ICERs range from £29K to £43K, from £22K to £33K, from £17K to £27K and

from £14K to £22K, respectively. For secondary prevention cohorts, all ICERs are at least £38K. Univariate and probabilistic sensitivity results were not presented for scenario 4.

4 Issues for consideration

4.1 Clinical effectiveness

- All of the trials are short-term and none report clinical endpoints. Is it reasonable to assume that short-term lipid changes will be maintained over long time periods and translate into reductions in CV events?

- Owing to the lack of information on pre-trial treatment history, previous treatment success and the washout periods used in the study designs, the populations in the RCTs might not accurately reflect the target population. The effectiveness of adding ezetimibe to existing treatment regimens in routine clinical practice could be underestimated or overestimated.

- There is no statistically significant evidence to suggest that ezetimibe is more or less effective in any subgroup.

4.2 Adverse events

- There might be long-term adverse effects associated with ezetimibe that are not yet known.

4.3 Cost effectiveness

- The Assessment Group's economic model uses a reported link between statin induced changes in lipids and reductions in CV risk. There is currently no evidence to support the assumption that this relationship is generalisable to ezetimibe-induced changes in LDL-c. There is, however, evidence that treatment to lower LDL-c levels is associated with CV outcome benefits independent of the treatment used.

- There is further uncertainty in the cost effectiveness results owing to: the need to translate changes in surrogate outcomes to reductions in CV

events and to extrapolate well beyond the RCT evidence; the lack of robust clinical-effectiveness evidence derived from people whose lipid levels fail to achieve their goals on optimal statin therapy or people who are intolerant to statins; and the assumption that there are no serious long-term effects of ezetimibe.

- For people who are tolerant to statin therapy, the Assessment Group estimated the cost effectiveness of ezetimibe using three scenarios (scenarios 1, 3 and 4), which produced very different results. In each scenario, a strategy of adding ezetimibe to current statin therapy is compared with a strategy of increasing the dose or potency of current statin therapy. Which scenario best reflects the place of ezetimibe in the pathway of care?

- The Assessment Group's cost-effectiveness analysis for people who require more potent statins to achieve lipid targets (scenario 4), is based on a non-statistically significant difference in effectiveness rates for people with and without HeFH and on baseline LDL-c values that are outside the range of values used to establish the link between LDL-c and reductions in CV events. These factors increase the uncertainty around the results for this subgroup.

- Which effectiveness rates should inform the economic analyses? The Assessment Group's analysis uses data from a meta-analysis of 12-week studies, which included a washout period of ongoing lipid-regulating drugs. However, when data for scenarios 1 and 3 are derived from a meta-analysis of 6 to 8 studies, where ezetimibe was given to people in addition to their ongoing statin therapy, the ICERs fall by 50% and 75%, respectively.

- There is insufficient evidence to establish whether there is a difference in effectiveness rates between alternative regimens involving ezetimibe coadministered with a statin. The results of the Assessment Group's economic evaluation are therefore entirely dependent on the incremental cost of the treatment strategies being used.

- The Assessment Group's cost-effectiveness results vary according to the time horizon used and are most favourable when a lifetime horizon is used. A lifetime horizon captures all costs and benefits as a result of treatment, but greater uncertainty results from extrapolating the data beyond the 12-week RCTs used to inform the analysis.

- The Assessment Group's cost-effectiveness results are more favourable in primary prevention than secondary prevention populations. This differs from the results of the economic model for the statins appraisal, whereby the results were more favourable in secondary prevention populations. The Assessment Group note that this is because people with CVD commence the analysis in a health state that incurs ongoing costs and disutilities, whereas people with no history of CVD commence the analysis in an event-free health state and only incur treatment costs.

- Lipid-regulating drugs, other than statins, were not included in the Assessment Group's model as comparators owing to a lack of robust evidence on effectiveness rates (for statin-tolerant people) or expert opinion (for people intolerant or contraindicated to statins).

5 Ongoing research

The following ezetimibe trials are expected to report in 2008–10.

- The ENHANCE study –ezetimibe plus simvastatin versus simvastatin monotherapy in people with HeFH using mean change in carotid artery intima-media thickness as a marker of early atherosclerosis.

- The SHARP study – the effect on major vascular events of ezetimibe plus simvastatin versus placebo in patients with chronic kidney disease.

- The IMPROVE IT study - the effect on CV outcomes of ezetimibe plus simvastatin compared with simvastatin monotherapy in treating high-

risk patients with coronary artery disease presenting with acute coronary syndromes.

- The SEAS trial in aortic stenosis patients – the effect on major CV events of ezetimibe plus simvastatin versus placebo in people with asymptomatic atherosclerosis.

6 Authors

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7 Appendix A. Sources of evidence considered in the preparation of the overview

A Ara R, Tumur I, Pandor A et al, The University of Sheffield, School of Health and Related Research, *Ezetimibe for the treatment of hypercholesterolaemia,* December 2006.

B Submissions from the following organisations:

I Manufacturer/sponsors:

- Merck Sharp and Dohme Limited and Schering-Plough Limited

II Professional/specialist and patient/carer groups:

- The British Cardiac Society and the Royal College of Physicians (joint submission)
- Diabetes UK
- Heart UK
- The Primary Care Cardiovascular Society
- The Royal College of General Practitioners
- The South Asian Health Foundation