NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (review of TA132)

Draft scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ezetimibe within its licensed indication for treating primary hypercholesterolaemia in adults.

Background

Hypercholesterolaemia is the presence of high concentrations of cholesterol in the blood, typically including elevated low-density lipoprotein (LDL) cholesterol. Primary hypercholesterolaemia is associated with an underlying genetic cause, which may be caused by a single genetic defect (familial), or more commonly, by the interaction of several genes with dietary and other factors such as smoking or physical inactivity (non-familial). In heterozygous-familial hypercholesterolaemia, one of the pair of LDL cholesterol receptor genes is defective or mutated and impairs the LDL cholesterol receptor activity.

Most people with hypercholesterolaemia have cholesterol concentrations that are only mildly or moderately elevated, and show no clinical symptoms. Severe hypercholesterolaemia, however, can cause xanthomas (lesions on the skin containing cholesterol and fats) and arcus corneae (cholesterol deposits in the eyes).

Primary non-familial hypercholesterolaemia affects about 4% of the adult population, totalling approximately 1.5 million people in England, of whom an estimated 600,000 are diagnosed and 460,000 are receiving treatment. Primary heterozygous-familial hypercholesterolaemia affects an estimated 1 in 500 people, totalling 106,000 in England (although only 15–17% are diagnosed).

People 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 (atherosclerosis). The narrowed arteries can cause diseases such as angina, myocardial infarction and stroke, particularly in familial hypercholesterolaemia. CVD is a common cause of death in the UK, accounting for approximately 160,000 deaths in 2011, and it is a major cause of disability and reduced quality of life.

The current management of primary hypercholesterolaemia involves dietary and lifestyle changes such as smoking cessation, weight loss and increased physical activity. The initiation of therapy with a lipid-regulating drug is generally based on an assessment of the person's cardiovascular risk. Statins are usually the first-choice drugs, but other lipid-regulating drugs such as fibrates, nicotinic acid derivatives or bile acid sequestrants may also be used. NICE clinical guideline 181 recommends that when a decision is made to prescribe a statin, a statin of high intensity and low acquisition cost should be used. It recommends atorvastatin 20 mg for the primary prevention of CVD in people who have a 10% or greater 10-year risk of developing CVD, as estimated using the QRISK2 assessment tool.

NICE technology appraisal 132 recommends ezetimibe as an option for treating heterozygous familial hypercholesterolaemia, as a monotherapy when statins are contraindicated or not tolerated and in combination with statins when initial statin therapy does not provide appropriate control of LDL-cholesterol.

The technology

Ezetimibe (Ezetrol, Merck Sharp and Dohme) is a cholesterol absorption inhibitor that blocks the intestinal absorption of dietary and biliary cholesterol and related plant sterols, without affecting the uptake of triglycerides or fat-soluble vitamins. Because of this mechanism of action, ezetimibe can be combined with a statin to provide complementary cholesterol reduction. Ezetimibe is administered orally at a dose of 10 mg once daily.

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

A fixed-dose combination of ezetimibe and simvastatin (ezetimibe 10 mg; simvastatin either 20, 40 or 80 mg) is available (Inegy, Merck Sharp and Dohme). It has a marketing authorisation in the UK as an adjunctive therapy to diet for primary heterozygous-familial or non-familial hypercholesterolaemia that is not appropriately controlled with a statin alone, or that has already been treated with a statin and ezetimibe.

Intervention(s)	Ezetimibe alone or in combination with a statin
Population(s)	People with primary heterozygous familial or non-familial hypercholesterolaemia: • whose condition is not appropriately controlled with a statin alone **or** • in whom a statin is considered inappropriate or is not tolerated.
Comparators	For people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone: • Optimal statin therapy For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated: • Other lipid regulating drugs
Outcomes	The outcome measures to be considered include: • survival/mortality • fatal and non-fatal cardiovascular events • coronary events • stroke • change in LDL cholesterol • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	Appropriate control of cholesterol concentrations should be based on individualised risk assessment in line with NICE clinical guideline 71. Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 132, November 2007, 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia'. Related Guidelines: Clinical Guideline No. 181, July 2014, 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease'. Review Proposal Date September 2016. Clinical Guideline No. 71, August 2008, 'Identification and management of familial hypercholesterolaemia'. Review Proposal Date September 2016. Related Quality Standards Quality Standard No. 41, August 2013, 'Familial hypercholesterolaemia'. Review Proposal Date August 2018. http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp Related NICE Pathways NICE Pathway: Familial hypercholesterolaemia, Pathway created: August 2013. http://pathways.nice.org.uk/
Related National Policy	National Service Frameworks: Coronary Heart Disease

Questions for consultation

The IMPROVE-IT study evaluated the effect of adding ezetimibe to simvastatin 40 mg on a primary endpoint comprising a composite of cardiovascular death, myocardial infarction, unstable angina requiring rehospitalisation, coronary revascularisation, or stroke:

- Primary endpoint events occurred in 34.7% of the control group versus 32.7% of the treatment group, representing a relative risk reduction of

6.4% (HR 0.936, CI 0.887 to 0.988, p=0.016) and an absolute risk reduction of 2%.

- Overall, there was a 10% reduction in the risk of combined cardiovascular death, non-fatal MI, or non-fatal stroke (HR 0.90, CI 0.84 to 0.97, p=0.003). However, there was no difference in cardiovascular death or death from any cause.

Is it appropriate to review the guidance on ezetimibe (NICE technology appraisal guidance 132) based on this new evidence or should the guidance be moved to the static list?

Have all relevant comparators for ezetimibe been included in the scope? Which treatments are considered to be established clinical practice in the NHS for primary hypercholesterolaemia?

- For people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone, should a statin in combination with other lipid-regulating drugs (such as fibrates, bile acid sequestrants, and nicotinic acid/acipimox) be included as a comparator?
- For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated, which lipid-regulating drugs (for example, fibrates, bile acid sequestrants, and nicotinic acid/acipimox) would be considered comparators?

Are there any subgroups of people in whom ezetimibe is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider ezetimibe will fit into the existing NICE pathway, Familial hypercholesterolaemia?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which ezetimibe is licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider ezetimibe to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of ezetimibe can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)