NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Final 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.

NICE technology appraisal 132 recommends ezetimibe as an option for treating primary (heterozygous familial or non-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. 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.

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: • plasma lipid and lipoprotein levels, including LDL cholesterol, non-HDL cholesterol, apolipoprotein B and lipoprotein a • requirement of procedures including LDL apheresis and revascularisation • fatal and non-fatal cardiovascular events • coronary events • stroke • mortality • 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	Guidance will only be issued in accordance with the marketing authorisation. If the evidence allows, consideration will be given to the following subgroups: • Presence or risk of cardiovascular disease • People with heterozygous familial hypercholesterolaemia • People with statin intolerance • Severity of hypercholesterolaemia
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