NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Mipomersen for the prevention of cardiovascular events due to homozygous or severe heterozygous familial hypercholesterolaemia

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of mipomersen within its licensed indication for the prevention of cardiovascular events in people with homozygous or severe heterozygous familial hypercholesterolemia.

Background

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 familial hypercholesterolaemia (FH), or more commonly, polygenic hypercholesterolaemia where a number of genes interact with dietary and other factors such as physical inactivity. FH is characterised by raised low-density lipoprotein (LDL) cholesterol concentrations in the blood from birth that persists throughout life and can lead to the early development of atherosclerosis and coronary heart disease.

Most people with FH have inherited a defective gene for FH from only one parent and are therefore heterozygous (He-FH). The elevated serum LDL cholesterol concentration (typically defined as a LDL cholesterol level above 4.9mmol/l) that characterise He-FH lead to a greater than 50% risk of coronary heart disease by the age of 50 years in men and at least 30% in women by the age of 60 years. The prevalence of He-FH in the UK population is estimated to be 1 in 500, affecting approximately 122,000 people. Severe He-FH is a small subset of the total He-FH population and includes people who are on maximally tolerated lipid lowering therapies with LDL cholesterol level ≥5.2 mmol/L plus coronary heart disease or LDL cholesterol level ≥7.8mmol/L who are at high risk of coronary heart disease.

Rarely, a person will inherit a genetic defect from both parents and will have homozygous FH (Ho-FH). In Ho-FH, LDL cholesterol levels are markedly elevated (typically greater than 13 mmol/l). People with Ho-FH are at particular risk of developing premature cardiovascular disease because long-term elevations of cholesterol accelerate the build up of fatty deposits in the arteries, a process known as atherosclerosis. If untreated, people with Ho-FH generally die before the age of 30 years. The prevalence of Ho-FH in the UK population is estimated to be 1 in one million, affecting approximately 61 people.

A number of interventions are used for the management of familial hypercholesterolaemia. NICE Clinical Guideline 71 (CG71) recommends that statins should be the initial lipid lowering pharmacological treatment. Where appropriate dose titration of initial statin therapy fails to control LDL cholesterol, or in cases of intolerance of dose titration, ezetimibe, coadministered with initial statin therapy is recommended. Ezetimibe monotherapy is recommended if the initial statin therapy is contraindicated or there is intolerance to statins. CG71 further recommends that people with FH with intolerance or contraindications to statins or ezetimibe should be referred to a specialist and consider treatment with either a bile acid sequestrant (resin), nicotinic acid, or a fibrate. CG71 recommends LDL apheresis for the treatment of people with Ho-FH if their condition does not respond to lipid-modifying drug therapy. CG71 also recommends LDL apheresis for the treatment of people with He-FH in exceptional instances for example when a patient also has progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy.

The technology

Mipomersen (Kynamro, Genzyme) is a short antisense nucleic acid polymer which interferes with the production of apolipoprotein B-100. Apolopoprotein B-100 is the main protein component of LDL, which in high levels can lead to the development of atherosclerosis. It is administered by subcutaneous injection.

Mipomersen does not currently have a UK marketing authorisation. It has been studied as an adjunctive treatment to conventional lipid lowering therapies compared with placebo plus lipid lowering therapy in people with Ho-FH. It has also been studied in people with severe He-FH (LDL-C ≥ 5.2 mmol/L) and coronary heart disease, and in people with severe He-FH (LDL-C ≥ 7.8 mmol/L) who are at high risk of coronary heart disease.

Intervention(s)	Mipomersen in combination with maximum tolerated doses of lipid lowering therapy
Population(s)	People at high risk of cardiovascular events due to homozygous familial hypercholesterolaemia or severe heterozygous familial hypercholesterolaemia which has not been adequately managed with maximally tolerated lipid lowering treatment
Comparators	• Best supportive care (without mipomersen) • LDL-apheresis

Outcomes	The outcome measures to be considered include: • fatal and non-fatal cardiovascular events • mortality • adverse effects of treatment • health-related quality of life. Where information on clinical end-points is unavailable, consideration may be given to surrogate end-points such as LDL cholesterol and apolipoprotein B levels, if an association of the surrogate measure with survival or health-related quality of life has been clearly demonstrated.
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 the following subgroups will be considered: • people with different types of familial hypercholesterolemia (homozygous and heterozygous) • people with severe He-FH with LDL cholesterol levels ≥5.2 mmol/L and coronary heart disease and people with severe He-FH with LDL cholesterol levels ≥7.8 mmol/L at high risk of coronary heart disease

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 132, November 2006, Ezetimibe for the treatment of primary (heterozygous familial and non familial) hypercholesterolemia. Review under consideration. Related Clinical Guidelines: Clinical Guideline No. 67, May 2008 (reissued March 2010), 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease'. Currently being updated. Earliest date of publication TBC. Clinical Guideline No. 71, Aug '2008 (reissued August 2011), Familial hypercholesterolaemia: identification and management of familial hypercholesterolaemia'. Review date: August 2014.