Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

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

Draft scope (Pre-referral)

Draft 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, non-familial hypercholesterolaemia where a number of genes interact with dietary and other factors such as smoking and physical inactivity. FH is characterized by raised 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 low-density lipoprotein (LDL) cholesterol concentration (typically defined as a LDL cholesterol level above 4.9mmol/l) that characterise heterozygous 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 with LDL cholesterol levels >5.2 mmol/L while on a maximally tolerated dose of lipid lowering therapy, or >7.8 mmol/L for people with or without 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) with other forms of cholesterol remaining normal. 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 thirty. 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. NICE clinical guideline 71 further recommends that people with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist for consideration for 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 they have coronary heart disease or if they are not responding to lipid-modifying drug therapy. CG71 also recommends LDL apheresis for the treatment of people with He-FH in exceptional instances for example when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy.

The technology

Mipomersen (Kynamro, Genzyme Therapeutics) is a short 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 and in people with He-FH and coronary heart disease. It has also been studied in people with severe hypercholesterolemia (LDL-C ≥ 5.2 mmol/L) and coronary heart disease, and in people with hypercholesterolemia (LDL-C ≥ 2.6 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 risk of cardiovascular events due to homozygous familial hypercholesterolaemia or severe heterozygous familial hypercholesterolaemia which has not been adequately managed with lipid lowering treatment
Comparators	Standard management without mipomersen

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) • severity of hypercholesterolemia • presence of coronary heart disease or other risk factors

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, Review decision date: November 2011. 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'. Review decision date: September 2011. Clinical Guideline No. 71, Aug '2008 (reissued August 2011), Familial hypercholesterolaemia: identification and management of familial hypercholesterolaemia'. Review date: August 2014

Questions for consultation

Is the definition of severe heterozygous familial hypercholesterolaemia appropriate? How many people have severe He-FH in England and Wales?

Would mipomersen also be considered as an appropriate treatment for people with moderate He-FH?

Is mipomersen likely to be used as monotherapy for people with familiar hypercholesterolaemia?

Have the most appropriate comparators for mipomersen for the prevention of cardiovascular events due to homozygous familial hypercholesterolaemia and severe heterozygous familial hypercholesterolaemia been included in the scope?

- How should standard management without mipomersen be defined?
- Should the comparators for Ho-FH and He-FH be different?

Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of patients in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Please consider whether in the remit or the scope there are any issues relevant to equality. Please pay particular attention to whether changes need to be made to the remit or scope in order to promote equality, eliminate unlawful discrimination, or foster good relations between people who share a characteristic protected by the equalities legislation and those who do not

share it, or if there is information that could be collected during the assessment process which would enable NICE to take account of equalities issues when developing guidance.

Do you consider mipomersen 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 the technology 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)