NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of alirocumab within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia.

Background

Dyslipidaemia is a broad term describing a number of conditions, including hypercholesterolaemia, hyperlipidaemia and mixed dyslipidaemia, in which disturbances in fat metabolism lead to changes in the concentrations of lipids in the blood. 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).

Mixed dyslipidaemia is defined as elevations in LDL cholesterol and triglyceride levels that are often accompanied by low levels of high-density lipoprotein (HDL) cholesterol.

It is estimated that 6 in 10 adults in England have cholesterol levels above 5 mmol/litre. 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 high cholesterol 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). CVD is a common cause of death in England, accounting for approximately 148,000 deaths in 2012, and it is a major cause of disability and reduced quality of life.

The current management of primary hypercholesterolaemia and mixed dyslipidaemia involves dietary and lifestyle changes such as smoking cessation, weight loss and increased physical activity. NICE clinical guideline 181 for lipid modification to prevent cardiovascular disease and NICE clinical guideline 71 for familial hypercholesterolaemia recommend initial treatment with statins. NICE technology appraisal 132 recommends ezetimibe as an option for treating primary 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. LDL apheresis (a process similar to dialysis which removes low density lipoprotein from the blood stream) may be considered in exceptional instances for people with heterozygous familial hypercholesterolaemia.

The technology

Alirocumab (brand name unknown, Sanofi and Regeneron) is a fully-human monoclonal antibody that targets proprotein convertase subtilisin/kextin type 9 (PCSK9). It prevents degradation of LDL receptors in the liver, thereby facilitating LDL clearance from circulation and lowering LDL-C levels in the blood. It is self-administered subcutaneously.

Alirocumab does not currently have a marketing authorisation in the UK for primary hypercholesterolaemia and mixed dyslipidaemia. It has been studied in clinical trials in adults with primary heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia or mixed dyslipidaemia compared with placebo, statins with or without ezetimibe, and ezetimibe alone.

Intervention(s)	Alirocumab
Population(s)	People with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-modifying therapies, in line with current NICE guidance, would be considered.
Comparators	• Ezetimibe in combination with a statin (when optimised statin therapy does not appropriately control LDL-C) • Ezetimibe (when statins are contraindicated or not tolerated)

Outcomes	The outcome measures to be considered include: • plasma lipid and lipoprotein levels, including LDL cholesterol and non-HDL cholesterol • requirement of procedures including LDL apheresis and revascularisation • fatal and non-fatal cardiovascular events • 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	If the evidence allows, consideration will be given to the following subgroups: • Presence or risk of cardiovascular disease • Patients with heterozygous familial hypercholesterolaemia • Patients with statin intolerance • Severity of hypercholesterolaemia Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
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'. Earliest anticipated date of publication May 2016. Proposed Technology Appraisal, 'Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia'. Publication TBC.

	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 tbc. Clinical Guideline No. 71, August 2008, 'Identification and management of familial hypercholesterolaemia'. Review Proposal Date August 2014. Related Quality Standards Quality Standard No. 41, August 2013, 'Familial hypercholesterolaemia'. Review Proposal Date August 2018. http://www.nice.org.uk/guidance/QS41 Related NICE Pathways NICE Pathway: Familial hypercholesterolaemia, Pathway created: August 2013. http://pathways.nice.org.uk/pathways/familial-hypercholesterolaemia NICE Pathway: Cardiovascular disease prevention, Pathway created: July 2014. http://pathways.nice.org.uk/pathways/cardiovascular-disease-prevention
Related National Policy	National Service Frameworks: Coronary Heart Disease Department of Health (2013): NHS Outcomes Framework 2014–2015 NHS England (November 2012) Inherited Heart Disease Services - Familial hypercholesterolaemia: services for these patients are commissioned by Clinical Commissioning Groups. Source: Manual for prescribed specialised services Page 32

Questions for consultation

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

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

Where do you consider alirocumab 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 alirocumab will be 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 alirocumab 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 alirocumab 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/article/pmg19/chapter/1-Introduction)