

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**Single Technology Appraisal****Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia****Final scope****Remit/appraisal objective**

To appraise the clinical and cost effectiveness of evolocumab 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, 1 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 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 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 (currently being reviewed) 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

Evolocumab (Repatha, Amgen) is a monoclonal antibody which inhibits an enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9) involved in down-regulation of low-density lipoprotein receptors. Evolocumab therefore increases receptor density and lowers LDL- cholesterol. It is administered by subcutaneous injection.

Evolocumab does not currently have a marketing authorisation in the UK for primary hypercholesterolaemia and mixed dyslipidaemia. It has been studied in clinical trials for treating primary hypercholesterolemia and mixed dyslipidaemia, both alone (as a monotherapy) and in combination with other lipid-modifying therapies, compared with placebo, ezetimibe, statins and other lipid-modifying therapies.

Intervention(s)	Evolocumab alone or in combination with a statin with or without ezetimibe, or in combination with ezetimibe.
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	<ul style="list-style-type: none"> • When optimised statin therapy does not appropriately control LDL-C: <ul style="list-style-type: none"> ○ Ezetimibe in combination with a statin • When statins are contraindicated or not tolerated: <ul style="list-style-type: none"> ○ Ezetimibe
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • 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 • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>
Other considerations	<p>If the evidence allows, consideration will be given to the following subgroups:</p> <ul style="list-style-type: none"> • Presence or risk of cardiovascular disease • People with heterozygous familial hypercholesterolaemia • People with statin intolerance • Severity of hypercholesterolaemia <p>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.</p>

<p>Related NICE recommendations and NICE Pathways</p>	<p>Related Technology Appraisals:</p> <p>Technology Appraisal No. 132, November 2007, 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia'. Currently being reviewed, earliest anticipated date of publication May 2016.</p> <p>Proposed Technology Appraisal, 'Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia'. Earliest anticipated date of publication TBC.</p> <p>Related Guidelines:</p> <p>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.</p> <p>Clinical Guideline No. 71, August 2008, 'Identification and management of familial hypercholesterolaemia'. Review Proposal Date September 2016.</p> <p>Related Quality Standards:</p> <p>Quality Standard No. 41, August 2013, 'Familial hypercholesterolaemia'. Review Proposal Date August 2018.</p> <p>http://www.nice.org.uk/guidance/QS41</p> <p>Related NICE Pathways:</p> <p>NICE Pathway: Familial hypercholesterolaemia. Pathway created August 2013.</p> <p>http://pathways.nice.org.uk/pathways/familial-hypercholesterolaemia</p> <p>NICE Pathway: Cardiovascular disease prevention, Pathway created: July 2014.</p> <p>http://pathways.nice.org.uk/pathways/cardiovascular-disease-prevention</p>
<p>Related National Policy</p>	<p>National Service Frameworks: Coronary Heart Disease</p> <p>Department of Health (2013): NHS Outcomes Framework 2014–2015</p> <p>NHS England (November 2012) Inherited Heart Disease Services - Familial hypercholesterolaemia: services for these patients are commissioned by Clinical Commissioning Groups. Source: Manual for prescribed</p>

	specialised services Page 32
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