NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Evolocumab for treating hyperlipidaemia and mixed dyslipidaemia (excluding homozygous familial hypercholesterolaemia)

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of evolocumab within its licensed indication for hyperlipidaemia and mixed dyslipidaemia (excluding homozygous familial hypercholesterolaemia).

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 defined as a raised level of cholesterol in the blood, typically including elevated low-density lipoprotein cholesterol (LDL-C). Hyperlipidaemia refers to raised cholesterol and/or raised triglycerides, and mixed dyslipidaemia is a wider term that encompasses hyperlipidaemia as well as decreased levels of high-density lipoprotein cholesterol (HDL-C). Along with other risk factors, dyslipidaemia may lead to the development of atherosclerosis and cardiovascular disease.

Primary dyslipidaemia – that is, dyslipidaemia that arises spontaneously and is not caused by another condition or treatment – may be caused by a mixture of environmental factors and genetic predisposition (termed ‘non-familial’) or by an inherited genetic defect (termed ‘familial’). In particular, familial hypercholesterolaemia may be heterozygous (inherited from 1 parent) or, rarely, homozygous (inherited from both parents). People with familial hypercholesterolaemia have marked elevations in cholesterol and are at particular risk of developing premature cardiovascular disease. This appraisal includes people with hyperlipidaemia or mixed dyslipidaemia, including heterozygous familial hypercholesterolaemia; homozygous familial hypercholesterolaemia is a distinct condition, affecting a different population and with a different prognosis and treatment pathway, and so is excluded from this appraisal.

It is estimated that 6 in 10 adults in England have cholesterol levels above 5 mmol/litre, and more than half of cardiovascular disease-associated events are attributed to high cholesterol. Primary non-familial hyperlipidaemia 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. Familial hypercholesterolaemia is less common, with

heterozygous familial hypercholesterolaemia affecting an estimated 1 in 500 people, totalling 106,000 in England (although only 15–17% are diagnosed).

Management of dyslipidaemia involves a combination of lifestyle changes (such as diet changes, weight loss, stopping smoking and alcohol reduction) and lipid-modifying drugs including statins, ezetimibe, nicotinic acid, fibrates and bile acid sequestrants (anion exchange resins). For lipid modification to prevent cardiovascular disease, NICE clinical guideline 67 recommends statins as initial therapy, with fibrates, nicotinic acid and bile acid sequestrants recommended for secondary prevention of cardiovascular disease in people who are not able to tolerate statins. For familial hypercholesterolaemia, NICE clinical guideline 71 recommends statins as the initial treatment. Treatment with a bile acid sequestrant, nicotinic acid or a fibrate is recommended for people with intolerance or contraindications to statins or ezetimibe. LDL-C 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. NICE technology appraisal 132 recommends ezetimibe as an option for heterozygous 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-C.

The technology

Evolocumab (brand name unknown, Amgen) is a monoclonal antibody which targets an enzyme involved in the regulation of lipid levels in the blood, known as proprotein convertase subtilisin/kexin type 9 (PCSK9). Evolocumab is administered by subcutaneous injection.

Evolocumab does not currently have a marketing authorisation in the UK. It has been studied in clinical trials for treating hyperlipidaemia 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 other lipid-modifying therapies
Population(s)	People with hyperlipidaemia or mixed dyslipidaemia (excluding homozygous familial hypercholesterolaemia) for whom lipid-modifying therapies would be considered in line with current NICE guidance

Comparators	• Statins
	• Ezetimibe (when statins are contraindicated or not tolerated)
	• Ezetimibe in combination with a statin (when initial statin therapy does not appropriately control LDL-C)
	• When statins and ezetimibe are not tolerated:
	  ○ Fibrates
	  ○ Nicotinic acid
	  ○ Bile acid sequestrants

Outcomes	The outcome measures to be considered include: • plasma lipid and lipoprotein levels, including LDL-C • 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 evidence allows, consideration will be given to subgroups according to risk of cardiovascular disease. Homozygous familial hypercholesterolaemia is excluded from this appraisal. 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	Related Technology Appraisals:

recommendations and NICE Pathways	Technology Appraisal No. 132, Nov 2007, 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia'. Review in progress, expected Jan 2016. Technology Appraisal No. 94, Jan 2006, 'Statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease'. Review in progress, within update of clinical guideline 67. Related Guidelines: Clinical Guideline No. 71, Aug 2008, 'Identification and management of familial hypercholesterolaemia'. Review proposal date Aug 2014. Clinical Guideline No. 67, May 2008, 'Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease'. Update in progress, expected July 2014. Related Quality Standards: Quality Standard No. 41, Aug 2013, 'Familial hypercholesterolaemia'. Review proposal date not specified. Related Diagnostics Guidance: Diagnostics Guidance No. 2, Dec 2011, 'Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia'. Related NICE Pathways: NICE Pathway: Familial hypercholesterolaemia. Pathway created Aug 2013: http://pathways.nice.org.uk/pathways/familial-hypercholesterolaemia
Related National Policy	Department of Health, March 2000, 'National Service Framework for Coronary Heart Disease'

Questions for consultation

For which patient groups would evolocumab be used in clinical practice? Would it be considered only for people for whom statins are contraindicated, not tolerated or unable to provide appropriate control of LDL-C?

Have all relevant comparators for evolocumab been included in the scope?

- Which treatments are considered to be established clinical practice in the NHS for hyperlipidaemia and dyslipidaemia?

- Is nicotinic acid commonly used for treating these conditions?
- How frequently is LDL-C apheresis used to treat heterozygous familial hypercholesterolaemia?

Have all relevant outcomes been included in the scope?

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

Where do you consider evolocumab 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 evolocumab 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 evolocumab 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 evolocumab 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)