NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of bempedoic acid within its marketing authorisation for treating primary hypercholesterolaemia or 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 (non-familial).

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.

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 124,641 deaths in 2017[1], and it is a major cause of disability and reduced quality of life.

Approximately 7% of the population in England have been diagnosed with primary (familial and non-familial) hypercholesterolaemia, totalling approximately 3.5 million people in England, of whom about a third are receiving lipid-modifying treatment[2]. Primary heterozygous familial

hypercholesterolaemia is estimated to affect between 1 in 250 and 1 in 500 people, totalling approximately 130,000 to 260,000 in England (although only 15–17% are diagnosed).

Managing 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 385 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. NICE technology appraisals 393 and 394 recommend alirocumab and evolocumab as options for treating primary hypercholesterolaemia and mixed dyslipidaemia, depending on LDL concentrations. 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

Bempedoic acid (brand name unknown, Esperion Therapeutics, UK commercialisation by Daiichi Sankyo) is a pro-drug that is activated in the liver. It inhibits adenosine triphosphate citrate lyase, increasing clearance of LDL-cholesterol. It is administered as an oral tablet, either alone or as a fixed dose combination with ezetimibe.

Bempedoic acid does not currently have a marketing authorisation in the UK for treating primary hypercholesterolaemia or mixed dyslipidaemia. It has been studied in clinical trials alone and with ezetimibe or other lipid-modifying therapy compared with placebo or ezetimibe in people with hyperlipidaemia or hypercholesterolaemia.

Intervention(s)	• Bempedoic acid, alone or with a statin, with or without other lipid-lowering therapy • Bempedoic acid in a fixed dose combination with ezetimibe, alone or with a statin
Population(s)	People with primary hypercholesterolaemia or mixed dyslipidaemia
Comparators	When statins are contraindicated or not tolerated: • Ezetimibe • Evolocumab (with or without another lipid-lowering therapy) • Alirocumab (with or without another lipid-lowering

	therapy) When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C: • Ezetimibe (when evolocumab and alirocumab are not appropriate) • Evolocumab (with or without another lipid-lowering therapy) • Alirocumab (with or without another lipid-lowering therapy) When maximally tolerated statin dose does not appropriately control LDL-C: • Ezetimibe with a statin • Evolocumab with a statin (with or without another lipid-lowering therapy) • Alirocumab with a statin (with or without another lipid-lowering therapy) When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: • Ezetimibe with a statin (when evolocumab and alirocumab are not appropriate) • Evolocumab with a statin (with or without another lipid-lowering therapy) • Alirocumab with a statin (with or without another lipid-lowering therapy)
Outcomes	The outcome measures to be considered include: • 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	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.

	If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.
Other considerations	If the evidence allows the following subgroups will be considered: • Presence or risk of cardiovascular disease • People with heterozygous familial hypercholesterolaemia • People 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: Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (2016). NICE technology appraisal 393. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (2016). NICE technology appraisal 394. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (2016). NICE technology appraisal 385. Review date to be confirmed. Related guidelines: Cardiovascular disease: risk assessment and reduction,

	including lipid modification (2014). NICE guideline CG181. Reviewed 2018 - update to be scheduled. Familial hypercholesterolaemia: identification and management (2008, updated 2017). NICE guideline CG71. Related quality standards: Cardiovascular risk assessment and lipid modification (2015). NICE quality standard 100. Familial hypercholesterolaemia (2013). NICE quality standard 41. Related NICE Pathways: Cardiovascular disease prevention (2017) NICE Pathway Familial hypercholesterolaemia (2017) NICE Pathway.
Related National Policy	NHS England (2018) Manual for prescribed specialised services 2018/19 Chapter 7 section C Inherited Cardiac Condition Services NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Department of Health and Social Care (2016) NHS Outcomes Framework 2016-2017: Domains 1 and 2.

References

1 British Heart Foundation. England Factsheet, November 2018. Accessed November 2018

2 NHS Digital. Use of NICE appraised medicines in the NHS in England – 2010 and 2011, Experimental statistics: Report, October 2012. Accessed March 2019.