NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Final scope

Remit/evaluation objective

To appraise the clinical and cost effectiveness of evinacumab within its marketing authorisation for treating homozygous familial hypercholesterolaemia in people aged 12 years and over.

Background

Familial hypercholesterolaemia (FH) is an inherited disorder where the liver is incapable of metabolising or removing excess low-density lipoprotein cholesterol (LDL-C) caused by a genetic defect.[1] This can lead to very high LDL-C levels which increase the risk of premature cardiovascular disease (CVD). There are 2 forms of FH: homozygous and heterozygous. Homozygous FH (HoFH) is much less common than heterozygous FH and is more severe. In HoFH, the inherited gene mutations affecting LDL-C is from both parents (so the individual has 2 genetic mutations).[2]

The Clinical Commissioning Policy for lomitapide estimates that the prevalence of HoFH is between 1 in 670,000 adults and 1 in 1 million people in England.[3] According to the 2020 mid-year population estimates, this would equate to between 48 and 72 people aged 12 and over with HoFH in England.[4] However, HoFH is likely to be underdiagnosed and may affect as many as 1 in 160,000 to 1 in 300,000 people, equating to between 161 and 302 cases in people aged 12 and over in England.[5]

The signs of HoFH are lumps and bumps around the knuckles or Achilles tendon (caused by cholesterol deposits), yellow cholesterol build-up around the eyes and eyelids, or a pale ring around the iris of the eye.[6] People with HoFH have severe hypercholesterolaemia, with an LDL-C concentration of greater than 13 mmol/l at diagnosis in adults. Long-term exposure to hypercholesterolaemia greatly accelerates the build-up of fatty deposits (atherosclerosis) in the coronary arteries and all major arteries in the body. Cholesterol and calcium deposits can also cause supravalvular aortic stenosis, where the aortic valve becomes narrowed and stiff. This leads to signs of heart failure, including breathlessness, chest pain and blackouts. The first major cardiovascular event in people with HoFH frequently occurs during adolescence, with angina and myocardial infarction in early childhood.[7] If left untreated, people with HoFH typically live to around 18 years old.[8] Around 25% of patients have LDL receptor (LDLR)-negative HoFH, which means they have less than 2% of normal LDL receptor activity. This results in a worse prognosis and lower response to current treatments compared with HoFH that is LDLR defective (who have 2 to 25% of normal LDL receptor activity).[9]

Treatment for HoFH follows a stepped approach. LDL-C concentrations are assessed periodically, and if they are above target levels then clinicians can consider adding the next treatment to reduce them. NICE clinical guideline 71 recommends statins as the initial treatment for all adults with FH in addition to dietary and lifestyle

advice. But people with HoFH are unlikely to achieve LDL-C targets with this approach. The Heart UK consensus statement on the management of HoFH says all adults should be offered a statin combined with ezetimibe.[9] Bile acid sequestrant can then be added, if required. If LDL-C concentration remains above targets, evolocumab can be offered to people with HoFH that is LDLR defective or unknown. Depending on a person's response to lipid-modifying drug therapy and the presence of coronary heart disease, healthcare professionals should consider offering LDL apheresis (a process similar to dialysis which removes cholesterol from the blood stream). Lomitapide can then be considered for adults who are at high risk of CVD and whose HoFH is not adequately controlled by existing treatments, including statins, ezetimibe, evolocumab (if appropriate) and LDL apheresis. If disease progression occurs despite treatment with lipid-lowering treatment and LDL apheresis, liver transplantation can be considered. For children, LDL apheresis should be started as soon as possible, combined with a statin and ezetimibe. Bile acid sequestrant may also be added. Evolocumab should be considered from the age of 12 if treatment targets are not achieved.

The technology

Evinacumab (Evkeeza, Ultragenyx) has marketing authorisation in the UK as an adjunct to diet and other LDL-C lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with HoFH.

Intervention(s)	Evinacumab as an adjunct to diet and other LDL-C lowering therapies
Population(s)	People with homozygous familial hypercholesterolaemia aged 12 years and over
Subgroups	If the evidence allows the following subgroups will be considered: • People aged 12 to 17 years inclusive • Presence or level of risk of cardiovascular disease • Mutational status (e.g. LDLR status, compound heterozygotes, double heterozygotes)
Comparators	**For people aged 18-years and older:** Established clinical management without evinacumab (including but not limited to statins, diet and lifestyle changes, ezetimibe, lomitapide, evolocumab and LDL apheresis) **For people aged 12-17:** Established clinical management without evinacumab (including but not limited to statins, diet and lifestyle changes, ezetimibe, evolocumab and LDL apheresis)
Outcomes	The outcome measures to be considered include:

	• plasma lipid and lipoprotein levels, including LDL-C, 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. 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	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	**Related technology appraisals:** Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (2021) NICE technology appraisals guidance TA694 Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (2016) NICE technology appraisals guidance TA393 Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (2016) NICE technology appraisals guidance TA394 Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia NICE technology appraisals guidance (2016) NICE technology appraisals guidance TA385

	Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia (2021) NICE technology appraisals guidance TA733 **Related NICE guidelines:** Familial hypercholesterolaemia: identification and management (2008 updated 2019) NICE guideline CG71 **Related quality standards:** Familial hypercholesterolaemia (2013) NICE quality standard QS41
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018) Clinical Commissioning Policy: Lomitapide for treating homozygous familial hypercholesterolaemia (adults) NHS England (2018) NHS England Funding and Resource 2018/19: Supporting 'Next Steps for the NHS Five Year Forward View' NHS England (2018) Manual for prescribed specialised services 2018/19 Chapter 7 section C Inherited Cardiac Condition Services Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 and 2. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

References

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4. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2020 (2021). Accessed November 2022.

5. Cuchel, M., et al. (2014). Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. European heart journal, 35(32), 2146-2157

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7. Sharifi M et al. (2016) Cardiovascular risk stratification in familial hypercholesterolaemia. Heart 102(13): 1003-8

8. Thompson, Gilbert R., et al. Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol. European Heart Journal 39.14 (2018): 1162-1168.

9. France M et al. (2016) HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. Atherosclerosis 255: 128-139