NICE National Institute for Health and Care Excellence

Highly Specialised Technologies (HST) criteria checklist

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over TA ID 2704

Introduction

The NICE HST criteria checklist is to highlight where a technology meets/partially meets or does not meet the criteria for routing to the HST programme. Its purpose is to show the details of why a technology may not be appropriate for HST evaluation, but also where it has been identified as suitable. For more information, please see section 7 of NICE health technology evaluation topic selection: the manual

Key – Please use the colour key to advise if the technology meets the criteria

Met	There is clear and strong evidence that the criterion is met
Not met	There is no evidence or limited evidence that the criterion is met.

MA wording: Treating homozygous familial hypercholesterolaemia in people aged 12 and over

Number	Criterion	Description of how the technology meets the criteria	Does the technology meet the criteria?
1.	The disease is very rare defined by 1:50,000 in England	The scoping report states the following: Prevalence estimates for homozygous familial hypercholesterolaemia (HoFH) in England range from 1 in 670,000 people to 1 in 1 million people.[1] 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.[2] However, HoFH is likely to be underdiagnosed and	Not met

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		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.[3] If 'the disease' is considered to be familial hypercholesterolaemia (including both homozygous and heterozygous FH), the prevalence is much higher. The prevalence of heterozygous FH in the UK population is estimated to be between 1 in 250 and 1 in 500.[4] The company states that this criterion is met, based on considering the homozygous population only. If the full population is considered (homozygous and heterozygous FH), the criterion is not met. NICE applies this criterion to the full population. Therefore, the criterion is not met.	
2.	Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications	As noted above, the estimated population for the technology in England in its licensed indication is 48-302 people. The scoping report states the following: • *As the company intends to position evinacumab for people unable to achieve LDL-C goals on statins, PCSK9 inhibitors and/or ezetimibe, the actual population size for evinacumab will be lower than this estimate.* The company agrees that this criterion is met. They anticipate that evinacumab will be used as an alternative to lomitapide at the same point in the treatment pathway [redacted] NHS England estimated that in total, 47 people would be eligible for treatment with lomitapide in NHS practice in England. Since evinacumab can be used in a younger age group (12yrs+	Met

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		rather that 18yrs+), the company estimates that approximately 50 to 60 people would be eligible for evinacumab in its proposed positioning. However, for the purpose of this checklist, the full population eligible in its licensed indication should be considered. This is broader than the proposed positioning and includes up to 302 people. There are currently no other licensed indications for evinacumab. It is being studied in severe hypertriglyceridemia.	
3.	The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life	The draft scope (which was changed after the workshop) states the following: *Familial hypercholesterolaemia (FH) is an inherited disorder where the liver is incapable of metabolising or removing excess low-density lipoprotein (LDL) cholesterol caused by a genetic defect. This can lead to very high LDL 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 is from both parents (so the individual has 2 genetic mutations).* *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. People with HoFH have severe hypercholesterolaemia, with an LDL 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.* *The first major cardiovascular event in people with HoFH frequently occurs during adolescence, with angina and myocardial infarction in early childhood. If left untreated,*	Not met

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		people with HoFH typically live to around 18 years old.[5] Around 25% of patients have LDL receptor (LDLR)-negative HoFH, with a worse prognosis and lower response to current treatments compared with HoFH that is either LDLR defective or unknown. However, prompt diagnosis and treatment with existing therapies can improve the prognosis and extend the time to major cardiovascular event. The resulting impact of existing therapies on life expectancy is difficult to quantify, so it is unclear if life is shortened with existing standard of care. Modelling data from South Africa suggests that median life expectancy for people taking lomitapide plus statins, ezetimibe and apheresis is 59.2 years (vs 48.0 years without lomitapide). Of the four models explored in the study this was considered by the authors to be "the most plausible as it is based on risk reductions derived from an actual HoFH population". Other estimates for median life expectancy within the study for people taking lomitapide (using different modelling methodologies), ranged from 50.1-66.6years). However it is unclear how the modelling data compares to the life expectancy of the general population as the sample population was not representative of the wider South African population.[6] Evidence shows that HoFH can impact quality of life. The impact relates to the physical and psychological manifestations of the disease, cardiovascular morbidity, and negative consequences associated with treatment.[7] A meta-analysis found that relative to the general population, HoFH patients demonstrated poorer HRQL in multiple dimensions, including physical functioning (SMD -0.37; 95% CI: -0.60, -0.15), role limitations due to physical health (SMD -0.63; 95% CI: -1.24, -0.02), social functioning (SMD -0.61; 95% CI: -1.19, -0.03), bodily pain (SMD -0.24; 95% CI: -0.46, -0.01), and general health (SMD -1.55; 95% CI: -1.80, -1.31).[8] A recent Dutch study found that the median EQ-5D-5L health utility score for 20 adult patients with HoFH (0.839) was only 5% below the Dutch population (0.887).[9] The	

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		authors said this was due to the use of effective coping mechanisms and high confidence in treatment by a dedicated HoFH centre. It is therefore unclear whether HoFH which is being treated effectively with current standard of care has a 'severe impact' on Quality of Life. The company considers this criteria is met, based on the points below: • There is unanimous agreement amongst clinical experts in lipidology and cardiovascular healthcare that the burden caused by premature death is substantial, even with optimal treatment. This is because lipid targets are difficult to achieve using the currently available therapeutic options.[10] • A retrospective study of patients with HoFH from South Africa and the UK reported that one-third of subjects died during the 25-year follow-up of the study, and 60% experienced a CV event, despite their young age at study entry (median age 15 years, interquartile range 7 to 22 years). They also note that a dose-response relationship was established between LDL-C levels and mortality, with people in the highest LDL-C baseline quartile experiencing significant excess mortality relative to the other groups. They noted that this emphasises the need for effective treatments to reduce LDL-C levels. • The company notes that the median life expectancy seen in the study is a reduction in life expectancy compared with population norms. • The "principal effect of concern with HoFH is the greatly elevated risk of CV events, even with maximal tolerated treatment". They note that serious CV events, such as MI, angina and stroke causes "a catastrophic loss of well-being on an individual level" which has a negative impact on utility. The tech team considers that:	

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		• It is reasonable to conclude that HoFH reduces quality and quantity of life. However there is considerable uncertainty about the size of this effect. • This uncertainty is both due to paucity of data and also the time lag involved in seeing the benefits of optimal treatment (as early treatment reduces lifetime CV risks). • It is therefore unclear whether HoFH, with optimal treatment, shortens life *significantly* or impairs quality of life *severely*. So, it has been categorised as 'Not met'.	
4.	There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.	The current treatment pathway, as per commissioning policy[1] and scope report, is the following: **Availability of satisfactory treatment options**	Not met

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		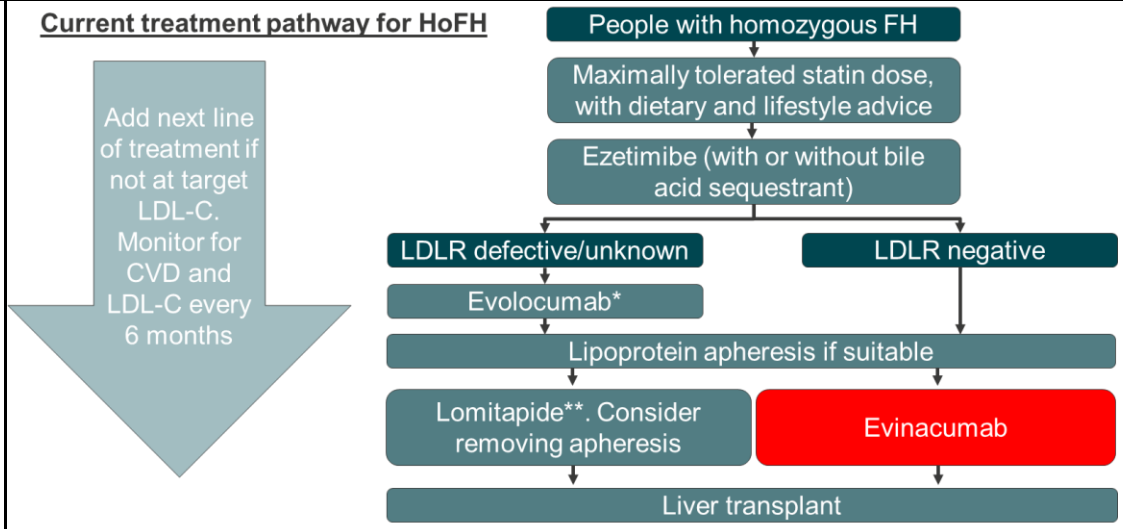 * Alirocumab, another PCSK9 inhibitor, is not approved for HoFH ** Lomitapide recommended through NHSE Clinical Commissioning Policy Existing standard of care is also described by Heart UK and NICE Clinical Guideline No. 71.[11, 4] Lomitapide was agreed to be the most appropriate comparator for people who are able to tolerate lomitapide. For people who are unable to tolerate lomitapide, best supportive care was deemed to be the most suitable comparator for evinacumab. From the treatment pathway, it is clear that other satisfactory treatment options are available, such as statins or ezetimibe, as well as the option of a liver transplant. Existing therapies have varied mechanisms of action and reduce LDL-C levels by 6.0-71%.[12]	

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		The company considers that the criteria is met, based on the following points: • Lomitapide is not suitable for people aged <18 years, so and so cannot be used early in the process of preventing atherosclerosis, despite early treatment being regarded as fundamental in the reduction of lifetime CV risks • Statins and PCSK9 inhibitors are ineffective in people with LDL receptor-negative HoFH (as their effect depends on residual LDL receptor activity). • Some people have tolerability issues with lomitapide (e.g. GI issues) The company cites data from the LOWER registry where 86 patients taking lomitapide (46.5%) experienced adverse events leading to dose reductions, 66 (35.7%) had events that required additional diagnostic testing, and 43 (23.2%) discontinued treatment because of adverse events.[13] These tolerability issues can result in dose reductions, which impact the real world efficacy of lomitapide. • LDL apheresis typically requires outpatient treatment sessions at least once every 2 weeks, which carries and infection risk and can also cause issues with respect to geographical inequality (due to proximity to specialist centres). The technical team acknowledges that: • Not all therapies are suitable or effective for all patients. • Most patients with HoFH do not achieve recommended LDL-C targets and remain at elevated CV risk.[10] • There are unmet clinical needs for people with HoFH However, all patient groups have one or more effective option.	

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		Benefits of evinacumab over existing therapies The company states that evinacumab "offers significant additional benefit over existing treatment options". • Trial data demonstrates that evinacumab can give additional benefit over existing therapies.[14] Among patients receiving maximum doses of background lipid-lowering therapies, LDL cholesterol level reduced by 47.1% in the evinacumab group, compared to a 1.9% increase in the placebo group (at week 24). While there was no event data in the trial, the paper says 'it is well established that LDL cholesterol levels predict cardiovascular risk and that cardiovascular benefit from lipid-lowering therapies is proportional to the absolute reduction in the LDL cholesterol level.' Evinacumab showed benefit regardless of underlying mutational status or background therapies (including statins, ezetimibe, lomitapide, evolocumab and apheresis). The technical team acknowledges that: • Evinacumab is effective in further reducing LDL cholesterol level for people who are already on optimal treatment • This reduction in LDL cholesterol is likely to reduce the risk of CV events • These benefits are not dependent on mutational status, so it is particularly a valuable option for people with LDL receptor (LDLR)-negative HoFH who typically do not respond to statins or PCSK9 inhibitors However the impact on cardiovascular events or life expectancy has not been directly demonstrated and it is unclear whether the observed benefits are 'significant'.	

1. NHS England. Clinical Commissioning Policy: Lomitapide for treating homozygous familial hypercholesterolaemia (adults) (2018). Accessed November 2022.

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

3. FH Europe. Homozygous FH. Accessed November 2022.

4 NICE (2019). Familial hypercholesterolaemia: identification and management [CG71]. Accessed Jan 2023.

5. 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.

6 Leipold, R., Raal, F., Ishak, J., Hovingh, K., & Phillips, H. (2017). The effect of lomitapide on cardiovascular outcome measures in homozygous familial hypercholesterolemia: a modelling analysis. European Journal of Preventive Cardiology, 24(17), 1843-1850.

7 Alothman L, Bélanger AM, Ruel I, Brunham LR, Hales L, Genest J, et al. Health-related quality of life in homozygous familial hypercholesterolemia: A systematic review and meta-analysis. J Clin Lipidol. 2022;16(1):52-65.

8. Alothman, L., Bélanger, A. M., Ruel, I., Brunham, L. R., Hales, L., Genest, J., & Akioyamen, L. E. (2021). Health-related quality of life in homozygous familial hypercholesterolemia: A systematic review and meta-analysis. Journal of Clinical Lipidology.

9 Mulder, J. Wet al. (2022). Quality of life and coping in Dutch homozygous familial hypercholesterolemia patients: A qualitative study. Atherosclerosis, 348, 75-81.

10 Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, et al. 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. Eur Heart J. 2014;35(32):2146-57.

11 Heart UK. Treatment for HoFH. Accessed Jan 2023.

12 Alonso R et al. Current Therapy for Homozygous Familial Hypercholesterolaemia. EMJ. 2021;6[4]:76-86

13 Underberg JA, Cannon CP, Larrey D, Makris L, Blom D, Phillips H. Long-term safety and efficacy of lomitapide in patients with homozygous familial hypercholesterolemia: Five-year data from the Lomitapide Observational Worldwide Evaluation Registry (LOWER). Journal of Clinical Lipidology. 2020;14(6):807-17.

14. Raal, Frederick J., et al. "Evinacumab for homozygous familial hypercholesterolemia." New England Journal of Medicine 383.8 (2020): 711-720.