National Institute for Health and Care Excellence

Health Technology Evaluation

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

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Genetic Alliance UK	This condition sufficiently meets the first three criteria for routing via the HST pathway. With such a small population number this treatment would be a good case to exercise flexibility with regards to the fourth HST criteria, especially as the alternative treatment options available are not entirely effective and most are only available for adults whereas this treatment is applicable to people aged 12 years and older.	Thank you for your comment. Following the consultation it was decided that this topic will proceed as a Single Technology Appraisal, in accordance with the highly specialised technologies routing criteria. This decision was informed by a number of factors, including the availability of existing treatments for people with HoFH. The fact that

Section	Stakeholder	Comments [sic]	Action
			evinacumab is suitable for people aged 12 years or over was part of this consideration.
	HEART UK – The Cholesterol Charity	This is very appropriate as we need more treatments for children and young people. The only current treatment for children is apheresis and this causes a big impact on family and school life.	Thank you for your comment. No action required.
	Ultragenyx	We believe the most appropriate route for the topic is through the NICE Highly Specialised Technologies (HST) programme. This is because evinacumab meets the four criteria for this programme. The company has submitted a separate checklist to support this (Ultragenyx HST checklist – for company).	Thank you for your comment. Following the consultation it was decided that this topic will proceed as a Single Technology Appraisal. This decision was informed by a number of factors, including the availability of existing treatments for people with HoFH. The information provided in the Ultragenyx HST checklist was considered in the decision making.
Wording	Ultragenyx	The wording is aligned with the marketing authorisation and reflects the intended use of evinacumab. It is correct.	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
Timing	HEART UK – The Cholesterol Charity	Even though HoFH is rare and most are likely to be undiagnosed, there is an urgency to conduct this evaluation. Sadly, people will be dying prematurely either without diagnosis or without optimal treatment.	Thank you for your comment. No action required.
	Ultragenyx	As discussed in the checklist to support adoption into the HST programme, many people with HoFH have unmet needs, as clinicians are currently unable to adequately treat all patients with HoFH with existing treatment options. Without adequate management patients are at risk of a significant cardiovascular (CV) event resulting in disability or death. Access to effective treatment is therefore a matter of urgency. Further information is presented in the checklist to support adoption into the HST program.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	HEART UK – The Cholesterol Charity	You state CG71 in this scope document but this is for heterozygous FH and should not be used for HoFH. Therefore we suggest you remove any reference to CG71 and instead refer to the HEART UK Statement of Care – your reference 9.	Thank you for your comment. Adults with FH are defined in CG71 as “all persons with familial hypercholesterolaemia (FH; heterozygous or homozygous) who are 16 years and older.” However it is acknowledged that some of the content is not relevant to HoFH.

Section	Consultee/ Commentator	Comments [sic]	Action
			Additional information from the HEART UK Statement of Care has been added to the background section.
	Ultragenyx	LDL-C terminology 1st and 2nd sentences under the background section. This needs to either include the term 'cholesterol' after LDL (throughout) or define LDL-C at the first mention. Prevalence The draft scope estimates that there are "between 161 and 302 cases [of HoFH] in people aged 12 and over in England". However, the reference for this figure is a patient advocacy website (FH Europe) and we cannot find these data reported in this source. The data seems to have been calculated from the figure of 1 in 160,000 to 1 in 300,000; this should probably be attributed to the 2014 European Atherosclerosis Society (EAS) consensus guidelines (Cuchel et al.,2014) [1]. Estimates concerning the true prevalence of HoFH vary depending on methodology (e.g. extrapolation from known prevalence of HeFH or direct empirical evidence), definitions, and settings. However, although it is believed the condition is under-diagnosed from a global perspective [2], these figures (161 to 302 people in England) are probably an over-estimate, especially the upper limit. In the commissioning document for lomitapide, it was estimated by NHS England that there are between 43 and 66 adult patients in England with HoFH, with around 1 new case of HoFH every year [3].	Thank you for your comment. This has been updated throughout. Thank you for your comment. The reference has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		Signs and symptoms "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" This text is not particularly impactful and could be seen to trivialise the condition (considering the limited word count of the section). We suggest using more scientific language (e.g. xanthomas) and focus on more critical issues (e.g. aortic stenosis). CG71 Citing CG71 should be made with the caveat this guideline is on FH and makes recommendations almost exclusively on HeFH. These are not always relevant to HoFH. Heart UK Consensus (France et al., 2016) would be a better source of information. Treatment The draft scope states that treatment is escalated if LDL-C targets are not met on the current level of treatment. Whilst this is technically true, it could be misleading because the large majority of HoFH patients do not achieve their LDL-C targets, even on maximal levels of treatment available as standard of care. Once all current pharmacological options and LDL apheresis are administered, the only remaining option is liver transplantation. However, this is not usually a viable option due to donor availability A sentence should be added to clarify this.	Thank you for your comment. We aim to use accessible language in our content. Aortic stenosis has been added to the background section. Thank you for your comment. Additional information from the HEART UK Statement of Care has been added to the background section. Thank you for your comment. This section has been amended to note that most people with HoFH do not achieve their LDL-C targets.

Section	Consultee/ Commentator	Comments [sic]	Action
		Mutation status The draft scope states “evolocumab can be offered to people with HoFH that is LDLR defective or unknown”. However, the concept “defective” relative to other terms used to describe LDLR functionality (e.g. deficient, negative) have not been defined. For the purposes of this document it should be simplified that evolocumab is not effective in all HoFH patients. Indication for lomitapide The draft scope states “Lomitapide can then be considered for adults who are at high risk of CVD and whose HoFH is not adequately controlled by existing treatments”. Although this is taken from the NHS England commissioning policy document [3], all HoFH patients are at high risk of CVD, therefore this part of the indication statement is redundant.	Thank you for your comment. The text has been updated to define LDL receptor defective HoFH. Thank you for your comment. The wording has been kept consistent with the NHS England commissioning document for completeness and consistency. No action required.
Population	HEART UK – The Cholesterol Charity	Yes (defined appropriately)	Thank you for your comment. No action required.
	Ultragenyx	The population is correct.	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Subgroups	Ultragenyx	Current subgroups in Scoping document The subgroup “Presence or risk of cardiovascular disease” is redundant as this applies to all patients with HoFH. “Mutational status (e.g. LDLR status, compound heterozygotes, double heterozygotes)”. Whilst it is true that mutational status is an important factor in the consideration of the suitability/efficacy of some drugs (in particular, evolocumab), evinacumab acts independently of LDLR status [4]. This is also thought to be true of lomitapide, although these data were not available in the pivotal trial for this drug [5]. Eligibility for treatment with third-line agents should be decided on the basis of LDL-C levels and cardiovascular risk *irrespective of mutational status.* For these reasons, this subgroup of patients will not be considered in the economic analysis. Additional subgroup of interest	Thank you for your comment. It may still be possible to stratify people by CVD risk/severity, so the wording has been updated to clarify this. . Thank you for your comment. Although evinacumab acts independently of LDLR status, the comparators may vary by LDLR status. If subgroup analysis cannot be conducted, the rationale for this can be included in the company submission. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Another subgroup of interest is people with HoFH aged 12 to 18 years. Evinacumab is indicated for and licensed for this population (termed adolescents), and the company has long-term data to support the efficacy and safety of the drug in this group. We intend to present this data in the submission dossier. Lomitapide is not licensed or indicated in this population therefore there is a specific unmet need in this subgroup that needs to be addressed for reasons of equity and equality.	Thank you for your comment. This subgroup has been added.
Comparators	Ultragenyx	The current comparator described in the draft scope is standard of care: "Established clinical management without evinacumab (including but not limited to statins, diet and lifestyle changes, ezetimibe, lomitapide, evolocumab and LDL apheresis)". **<u>This is incorrect</u>**, as it implies that evinacumab is intended for use as an addition to standard of care, whereas **evinacumab is primarily intended to *replace the use of lomitapide* whilst being used adjunctively with other retained treatments as required.** Lomitapide is currently positioned as a third-line treatment by EAS consensus guidelines (after statins, ezetimibe, PCSK9 inhibitors where indicated, LDL apheresis where indicated) [1]. The NHS England commissioning policy document places lomitapide in the same position of the pathway [3], adding it may be possible to stop LDL apheresis depending on the patient response to lomitapide. Lomitapide has been recommended for use in this context [3]. [redacted] Whilst there are no known negative drug-drug interactions associated with the concomitant use of both lomitapide and evinacumab, with both drugs having different mechanisms of action likely having an additive effect [4], it is expected	Thank you for your comment. The marketing authorisation for evinacumab is not restricted based on prior treatment. It states that evinacumab is indicated as an "adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies". This also reflects the trial population. As such all the comparators listed are relevant. If the evidence allows, a narrower population can be proposed in the submission. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		that this combination would be prohibitively expensive for the NHS. The company contends that evinacumab should therefore be a *replacement* for lomitapide where it is prescribed, due to the following: • It is likely to be more effective than lomitapide (whilst there is a lack of head-to-head trials, this is strongly suggested by the evidence base of each drug). • It has a superior safety profile to lomitapide, with no material issues concerning drug intolerance, adherence, or forced cessation of the drug due to these issues. • It has no important contraindications and can be used in younger people. This rationale will be fully explored in the submission. **For these reasons, it should be made clear in the scope that lomitapide is the principal comparator of interest.** Standard of care without lomitapide would be a secondary comparator in people with HoFH who have not met LDL-C targets and are unable to take lomitapide (e.g. due to age, contraindications, or intolerance). However, this cohort will not be explored in the economic analysis due to a lack of relevant comparative data.	
Outcomes	Ultragenyx	Yes, the included outcomes are appropriate. Regarding the lipid parameters, the full list is as follows: • % reduction in LDL-C • % reduction in Apolipoprotein B • % reduction in Lipo-protein A • % change in TC • % change in TG • % change in HDL	Thank you for your comment. Data on additional outcomes can be included within the company submission for consideration by the committee.

Section	Consultee/ Commentator	Comments [sic]	Action
		• % change in non-HDL cholesterol As well as changes vs. baseline, the proportion of participants in a study achieving predefined LDL-C reductions (≥30%, ≥50%) will be considered. An additional measure that will be considered is the proportion of patients receiving the intervention or comparator that discontinue this treatment and the reasons for this.	
Equality	HEART UK – The Cholesterol Charity	The only issue here could be access to treatment depending on the criteria and where the funds sit – so if the funding is in a local area this could become a postcode lottery as we have seen with other specialist treatments and local authorities deciding not to fund these, therefore leaving patients at major health risk.	Thank you for your comment. When NICE recommends a treatment 'as an option', the NHS must make sure it is available within 3 months (unless otherwise specified) of its date of publication. The NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's technology appraisals.
	Ultragenyx	The current standard of care includes the proposed comparator drug, lomitapide. This drug is not indicated in people aged <18 years, in contrast to evinacumab, which can be used in people ≥12 years. Therefore, there is a specific unmet need in this age group (adolescents). Age is a protected characteristic.	Thank you for your comment. The scope has been updated to include 12-17 year olds as a sub-group. The comparators section

Section	Consultee/ Commentator	Comments [sic]	Action
			has also been updated to reflect that the comparators vary by age group. The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.
Questions for consultation	Ultragenyx	1) *Where do you consider evinacumab will fit into the existing care pathway for homozygous familial hypercholesterolaemia?* Response Evinacumab would be used as an alternative to lomitapide, both in patients who can and cannot take this drug. Typically this will be used as third-line treatment, if lipid targets are not met with treatment with statin + ezetimibe (first line), and evolocumab (second line). Treatment with evinacumab may be combined with LDL apheresis. 2) *Have all relevant comparators for evinacumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for homozygous familial hypercholesterolaemia?* Response The relevant comparator, lomitapide, is not clearly defined in the scope. Evinacumab would be used in addition to other standard of care therapies and instead of lomitapide.	Thank you for your comment. No action required. Thank you for your comment. The scope states that “Lomitapide can then be considered

Section	Consultee/ Commentator	Comments [sic]	Action
			for adults who are at high risk of CVD and whose HoFH is not adequately controlled by existing treatments". A narrower population than that included in the scope can be proposed in the submission. No action required.
		3) ***Are the subgroups suggested appropriate? Are there any other subgroups of people in whom evinacumab is expected to be more clinically effective and cost effective or other groups that should be examined separately*****?** Response No, the first subgroup (presence or risk of cardiovascular disease) is not relevant as this applies to all people diagnosed with HoFH. An additional subgroup of interest is adolescents with HoFH. See above.	Thank you for your comment. People aged 12-18 have been added as a subgroup.
		4) *Would evinacumab be a candidate for managed access?* Unsure at this stage	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		5) *Do you consider that the use of evinacumab can result in any potential 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 committee to take account of these benefits*. <u>Response</u> Evinacumab has demonstrated a favourable safety profile. Its use was not associated with any reduction in health-related quality of life (HRQoL measured using EQ-5D-5L) in the pivotal ELIPSE trial [6]. In contrast, lomitapide has been observed to be the cause of several adverse events and is poorly tolerated by a proportion of people, leading to a high discontinuation rate [5,7,8]. It also requires strict dietary restrictions. The effect of lomitapide on HRQoL has not been directly investigated in any study. However, it is likely that it will have a negative effect on HRQoL that is not captured in the model.	Thank you for your comment. The HRQoL benefits of evinacumab over its comparators can be included in the company submission. No action required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Neonatal and Paediatric Pharmacists Group (NPPG)