NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia [ID765]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **Amgen**
   - **HEART UK**
   - **Royal College of Pathologists**
   - **Merck Sharp & Dohme**

   ‘No comment’ response received from the Department of Health and Royal College of Nursing

   No web comments were received through the NICE Website

3. **Comments on the Appraisal Consultation Document from experts:**
   - Professor A Wierzbicki – clinical expert, nominated by HEART UK

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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.

Comments received from consultees

Consultee	Comment [sic]	Response
Amgen	**Summary** Thank you for the opportunity to respond to the second Appraisal Consultation Document (ACD) for evolocumab issued in January 2016. As noted during the first ACD consultation, we support the Committee's recognition of the clinical need for alternative treatments and their acknowledgement that evolocumab is a new therapy with a novel mechanism of action, which consistently reduced low-density lipoprotein cholesterol (LDL-C) concentrations compared with the current standard of care, while also being well tolerated by patients. We share the Committee's conclusion that evolocumab will likely be reserved for patients who are at particularly high risk of cardiovascular disease (CVD), including patients with heterozygous familial hypercholesterolaemia (HeFH) and those in whom LDL-C is not adequately controlled who are at the highest residual risk and are most vulnerable to cardiovascular (CV) events. We broadly welcome the Committee's revised preliminary recommendations which will allow some small subgroups of high risk patients to access evolocumab in the NHS. We have provided additional comments regarding selected aspects of the preliminary recommendations in this document. **1. Has all of the relevant evidence been taken into account?** We believe all of the relevant evidence has been taken into account. **2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We believe that the overall summaries of the clinical and cost effectiveness in the ACD are reasonable interpretations of the evidence. We have provided additional	Comment noted. Please see detailed responses below. Comment noted. No action required. Comment noted. No action required.

Consultee	Comment [sic]	Response
	information regarding the cost effectiveness results of the populations according to CVD history. **2.1 Cost effectiveness results based on CVD history** We note the Committee's doubts regarding the inconsistent incremental cost-effectiveness ratios (ICERs) in the HeFH population when considering patients with and without CVD. As a consequence, evolocumab is only recommended in a subset of patients with severe HeFH who cannot tolerate statins. As such, we wish to provide further information to support the Committee's interpretation of the cost-effectiveness evidence. ACD Section 4.24 states, *'The Committee noted that the ICERs for people without CVD were actually lower than those for people with CVD. This was inconsistent with the results for non-familial hypercholesterolaemia population and counter-intuitive because people with CVD have a higher risk of CVD, and so would be expected to gain more QALYs from treatment than those without CVD. The Committee heard from the company that people without CVD may be benefitting from the prevention of a first event of CVD. However, it considered that this did not explain why the non-familial hypercholesterolaemia population* without CVD would not benefit in the same manner, and have lower ICERs than the population with CVD.' Thereafter, ACD Section 4.30 states, *'…the Committee had serious doubts about the face validity of the ICERs for the heterozygous-familial hypercholesterolaemia population without CVD, mainly because the ICERs were inconsistent with the results for non-familial hypercholesterolaemia population, and counter-intuitive (see section 4.24). Because of this, it concluded to recommend evolocumab 140 mg every 2 weeks only for the subset of patients with severe heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia who have the highest clinical unmet need; that is, people who cannot tolerate statins.'* We appreciate the results in the HeFH population were deemed to be counter-intuitive given the Committee's interpretation regarding the role of CVD risk in determining the cost-effectiveness results. As clarified during the Apprasial Committee meeting, this form of counter-intuitive result has been documented in previous NICE technology appraisals in this therapy area. This counter-intuitive finding was observed most recently in NICE TA132 (2007) and previously in NICE TA94 (2006). The conclusions from the relevant Assessment Group reports have been extracted and provided below.	Comment noted. The committee noted this additional information. However, it considered that the ICERs for people without CVD would be expected to be higher than those for people with CVD, in line with the results for non-familial hypercholesterolaemia population, for the reasons set out in the FAD (see section 4.22 for further details). In addition, the committee was aware that in the ongoing appraisal of alirocumab the ICERs for heterozygous-familial hypercholesterolaemia were higher for people without CVD than those with CVD. For further details, see FAD sections 4.22 and 4.30.

Consultee	Comment [sic]	Response
	NICE TA132, Ezetimibe for the treatment of hypercholesterolaemia, Assessment Group report[1] (Section 6.3.4, page 140) concludes, *'The results for cohorts with no history of CVD are more cost effective than the results for cohorts with a history of CVD. While this appears to be counter-intuitive, the difference in the results is caused because all individuals in the cohorts with a history of CVD commence the analyses in a health state which incurs ongoing costs and disutilities while cohorts with no history of CVD commence the analyses in an event free health state and thus only incur treatment costs. Consequently, if a primary event is saved this accrues greater benefits in terms of the costs saved and the QALY gained from the event than a similar secondary event.'* Similarly, NICE TA94, Statins for the prevention of coronary events, Assessment Group report[2] (Section 4.4.4.4, page 183) concludes, '*In the CVD analysis the results of the primary prevention analyses are sometimes lower than the ICERs estimated for secondary prevention. This may seem counter intuitive as secondary care patients are at higher risk of CVD events and therefore statins offer the opportunity to avoid more events. However there are other factors involved - in primary prevention patients start in a "well" state with highest possible utility. Avoiding primary events prevents a large reduction in utility for the patient and also the costs associated with events. Costs include both the first year cost of the event itself and also follow-on costs in subsequent years following an event. In the secondary prevention analysis patients start in a CHD health state (stable angina, unstable angina or MI) and therefore they are already a cost to the NHS and have lower utility than the "well" population in primary prevention. This impact offsets the cost saving argument above. The difference is more noticeable in the analyses exploring the benefits associated with CVD as the relative risk of statin treatment is applied to primary stroke and TIA events in addition to the CHD events. Thus these analyses accrue a large amount of benefits from the patients remaining in the event free health state enhancing the benefits from secondary strokes avoided following a CHD event. In addition there are more patients dying at younger ages from secondary disease than primary, hence when treatment is commenced at young ages, the potential to avoid events over a lifetime is increased.'* We acknowledge the different trends in ICERs for the non-familial and HeFH populations based on CVD history. As per the conclusions from TA132 and TA94, the competing relationships between CVD risk, costs and utilities as patients' transition from no history of CVD to a first CV event determine the trend differences between a non-familial and HeFH population.	

Consultee	Comment [sic]	Response
	Of note, consistent with the reasoning given above, the HeFH cohort was younger than the non-familial cohort. HeFH manifests largely as a single pathological trait: elevated LDL-cholesterol. Therefore a powerful therapeutic designed specifically to lower LDL-C to 'normal' levels would be expected to have a profound effect on CVD risk in such patients. We hope this contextual information, including excerpts from two independent Academic Group assessment reports, helps to remove the doubts expressed by the Committee in the interpretation of the cost effectiveness evidence for evolocumab (ACD Sections 4.24 and 4.30). We note that the Committee have recommended an LDL-C threshold of above 4 mmol/litre, despite maximal tolerated lipid lowering therapy, and a required pre-treatment LDL-C level above 8 mmol/litre. The 4 mmol/litre threshold already serves to define a higher risk minority of the HeFH population, in whom we believe we have shown evolocumab to be a cost-effective treatment option. We believe all the above reasoning provides an opportunity for the Committee to consider evolocumab in HeFH patients without CVD, regardless of their ability to tolerate statins or their starting pre-treatment LDL-C levels; additional criteria that would exclude a small high risk cohort of HeFH patients.	Comment noted. The recommendations in FAD section 1 have changed. The committee agreed that a minimum LDL C concentration on repeated measures, rather than a single pre-treatment measure, would capture severe heterozygous-familial hypercholesterolaemia with less potential to exclude people at high risk of CVD. The committee concluded that it could recommend evolocumab for heterozygous-familial hypercholesterolaemia without CVD, only in people with persistently high LDL C concentrations above 5.0 mmol/litre (reflecting the current criteria for apheresis). For further details, see FAD section 4.30.
	3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? We broadly welcome the Committee's revised preliminary recommendations for evolocumab which will allow some small subgroups of high risk patients to access evolocumab in the NHS. These revised recommendations largely reflect the consultation comments from the Royal College of Pathologists as to where evolocumab would be particularly valued, but falls short of the populations put forward by HEART UK and endorsed by a large cohort of UK patients and clinicians. As such, aside from the above suggestions pertaining to non-CVD HeFH patients, we defer to wider clinical opinion regarding the anticipated populations where evolocumab would be used and whether the provisional recommendations in the ACD are a sound and suitable basis for guidance to the NHS.	Comment noted. The recommendations in FAD section 1 have changed. The committee checked proposed sets of recommendations guided by the clinical unmet need in the primary hypercholesterolaemia or mixed dyslipidaemia population against the ICERs estimated by the company. It used the suggestions from the Royal College of Pathologists and the clinical expert about the areas of high unmet need as a starting point in its decision-making, and took into account the responses to the 2 appraisal consultation documents, and the ongoing appraisal of alirocumab. For further details, see FAD sections
	4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any	

Consultee	Comment [sic]	Response
	group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? We do not believe that there are any particular equality-related issues needing special consideration in this appraisal. **References** 1. Ara R, Tumur I, Pandor A et al. Ezetimibe for the treatment of hypercholesterolaemia. Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence. The University of Sheffield, School of Health and Related Research. 2006. 2. Ward S, Jones ML, Pandor A et al. Statins for the Prevention of Coronary Events. Technology assessment report commissioned by the HTA Programme on behalf of The National Institute for Clinical Excellence. The University of Sheffield, School of Health and Related Research. 2005.	4.23–4.25. Comment noted. No action required.
HEART UK	HEART UK consulted on this submission and has additional support of 56 health professionals and 28 comments from the public and supporters. The authors and some of the listed supporters of this submission are leading experts in the UK and Worldwide. Additionally, HEART UK invited comments on the Appraisal Consultation Document from both health care professionals, patients and the public. HEART UK welcomes NICE's decision to recommend Evolocumab for patients with severe hyperlipidaemia and at high risk for cardiovascular disease. This will support clinicians to use this new class of lipid modifying agents for patients with most severe dyslipidaemias and high cardiovascular risk. As indicated by Heart UK's response to the earlier Evolocumab appraisal consultation document, we believe that restricting the use of Evolocumab to patients with high LDL-C above 4mmol/L will exclude patients at high cardiovascular risk with high LDL-C, whether due to poor response to statins, statin intolerance or a high baseline LDL-C level, who would benefit a lot from this new class of medication.	Comment noted. No action required. Comment noted. No action required. Comment noted. The recommendations in FAD section 1 have changed. Comment noted. The recommendations in FAD section 1 have changed. The committee accepted that requiring a minimum LDL-C concentration of 4.0 mmol/litre may exclude some people at high risk of CVD. It heard from the clinical experts that the benefit of treatment on CV outcomes below an LDL-

Consultee	Comment [sic]	Response
		C concentration of 3.5 mmol/litre was still being researched. Therefore, the committee concluded that: • For non-familial hypercholesterolaemia with CVD: it could recommend evolocumab in people with persistently high LDL-C concentrations above 3.5 mmol/litre, only if they have very high risk of CVD (as defined in FAD section 4.26). • For heterozygous-familial hypercholesterolaemia with CVD: it could recommend evolocumab in people at high risk of CVD (as defined in FAD section 4.26) whose LDL-C concentrations are persistently above 3.5 mmol/litre. For further details, see FAD sections 4.28 and 4.29.
	Response to statin treatment is very variable, for example, on 80mg (comments maximum statin therapy used in clinical practice) one sixth of patients will experience not the 55% reduction predicted but one of less than 39% reduction in LDL cholesterol. Therefore, we do not support restriction of use of Evolocumab to statin intolerant patients. In high risk primary prevention and in secondary we recommend an LDL-C threshold of 3.0 mmol/L for intervention. However, we recognise that health economic considerations do not always align with clinical need and recognize the need for the higher threshold of 4.0 mmol/L temporally. We are concerned the recommendation in its current form will bring inconsistency in patient care. The recommendation in its current form will disadvantage patients with severe hyperlipidaemia who are tolerating statin but remain at a very high cardiovascular risk because of high LDL cholesterol because of their very high pre-treatment LDL cholesterol or suboptimal response to statin therapy. Such patients may qualify for lipoprotein apheresis, which is not restricted to statin intolerant patients. These patients should have equal access to evolocumab, which is considerably cheaper than lipoprotein apheresis. We strongly urge NICE to amend their recommendation to allow treatment of patients at high cardiovascular risk and a high LDL-C. The cost-effectiveness calculations undertaken for evolocumab have not addressed this population.	Comments noted. The committee understood that only a few people would have absolute statin intolerance. However, some people may be misidentified as being unable to tolerate statins, and this may worsen the cost effectiveness of subsequent treatment. Because of this, the committee emphasised that its recommendations for evolocumab should only apply when maximal tolerated lipid-lowering therapy has failed. It clarified that this meant that either the maximum dose has been reached or further titration is limited by intolerance (as defined in NICE's guideline on familial hypercholesterolaemia: identification and management). For further details, see FAD sections 4.4 and 4.33.

Consultee	Comment [sic]	Response
	However, for Alirocomab combined with statin, analysis based on a baseline cholesterol of 4.2 mmol/L shown cost / QALY considerably less than £20,000. We therefore recommend allowing access to Evolocumab (and PCSK9 monoclonal antibodies as a class) for the following populations: • **primary non-familial hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic cardiovascular disease (CVD), and persistently high low-density lipoprotein cholesterol (LDL-C) concentrations above 3.0 mmol/litre despite maximum tolerated lipid-lowering therapy.** • **primary heterozygous-familial hypercholesterolaemia with progressive, symptomatic CVD, and persistently high LDL-C concentrations above 3.0 mmol/litre despite maximum tolerated lipid-lowering therapy.** • **severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD, with pre-treatment LDL-C concentrations above 8.0 mmol/litre and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximum tolerated lipid-lowering therapy.** Additionally, for consideration by NICE, ought to be the impact of recommendations and decisions it makes on this class of medicines and the following comments were received when HEART UK consulted widely on the ACD: "*There are not many patients like myself that despite taking all medications at maximum doses ie rosuvastatin and ezetimibe, ldl-aphersis. I still don't reach those allusive target figures especially those for lipoprotein a.* *I have read the NICE guidance and it is so unfair that it is staggering.* *All I can think is that FH patients with high LDL 4mmols on maximum treatment have been forgotten.* *We will not appear on any drug trials as often we are deemed to high risk to be allowed on a blind study and not get the medications we need to live.*	Comments noted. The recommendations in FAD section 1 have changed. The committee checked proposed sets of recommendations guided by the clinical unmet need in the primary hypercholesterolaemia or mixed dyslipidaemia population against the ICERs estimated by the company. It agreed that the suggestions from the Royal College of Pathologists and the clinical expert highlighting the areas where the clinical unmet need was highest, and used them as a starting point in its decision-making. The committee noted the subgroups suggested in other consultation comments. However, it considered that these would be difficult to implement in the NHS because the subgroups did not reflect clinical practice. The committee also took into account the responses to the 2 appraisal consultation documents, and the ongoing appraisal of alirocumab. For further details, see FAD sections 4.23–4.25. Comments noted. The recommendations in FAD section 1 have changed. The committee checked proposed sets of recommendations guided by the clinical unmet need in the primary hypercholesterolaemia or mixed dyslipidaemia population against the ICERs estimated by the company. It used the suggestions from the Royal College of Pathologists and the clinical expert about the areas of high unmet need as a starting point in its decision-making, and took into account the responses to the 2 appraisal consultation

Consultee	Comment [sic]	Response
	These studies therefore do not represent the effect a drug like this can have on a population like myself. *Currently LDL aphersis is the only way to remove most lipoprotein out of my blood my levels despite dual tablet therapy come in at over 3000 and I leave with them around 1000 this in combination with a high ldl level make for an aggressive form of vascular insult.* *In last 18 months I have had several events and I was hoping for the last piece in the jigsaw to fall in to place to control the factors me and my doctors can't control.* *I have been told all my life I was born a generation too early and have not only had to fight disease but also for treatment after the event.* *They need to be made aware that people with severe FH don't have a choice about whether a drug as side effects like statins because a side effect is a small price to pay for a active life.* *The same with apheresis it is not a choice; it has extended my life by 16 years and counting."* Dawn- patient "*My parents both died of heart disease. Had they been born a generation later, their lives may have been saved and transformed with today's generation of drugs. I believe everyone with high cholesterol should have equitable access to drugs, for their personal quality of life, in turn for their family's quality of life and, additionally, for the potential cost savings to the health service for heart disease averted or mitigated.* *My parents were German Jewish refugees - Ashkenazi Jews. Despite best attempts with diet and lifestyle, my cholesterol level remains stubbornly higher than it should be. I have never sought diagnosis of cholesterol-familial hypercholesterolemia, but there must be many descendants of Ashkenazi Jews like me who may need life-enhancing and life-saving drugs for this inherited condition.* *I applaud your energy and efforts into campaigning on behalf of us all.* *Thank you.*" **NAME REDACTED- patient**	documents, and the ongoing appraisal of alirocumab. For further details, see FAD sections 4.23–4.25. Comment noted. The committee was aware that apheresis is not only costly and onerous for the patient, but also difficult to access. The revised recommendations include people within the marketing authorisation for evolocumab who would be eligible for apheresis. For further details, see FAD sections 4.6 and 4.30.

Consultee	Comment [sic]	Response
	"*I support this campaign due to my mother has to have regular dialysis treatments due to FH this would thoroughly improve her condition of life and I believe that every Human being should have a right to this.* *She cannot move away or to other parts of the country as lack of these machines are available and if these inhibitor medicines will help her either to reduce treatment or not at all then I believe this to be more cost effective solution to treating her condition.*" **NAME REDACTED – patient** "*This is ridiculous that NICE plays a role of inhibitor as opposed to facilitator. I believe a campaign should be put in place to revisit the mission of NICE as we are fed up of medicine being denied to people who need it. This is valid for cancer, heart or any other life threatening conditions.* *Enough is enough!*" **NAME REDACTED - patient** "*As a sufferer of homozygous FH with pre-existing atherosclerosis at only 36 I am doing EVERYTHING I can to keep myself as healthy as possible. Having just had a child through surrogacy I want to do everything I can to see him grow up. Denying persons like myself access to these potentially vital new medications is tantamount to telling me to accept that NICE feels it's ok to limit my life expectancy due to a malignant atherosclerosis, a hard pill to swallow when I know there are options like this I'm being denied access to.* *I urge NICE to reconsider this.*" **NAME REDACTED - patient** "*As heart attacks are one of the biggest killers, anything that can prevent them should be supported*" **NAME REDACTED** - patient	Comment noted. Homozygous-familial hypercholesterolaemia is outside the remit of this appraisal, and so the recommendations do not cover it.
	I have an inherited form of hyperlipidemia/ cholesterolemia which did not respond to the highest doses of statins until it was brought under control with fenofibrates and Omacor. These drugs were prescribed only after extensive investigations, over ten years ago, carried out by consultant lipidologist, Dr Nair, at the Royal Free Hospital.	Comment noted. A consultant in metabolic medicine, and a consultant physician and endocrinologist, both nominated by HEART UK, gave their expert personal view by attending the

Consultee	Comment [sic]	Response
	I find it unbelievable that NICE could take a decision on PCSK9 inhibitors without taking the views and opinions of expert lipidologists. I am amazed that decisions are taken without a more rigorous approach to scientific evidence, such as that available from expert lipidologists. **NAME REDACTED - health care professional and patient** "*I am very concerned about the present NICE view and strongly support that lipidologists should have been represented on the committee* *I had a NSTEMI =+ one stent 2013 (58y - no other risk factors) , I have some arteriosclerosis in my carotid arteries and some small vessel disease)* *There is strong FH of polygenic dyslipidaemia* *I have Lipoprotein (a) over 1000 (was over 1400 before I started on Nicotinamide 2 gram per day)* *I am on rosuvastatin 20mgm etc* *I am under the Hammersmith lipid clinic.* *NICE are recommending that I should consider self funding for PCSK9 inhibitor treatment in the light of my high Lp(a) level- this must surely be available on the NHS for patients like myself."* **NAME REDACTED - GP and patient** Supporters for this submission include 56 health care professionals and 28 members of the public and patients. The names of these supporters have been provided to NICE.	initial committee discussion and providing a written statement to the committee. They were invited to comment on the ACD. Comment noted. A consultant in metabolic medicine, and a consultant physician and endocrinologist, both nominated by HEART UK, gave their expert personal view by attending the initial committee discussion and providing a written statement to the committee. They were invited to comment on the ACD.
Royal College of Pathologists	RCPath would like to thank NICE for the opportunity to comment on the ACD2. The RCPath welcomes the revised ACD which now recommends evolocumab as a treatment option, alone or in combination with other lipid lowering therapies, in the three groups identified in our previous submission as those with the greatest unmet clinical need. It is clear that the Committee has given careful consideration to the additional evidence presented in formulating the revised recommendations. However, although these three groups are clearly identified, the wording of the draft recommendations in 1.1 is ambiguous with the potential for misinterpretation without	Comment noted. No action required. Comments noted. The recommendations in FAD section 1 have changed. The committee checked proposed sets of recommendations guided by the clinical unmet need in the primary hypercholesterolaemia or mixed dyslipidaemia population against the ICERs estimated by the

Consultee	Comment [sic]	Response
	reference to the Overall Conclusion [4.31, p.61]. The description of the three patient categories/scenarios, which followed the suggestions of RCPath and the clinical expert, seemed clear, however the addition of qualifications regarding coexisting statin intolerance reduces the clarity of the recommendations. The intended meaning is more clearly expressed in 4.31 as follows: The person has an LDL-C concentrations persistently above 4.0 mmol/litre and 1. primary non-familial hypercholesterolaemia or mixed dyslipidaemia and CVD and statin therapy is not tolerated 2. primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia and CVD 3. severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD and pre-treatment LDL-C concentrations are above 8.0mmol/litre and statin therapy is not tolerated The RCPath is concerned that the qualifier “statin therapy is not tolerated” is has been added to the definitions of Categories 1 and 3. It is clear from paragraphs 4.28-4.30 that the rationale for adding the qualifier “statin therapy is not tolerated“ to Categories 1 and 3 and not to Category 2 was intended to restrict treatment to subgroups deemed to be at higher risk. However the RCPath believes that all patients in these three categories who are inadequately unresponsive to and/or intolerant of maximal conventional lipid lowering therapy and are thereby unable to achieve appropriate control (defined as persistently high non-HDL-C >5.0 mmol/L and/or equivalent LDL-C >4.0 mmol/L) are at very high risk and should have access to these therapies, the only alternative for them being LDL-apheresis. Secondly, the RCPath is also concerned that non-HDL-cholesterol>5.0 has been removed from the suggested definition of inadequate response to lipid lowering treatment which is in direct contradiction to the current NICE Guidance on Lipid Modification (CG181, July 2014). Finally, the RCPath would like to see recommendations of monitoring of treatment and a commitment from the manufacturers to make assays for measurement of drug and anti-drug antibody available to clinicians as may be required for investigating patients experiencing adverse drug reactions and/or secondary loss of treatment response (based on experience with other “biologic” therapies). Regarding the first point, in 1.1, the recommendation for each category of patient uses the wording suggested by the RCPath and the clinical expert to denote the patient who is not appropriately controlled with optimum use of currently available	company. It used the suggestions from the Royal College of Pathologists and the clinical expert about the areas of high unmet need as a starting point in its decision-making, and took into account the responses to the 2 appraisal consultation documents, and the ongoing appraisal of alirocumab. For further details, see FAD sections 4.23–4.25. In addition, the recommendations have been specified in a table to improve clarity.

Consultee	Comment [sic]	Response
	lipid lowering therapy (that being maximum tolerated dose of a high intensity statin combined with ezetimibe) viz. “persistently high low-density lipoprotein cholesterol (LDL-C) concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy”. This wording implies that either the maximum dose has been reached or further titration is limited by intolerance (as defined in CG71 1.3.1.11 and TA132 1.6). As statin intolerance is already captured in “despite maximal tolerated lipid-lowering therapy” addition of the qualifier “and statin therapy is not tolerated” to the definition of Groups 1 and 3 is appears to be a confusing and unnecessary duplication. However it is clear from the discussion in paragraph 4.28 that this qualifier was added to identify high risk subgroup within the non-FH CVD cases not adequately controlled. This is probably unnecessary as most cases of non-FH patients with progressive CVD are statin intolerant, although some may be able to tolerate small doses (e.g. non-daily rosuvastatin 5mg) with some beneficial effect. To disqualify such patients for persisting with a small but useful dose would be a perverse incentive to discontinuation. Except those with FH, few treatment adherent CVD patients who can tolerate maximum dose of high intensity statin and ezetimibe will fail to achieve appropriate control as defined above. The vast majority of non-FH CVD patients under consideration will not be treated with maximum dose of high intensity statin and ezetimibe because either 1. initial statin therapy is contraindicated 2. they are intolerant of statin therapy or 3. statin dose titration is limited by statin intolerance. The small number of inadequately controlled non-FH CVD cases who are not intolerant may be truly treatment resistant (e.g. due to very high lipoprotein(a) or other genetic factors) or may have no pre-treatment results available (e.g. FH presenting with acute MI). The qualifier “statin therapy is not tolerated” is also added to category 3 on the basis of the doubts expressed by the committee regarding the “face validity” of the more favourable ICER for people with a mean LDL-C of 6mmol/L without CVD compared to non-FH CVD patients with a mean LDL-C of 4.0 mmol/L, considering this to be this counterintuitive. The RCPath does not consider this ICER to be counterintuitive, as the risk attributable to LDL-C is in fact greater in FH patients without CVD, in whom other risk factors are typically well controlled, and few, if any non-FH CVD patients have LDL-C as high as 6.0 mmol/L. In addition to including patients with mutations conferring treatment resistance (e.g. PCSK9 gain of function, 2% of FH mutations) the severe FH patients have a higher risk due to elevated lipoprotein(a) (30% higher in FH than non-FH independent of isoform size) and early familial risk mediated by other genetic factors. Starting from pre-treatment LDL-C of up to 13	Comment noted. The committee understood that only a few people would have absolute statin intolerance. However, some people may be misidentified as being unable to tolerate statins, and this may worsen the cost effectiveness of subsequent treatment. Because of this, the committee emphasised that its recommendations for evolocumab should only apply when maximal tolerated lipid-lowering therapy has failed. It clarified that this meant that either the maximum dose has been reached or further titration is limited by intolerance (as defined in NICE’s guideline on familial hypercholesterolaemia: identification and management). For further details, see FAD sections 4.4 and 4.33.

Consultee	Comment [sic]	Response
	mmol/L (> 13 using homozygous) even those patients who can take maximum high intensity statins and ezetimibe (achieving 50-60% reduction at best) may fail to achieve adequate control and their risk remains extremely high. The best results will clearly be obtained when maximum high intensity statins and ezetimibe is combined with an anti-PCSK9 therapy. As with category 1 some may only be able to tolerate sub-maximal statin doses with some beneficial effect and to disqualify such patients for persisting with a submaximal dose would be a perverse incentive to discontinuation. The is no evidence to support the addition of the qualifier "statin therapy is not tolerated" to improve the ICER in this group and the RCPath recommends that this be removed from Category 3 as well as from Category 1. The measurement of non-HDL-cholesterol is preferred for monitoring of response to lipid lowering therapy as assessment of response to treatment as recommended in the NICE Lipid Modification guideline CG181 for reasons explained in the Full Guideline. This states that *"The measurement of cholesterol, cholesterol sub-fractions and triglycerides are necessary to ensure treatment is appropriate. The GDG discussed that the Friedewald equation for calculation of LDL-cholesterol as commonly used for risk assessment requires a fasting sample and triglycerides below 4.5 mmol/litre. It is derived from a small number of patients (130) and the original study included very few patients with diabetes (<30). The GDG were aware that a recent very large database analysis had revealed excess variance and bias in the calculation of LDL cholesterol such that a complicated table of correction factors would have to be applied by clinical laboratories. The formula was also limited in its utility at low LDL-cholesterol levels as seen with high-intensity statin treatment. The use of direct LDL-cholesterol measurement is limited by cost and availability in the NHS. Meta-analyses of CVD outcomes in relation to lipid fractions by the Emerging Risk Factors collaboration and others have consistently shown the superior predictive value of non-HDL cholesterol (that is, the difference between total and HDL cholesterol) on CV events. Non-HDL cholesterol does not require a fasting blood sample. The GDG decided that the use of non-HDL cholesterol was preferable to calculated or measured LDL cholesterol given its greater practicality"*. The equivalent non-HDL-cholesterol of 5 mmol/L was suggested after careful consideration by the RCPath, on the basis that the (non-HDL-cholesterol – LDL-cholesterol) difference of 1 mmol/L equates to the Friedewald calculated VLDL-cholesterol at a fasting triglyceride value of 2.2 mmol/L. This is likely to be more slightly more difficult to achieve than the corresponding LDL-C threshold and is not likely to affect the numbers of patients being considered eligible, except due to greater practicability of sample collection.	Comment noted. The clinical and cost-effectiveness evidence presented to the committee was based on LDL-C. In addition, the committee heard from the clinical experts that non-HDL-C may correspond to artificially high LDL-C concentrations in people with severe hypertriglyceridaemia. In the absence of evidence for non-HDL-C, the committee agreed to define the subgroups for whom evolocumab is recommended by LDL-C concentrations.

Consultee	Comment [sic]	Response
	The RCPath recommends therefore that this treatment should be an option for patients with • primary non-familial hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic cardiovascular disease (CVD) • primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic CVD • severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD, with pre-treatment LDL-C concentrations above 8.0 mmol/litre be considered for treatment if they have: • persistently high non-high density lipoprotein cholesterol (LDL-C) concentrations above 5.0 mmol/litre and/or low-density lipoprotein cholesterol (LDL-C) concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy • or initial statin therapy is contraindicated • or statin therapy is not tolerated • or statin dose titration is limited by intolerance The RCPath would like to see some guidance regarding frequency of monitoring as required to detect loss of response (which might potentially occur due to development of neutralizing antibodies). A three month interval for lipid monitoring in the first year, perhaps with less frequent monitoring in the second and subsequent years, would seem appropriate. Where there is secondary loss of response, access for clinicians to measurements of drug and anti-drug antibodies would of great value, and would be essential for investigation of suspected antibody mediated adverse reactions. The manufacturer should support the provision of such an analytical service.	Comment noted. The committee was not presented with any evidence about the frequency of monitoring response to treatment. Therefore, it could not make recommendations in this regard.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
HEART UK	Thank you for the opportunity to review the updated ACD on evolucumab. I agree with the document's strategy and suggested patient pathway. There are a couple of minor points of wording and clarification that need to be addressed.	Comments noted. No action required. Comment noted. The recommendations in FAD section 1 have changed. The committee checked proposed sets of recommendations guided by the clinical unmet need in the primary

Nominating organisation	Comment [sic]	Response
	1.1a This would be better phrased as the person has: • primary non-familial hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic cardiovascular disease (CVD), and persistently high low-density lipoprotein cholesterol (LDL-C) concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy **and** • high potency high dose statin therapy is not tolerated (as defined in NICE's guideline on familial hypercholesterolaemia: identification and management) This includes a tautology. NICE CG71relies on the prescription of high potency high dose statins. This clarifies the indication as high residual LDL-C despite highest tolerated dose of any statin. 1.1b This would be better phrased as primary ~~heterozygous-familial~~ hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic CVD, and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy This differentiates 1.1.b from 1.1a. There is a small population of individuals who do not have genetically proven familial hypercholesterolaemia but do have severe hypercholesterolaemia or mixed hyperlipidaemia of polygenic origin who cannot reach even population average lipid levels despite second-line agents due to partial or total statin intolerance. They often have aggressive coronary heart disease with no other treatment option except apheresis and evolucumab would be clinically indicated in this group. 1.1C severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD, with pre-treatment LDL-C concentrations above 8.0 mmol/litre and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy **and** • statin therapy is not tolerated (as defined in NICE's guideline on familial hypercholesterolaemia: identification and management) **or** • initial statin therapy is contraindicated	hypercholesterolaemia or mixed dyslipidaemia population against the ICERs estimated by the company. It used the suggestions from the Royal College of Pathologists and the clinical expert about the areas of high unmet need as a starting point in its decision-making, and took into account the responses to the 2 appraisal consultation documents, and the ongoing appraisal of alirocumab. For further details, see FAD sections 4.23–4.25.

Nominating organisation	Comment [sic]	Response
	The indication here is, I believe, meant to reflect primary prevention in patients with familial hypercholesterolaemia with severe disease (90th centile). Mixed dyslipidaemia should be excluded as no studies have evaluated the efficacy of evolucumab or any other PCSK-9 in patients with triglycerides >4.5mmol/L. There is a group of patients with other genetic disorders of lipid metabolism who can have high levels of triglycerides and total cholesterol and in whom inappropriate calculation (as opposed to measurement) of LDL-C may give rise to a 'high' LDL-C- many of whom will have remnant hyperlipidaemias. Use of evolocumab in this patient group has never been studied and should not be recommended at this time.	

Comments received from commentators

Commentator	Comment [sic]	Response
MSD	MSD welcomes the opportunity to comment on the appraisal consultation document (ACD) for evolocumab. MSD has comments on the following areas in the ACD recommendation, which are outlined in more detail below: • Misleading and inconsistent use of terminology between recommendation and NICE Lipid Modification Guideline (CG181) • Relevance of the patient access scheme to the recommendation **Misleading and inconsistent use of terminology between recommendation and NICE Lipid Modification Guideline (CG181)** • **'Lipid lowering therapies' & 'lipid lowering therapy'** In section 1.1, these terms are used interchangeably to encompass either a statin and ezetimibe (the only non-statin lipid lowering therapy recommended in CG181) or ezetimibe (the only non-statin lipid lowering therapy recommended in CG181). MSD is concerned this exchangeability of terms may cause confusion in the recommendations interpretation. This is compounded when referring to *'maximal tolerated lipid-lowering therapy'* where following language from CG181 we assume that the committee is talking about ezetimibe but the use of *'maximal tolerated'* suggests a statin also, as ezetimibe is only available as one dose (10mg).	Comments noted. Please see detailed responses below. Comment noted. In line with the marketing authorisation and the evidence base for evolocumab, 'other lipid-lowering therapy' refers to statins and/or ezetimibe. The qualifier 'alone or in combination with other lipid-lowering therapies' has been removed from section 1.1 of the FAD. The committee understood that some people may be misidentified as being unable to tolerate statins. Because of this, it emphasised that the

Commentator	Comment [sic]	Response
	For consistency, MSD suggests the removal of the term *'lipid lowering therapies'* and that where the term '*other lipid lowering therapy*' is used it refers only to ezetimibe and statins be mentioned separately to the term – this would be in line with terminology used in CG181 and be clear to readers. Consequently, MSD would also request the removal of '*maximal tolerated'* if '*lipid lowering therapy'* refers to ezetimibe only.	recommendations for evolocumab should only apply when maximal tolerated lipid-lowering therapy has failed. It clarified that this meant that either the maximum dose has been reached or further titration is limited by intolerance (as defined in NICE's guideline on familial hypercholesterolaemia: identification and management). For further details, see FAD sections 4.4 and 4.33.
	Relevance of the patient access scheme to the recommendation	
	The following comments are made on the assumption that a positive recommendation would not have been made in the absence of the patient access scheme. The text of the guidance document discusses a potential challenge around the applicability of the patient access scheme in relation to prescribing potentially occurring in primary care where the patient access scheme would not apply. The text of the document also is clear that it is expected that prescribing should only occur in secondary care. It is suggested that the recommendation 1.1, as currently worded, does not reflect the discussion and intention recorded in the document. A potential remedy for this would be to explicitly state in section 1 that, initial and repeat prescribing should occur only in a secondary care setting.	Comment noted. The committee considered that a recommendation about the care setting in which evolocumab should be used was not needed because the subgroups for which evolocumab is recommended have severe hypercholesterolaemia and a high risk of CVD, so people should continue treatment under secondary care where simple patient access schemes apply. The committee concluded that the discounted patient access scheme price of evolocumab would be consistently applied for all people for whom evolocumab is recommended. For further details, see FAD section 4.34.
	We would also note that in section 1.1 of the ACD, there is the statement making recommendations for: *"Severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD, with pre-treatment LDL-C concentrations above 8.0 mmol/litre"* MSD suggests the term severe is superfluous in this sentence.	Comment noted. The recommendations in FAD section 1 have changed. The committee checked proposed sets of recommendations guided by the clinical unmet need in the primary hypercholesterolaemia or mixed dyslipidaemia population against the ICERs estimated by the company. It used the suggestions from the Royal College of Pathologists and the clinical expert about the areas of high unmet need as a starting point in its decision-making, and took into account the responses to the 2 appraisal consultation documents, and the ongoing appraisal of alirocumab. For further details, see FAD sections

Commentator	Comment [sic]	Response
		4.23–4.25.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia

Response to appraisal consultation document

Prepared by:

26th February 2016

File name	Version	Contains confidential information	Date
		No	February 2016

Summary

Thank you for the opportunity to respond to the second Appraisal Consultation Document (ACD) for evolocumab issued in January 2016.

As noted during the first ACD consulation, we support the Committee's recognition of the clinical need for alternative treatments and their acknowledgement that evolocumab is a new therapy with a novel mechanism of action, which consistently reduced low-density lipoprotein cholesterol (LDL-C) concentrations compared with the current standard of care, while also being well tolerated by patients. We share the Committee's conclusion that evolocumab will likely be reserved for patients who are at particularly high risk of cardiovascular disease (CVD), including patients with heterozygous familial hypercholesterolaemia (HeFH) and those in whom LDL-C is not adequately controlled who are at the highest residual risk and are most vulnerable to cardiovascular (CV) events. We broadly welcome the Committee's revised preliminary recommendations which will allow some small subgroups of high risk patients to access evolocumab in the NHS.

We have provided additional comments regarding selected aspects of the preliminary recommendations in this document.

1. Has all of the relevant evidence been taken into account?

We believe all of the relevant evidence has been taken into account.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

We believe that the overall summaries of the clinical and cost effectiveness in the ACD are reasonable interpretations of the evidence. We have provided additional information regarding the cost effectiveness results of the populations according to CVD history.

2.1 Cost effectiveness results based on CVD history

We note the Committee's doubts regarding the inconsistent incremental cost-effectiveness ratios (ICERs) in the HeFH population when considering patients with and without CVD. As a consequence, evolocumab is only recommended in a subset of patients with severe HeFH who cannot tolerate statins. As such, we wish to provide further information to support the Committee's interpretation of the cost-effectiveness evidence.

ACD Section 4.24 states, *'The Committee noted that the ICERs for people without CVD were actually lower than those for people with CVD. This was inconsistent with the results for non-familial hypercholesterolaemia population and counter-intuitive because people with CVD have a higher risk of CVD, and so would be expected to gain more QALYs from treatment than those without CVD. The Committee heard from the company that people without CVD may be benefitting from the prevention of a first event of CVD. However, it considered that this did not explain why the non-familial hypercholesterolaemia population*

without CVD would not benefit in the same manner, and have lower ICERs than the population with CVD.' Thereafter, ACD Section 4.30 states, *'…the Committee had serious doubts about the face validity of the ICERs for the heterozygous-familial hypercholesterolaemia population without CVD, mainly because the ICERs were inconsistent with the results for non-familial hypercholesterolaemia population, and counter-intuitive (see section 4.24). Because of this, it concluded to recommend evolocumab 140 mg every 2 weeks only for the subset of patients with severe heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia who have the highest clinical unmet need; that is, people who cannot tolerate statins.'*

We appreciate the results in the HeFH population were deemed to be counter-intuitive given the Committee's interpretation regarding the role of CVD risk in determining the cost-effectiveness results. As clarified during the Apprasial Committee meeting, this form of counter-intuitive result has been documented in previous NICE technology appraisals in this therapy area. This counter-intuitive finding was observed most recently in NICE TA132 (2007) and previously in NICE TA94 (2006). The conclusions from the relevant Assessment Group reports have been extracted and provided below.

NICE TA132, Ezetimibe for the treatment of hypercholesterolaemia, Assessment Group report[1] (Section 6.3.4, page 140) concludes, *'The results for cohorts with no history of CVD are more cost effective than the results for cohorts with a history of CVD. While this appears to be counter-intuitive, the difference in the results is caused because all individuals in the cohorts with a history of CVD commence the analyses in a health state which incurs ongoing costs and disutilities while cohorts with no history of CVD commence the analyses in an event free health state and thus only incur treatment costs. Consequently, if a primary event is saved this accrues greater benefits in terms of the costs saved and the QALY gained from the event than a similar secondary event.'*

Similarly, NICE TA94, Statins for the prevention of coronary events, Assessment Group report[2] (Section 4.4.4.4, page 183) concludes, '*In the CVD analysis the results of the primary prevention analyses are sometimes lower than the ICERs estimated for secondary prevention. This may seem counter intuitive as secondary care patients are at higher risk of CVD events and therefore statins offer the opportunity to avoid more events. However there are other factors involved - in primary prevention patients start in a "well" state with highest possible utility. Avoiding primary events prevents a large reduction in utility for the patient and also the costs associated with events. Costs include both the first year cost of the event itself and also follow-on costs in subsequent years following an event. In the secondary prevention analysis patients start in a CHD health state (stable angina, unstable angina or MI) and therefore they are already a cost to the NHS and have lower utility than the "well" population in primary prevention. This impact offsets the cost saving argument above. The difference is more noticeable in the analyses exploring the benefits associated with CVD as the relative risk of statin treatment is applied to primary stroke and TIA events in addition to the CHD events. Thus these analyses accrue a large amount of benefits from the patients remaining in the event free health state enhancing the benefits from secondary strokes avoided following a CHD event. In addition there are more patients dying at younger ages from secondary disease than primary, hence when treatment is commenced at young ages, the potential to avoid events over a lifetime is increased.'*

We aknowledge the different trends in ICERs for the non-familial and HeFH populations based on CVD history. As per the conclusions from TA132 and TA94, the competing relationships between CVD risk, costs and utilities as patients' transition from no history of CVD to a first CV event determine the trend differences between a non-familial and HeFH population.

Of note, consistent with the reasoning given above, the HeFH cohort was younger than the non-familial cohort. HeFH manifests largely as a single pathological trait: elevated LDL-cholesterol. Therefore a powerful therapeutic designed specifically to lower LDL-C to 'normal' levels would be expected to have a profound effect on CVD risk in such patients.

We hope this contextual information, including excerpts from two independent Academic Group assessment reports, helps to remove the doubts expressed by the Committee in the interpretation of the cost effectiveness evidence for evolocumab (ACD Sections 4.24 and 4.30).

We note that the Committee have recommended an LDL-C threshold of above 4 mmol/litre, despite maximal tolerated lipid lowering therapy, and a required pre-treatment LDL-C level above 8 mmol/litre. The 4 mmol/litre threshold already serves to define a higher risk minority of the HeFH population, in whom we believe we have shown evolocumab to be a cost-effective treatment option. We believe all the above reasoning provides an opportunity for the Committee to consider evolocumab in HeFH patients without CVD, regardless of their ability to tolerate statins or their starting pre-treatment LDL-C levels; additional criteria that would exclude a small high risk cohort of HeFH patients.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

We broadly welcome the Committee's revised preliminary recommendations for evolocumab which will allow some small subgroups of high risk patients to access evolocumab in the NHS. These revised recommendations largely reflect the consultation comments from the Royal College of Pathologists as to where evolocumab would be particularly valued, but falls short of the populations put forward by HEART UK and endorsed by a large cohort of UK patients and clinicians. As such, aside from the above suggestions pertaining to non-CVD HeFH patients, we defer to wider clinical opinion regarding the anticipated populations where evolocumab would be used and whether the provisional recommendations in the ACD are a sound and suitable basis for guidance to the NHS.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

We do not believe that there are any particular equality-related issues needing special consideration in this appraisal.

References

1. Ara R, Tumur I, Pandor A et al. Ezetimibe for the treatment of hypercholesterolaemia. Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence. The University of Sheffield, School of Health and Related Research. 2006.
2. Ward S, Jones ML, Pandor A et al. Statins for the Prevention of Coronary Events. Technology assessment report commissioned by the HTA Programme on behalf of The National Institute for Clinical Excellence. The University of Sheffield, School of Health and Related Research. 2005.

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TO: NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

RE: Appraisal consultation document- Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia
Healthcare professional submission

FROM: [redacted]
HEART UK- The Cholesterol Charity

DATE: 26th February 2016

This submission from HEART UK has been prepared by [redacted] MSc, MD, FRCP [redacted] Medical Scientific & Research Committee, Consultant Physician and Endocrinologist & Clinical Lead Department of Medicine. [redacted] MD FRCP FRCPath [redacted] Medical Scientific & Research Committee, Consultant in Biochemistry& Metabolic Medicine [redacted] and [redacted] MBBS, MSc, FRCPath, Consultant Chemical Pathologist, [redacted].

HEART UK consulted on this submission and has additional support of 56 health professionals and 28 comments from the public and supporters. The authors and some of the listed supporters of this submission are leading experts in the UK and Worldwide.

Additionally, HEART UK invited comments on the Appraisal Consultation Document from both health care professionals, patients and the public.

HEART UK welcomes NICE's decision to recommend Evolocumab for patients with severe hyperlipidaemia and at high risk for cardiovascular disease. This will support clinicians to use this new class of lipid modifying agents for patients with most severe dyslipidaemias and high cardiovascular risk.

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As indicated by Heart UK's response to the earlier Evolocumab appraisal consultation document, we believe that restricting the use of Evolocumab to patients with high LDL-C above 4mmol/L will exclude patients at high cardiovascular risk with high LDL-C, whether due to poor response to statins, statin intolerance or a high baseline LDL-C level, who would benefit a lot from this new class of medication.

Response to statin treatment is very variable, for example, on 80mg (comments maximum statin therapy used in clinical practice) one sixth of patients will experience not the 55% reduction predicted but one of less than 39% reduction in LDL cholesterol. Therefore, we do not support restriction of use of Evolocumab to statin intolerant patients. In high risk primary prevention and in secondary we recommend an LDL-C threshold of 3.0 mmol/L for intervention. However, we recognise that health economic considerations do not always align with clinical need and recognize the need for the higher threshold of 4.0 mmol/L temporally.

We are concerned the recommendation in its current form will bring inconsistency in patient care. The recommendation in its current form will disadvantage patients with severe hyperlipidaemia who are tolerating statin but remain at a very high cardiovascular risk because of high LDL cholesterol because of their very high pre-treatment LDL cholesterol or suboptimal response to statin therapy. Such patients may qualify for lipoprotein apheresis, which is not restricted to statin intolerant patients. These patients should have equal access to evolocumab, which is considerably cheaper than lipoprotein apheresis.

We strongly urge NICE to amend their recommendation to allow treatment of patients at high cardiovascular risk and a high LDL-C. The cost-effectiveness calculations undertaken for evolocumab have not addressed this population. However, for Alirocomab combined with statin, analysis based on a baseline cholesterol of 4.2 mmol/L shown cost / QALY considerably less than £20,000.

We therefore recommend allowing access to Evolocumab (and PCSK9 monoclonal antibodies as a class) for the following populations:

- **primary non-familial hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic cardiovascular disease (CVD), and persistently high low-**

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density lipoprotein cholesterol (LDL-C) concentrations above 3.0 mmol/litre despite maximum tolerated lipid-lowering therapy.

- **primary heterozygous-familial hypercholesterolaemia with progressive, symptomatic CVD, and persistently high LDL-C concentrations above 3.0 mmol/litre despite maximum tolerated lipid-lowering therapy.**

- **severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD, with pre-treatment LDL-C concentrations above 8.0 mmol/litre and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximum tolerated lipid-lowering therapy.**

Additionally, for consideration by NICE, ought to be the impact of recommendations and decisions it makes on this class of medicines and the following comments were received when HEART UK consulted widely on the ACD:

"There are not many patients like myself that despite taking all medications at maximum doses ie rosuvastatin and estimibe, ldl-aphersis. I still don't reach those allusive target figures especially those for lipoprotein a.

I have read the NICE guidance and it is so unfair that it is staggering.

All I can think is that FH patients with high LDL 4mmols on maximum treatment have been forgotten.

We will not appear on any drug trials as often we are deemed to high risk to be allowed on a blind study and not get the medications we need to live.

These studies therefore do not represent the effect a drug like this can have on a population like myself.

Currently LDL aphersis is the only way to remove most lipoprotein out of my blood my levels despite dual tablet therapy come in at over 3000 and I leave with them around 1000 this in combination with a high ldl level make for an aggressive form of vascular insult.

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In last 18 months I have had several events and I was hoping for the last piece in the jigsaw to fall in to place to control the factors me and my doctors can't control.

I have been told all my life I was born a generation too early and have not only had to fight disease but also for treatment after the event.

They need to be made aware that people with severe FH don't have a choice about whether a drug as side effects like statins because a side effect is a small price to pay for a active life.

The same with apheresis it is not a choice; it has extended my life by 16 years and counting."
Dawn- patient

"My parents both died of heart disease. Had they been born a generation later, their lives may have been saved and transformed with today's generation of drugs. I believe everyone with high cholesterol should have equitable access to drugs, for their personal quality of life, in turn for their family's quality of life and, additionally, for the potential cost savings to the health service for heart disease averted or mitigated.

My parents were German Jewish refugees - Ashkenazi Jews. Despite best attempts with diet and lifestyle, my cholesterol level remains stubbornly higher than it should be. I have never sought diagnosis of cholesterol-familial hypercholesterolemia, but there must be many descendants of Ashkenazi Jews like me who may need life-enhancing and life-saving drugs for this inherited condition.

I applaud your energy and efforts into campaigning on behalf of us all.
Thank you."
NAME REDACTED- patient

"I support this campaign due to my mother has to have regular dialysis treatments due to FH this would thoroughly improve her condition of life and I believe that every Human being should have a right to this.

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She cannot move away or to other parts of the country as lack of these machines are available and if these inhibitor medicines will help her either to reduce treatment or not at all then I believe this to be more cost effective solution to treating her condition."
NAME REDACTED – patient

"This is ridiculous that NICE plays a role of inhibitor as opposed to facilitator. I believe a campaign should be put in place to revisit the mission of NICE as we are fed up of medicine being denied to people who need it. This is valid for cancer, heart or any other life threatening conditions.

Enough is enough!"
NAME REDACTED - patient

"As a sufferer of homozygous FH with pre-existing atherosclerosis at only 36 I am doing EVERYTHING I can to keep myself as healthy as possible. Having just had a child through surrogacy I want to do everything I can to see him grow up. Denying persons like myself access to these potentially vital new medications is tantamount to telling me to accept that NICE feels it's ok to limit my life expectancy due to a malignant atherosclerosis, a hard pill to swallow when I know there are options like this I'm being denied access to.

I urge NICE to reconsider this."
NAME REDACTED - patient

"As heart attacks are one of the biggest killers, anything that can prevent them should be supported"
NAME REDACTED - patient

I have an inherited form of hyperlipidemia/ cholesterolemia which did not respond to the highest doses of statins until it was brought under control with fenofibrates and Omacor. These drugs were prescribed only after extensive investigations, over ten years ago, carried out by consultant lipidologist, Dr Nair, at the Royal Free Hospital. I find it unbelievable that NICE could take a decision on PCSK9 inhibitors without taking the views and opinions of expert lipidologists. I am amazed that decisions are taken without a more rigorous approach to scientific evidence, such as that available from expert lipidologists.

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NAME REDACTED - health care professional and patient

"I am very concerned about the present NICE view and strongly support that lipidologists should have been represented on the committee

I had a NSTEMI =+ one stent 2013 (58y - no other risk factors) , I have some arteriosclerosis in my carotid arteries and some small vessel disease)

There is strong FH of polygenic dyslipidaemia

I have Lipoprotein (a) over 1000 (was over 1400 before I started on Nicotinamide 2 gram per day)

I am on rosuvastatin 20mgm etc

I am under the Hammersmith lipid clinic.

NICE are recommending that I should consider self funding for PCSK9 inhibitor treatment in the light of my high Lp(a) level- this must surely be available on the NHS for patients like myself."

NAME REDACTED - GP and patient

Supporters for this submission include 56 health care professionals and 28 members of the public and patients. The names of these supporters have been provide to NICE.

RCPath would like to thank NICE for the opportunity to comment on the ACD2.

The RCPath welcomes the revised ACD which now recommends evolocumab as a treatment option, alone or in combination with other lipid lowering therapies, in the three groups identified in our previous submission as those with the greatest unmet clinical need. It is clear that the Committee has given careful consideration to the additional evidence presented in formulating the revised recommendations. However, although these three groups are clearly identified, the wording of the draft recommendations in 1.1 is ambiguous with the potential for misinterpretation without reference to the Overall Conclusion [4.31, p.61]. The description of the three patient categories/scenarios, which followed the suggestions of RCPath and the clinical expert, seemed clear, however the addition of qualifications regarding coexisting statin intolerance reduces the clarity of the recommendations. The intended meaning is more clearly expressed in 4.31 as follows:

The person has an LDL-C concentrations persistently above 4.0 mmol/litre and
1. primary non-familial hypercholesterolaemia or mixed dyslipidaemia
and CVD
and statin therapy is not tolerated
2. primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia
and CVD
3. severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD
and pre-treatment LDL-C concentrations are above 8.0mmol/litre
and statin therapy is not tolerated

The RCPath is concerned that the qualifier "statin therapy is not tolerated" is has been added to the definitions of Categories 1 and 3. It is clear from paragraphs 4.28-4.30 that the rationale for adding the qualifier "statin therapy is not tolerated" to Categories 1 and 3 and not to Category 2 was intended to restrict treatment to subgroups deemed to be at higher risk. However the RCPath believes that all patients in these three categories who are inadequately unresponsive to and/or intolerant of maximal conventional lipid lowering therapy and are thereby unable to achieve appropriate control (defined as persistently high non-HDL-C >5.0 mmol/L and/or equivalent LDL-C >4.0 mmol/L) are at very high risk and should have access to these therapies, the only alternative for them being LDL-apheresis. Secondly, the RCPath is also concerned that non-HDL-cholesterol>5.0 has been removed from the suggested definition of inadequate response to lipid lowering treatment which is in direct contradiction to the current NICE Guidance on Lipid Modification (CG181, July 2014). Finally, the RCPath would like to see recommendations of monitoring of treatment and a commitment from the manufacturers to make assays for measurement of drug and anti-drug antibody available to clinicians as may be required for investigating patients experiencing adverse drug reactions and/or secondary loss of treatment response (based on experience with other "biologic" therapies).

Regarding the first point, in 1.1, the recommendation for each category of patient uses the wording suggested by the RCPath and the clinical expert to denote the patient who is not appropriately controlled with optimum use of currently available lipid lowering therapy (that being maximum tolerated dose of a high intensity statin combined with ezetimibe) viz. "persistently high low-density lipoprotein cholesterol (LDL-C) concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy". This wording implies that either the maximum dose has been reached or further titration is limited by intolerance (as defined in CG71 1.3.1.11 and TA132 1.6).

As statin intolerance is already captured in "despite maximal tolerated lipid-lowering therapy" addition of the qualifier "and statin therapy is not tolerated" to the definition of Groups 1 and 3 is appears to be a confusing and unnecessary duplication. However it is clear from the discussion in paragraph 4.28 that this qualifier was added to identify high risk subgroup within the non-FH CVD cases not adequately controlled. This is probably unnecessary as most cases of non-FH patients with progressive CVD are statin intolerant, although some may be able to tolerate small doses (e.g. non-daily rosuvastatin 5mg) with some beneficial effect. To disqualify such patients for persisting with a small but useful dose would be a perverse incentive to discontinuation. Except those with FH, few treatment adherent CVD patients who can tolerate maximum dose of high intensity statin and

ezetimibe will fail to achieve appropriate control as defined above. The vast majority of non-FH CVD patients under consideration will not be treated with maximum dose of high intensity statin and ezetimibe because either 1. initial statin therapy is contraindicated 2. they are intolerant of statin therapy or 3. statin dose titration is limited by statin intolerance. The small number of inadequately controlled non-FH CVD cases who are not intolerant may be truly treatment resistant (e.g. due to very high lipoprotein(a) or other genetic factors) or may have no pre-treatment results available (e.g. FH presenting with acute MI).

The qualifier "statin therapy is not tolerated" is also added to category 3 on the basis of the doubts expressed by the committee regarding the "face validity" of the more favourable ICER for people with a mean LDL-C of 6mmol/L without CVD compared to non-FH CVD patients with a mean LDL-C of 4.0 mmol/L, considering this to be this counterintuitive. The RCPath does not consider this ICER to be counterintuitive, as the risk attributable to LDL-C is in fact greater in FH patients without CVD, in whom other risk factors are typically well controlled, and few, if any non-FH CVD patients have LDL-C as high as 6.0 mmol/L. In addition to including patients with mutations conferring treatment resistance (e.g. PCSK9 gain of function, 2% of FH mutations) the severe FH patients have a higher risk due to elevated lipoprotein(a) (30% higher in FH than non-FH independent of isoform size) and early familial risk mediated by other genetic factors. Starting from pre-treatment LDL-C of up to 13 mmol/L (> 13 using homozygous) even those patients who can take maximum high intensity statins and ezetimibe (achieving 50-60% reduction at best) may fail to achieve adequate control and their risk remains extremely high. The best results will clearly be obtained when maximum high intensity statins and ezetimibe is combined with an anti-PCSK9 therapy. As with category 1 some may only be able to tolerate sub-maximal statin doses with some beneficial effect and to disqualify such patients for persisting with a submaximal dose would be a perverse incentive to discontinuation. The is no evidence to support the addition of the qualifier "statin therapy is not tolerated" to improve the ICER in this group and the RCPath recommends that this be removed from Category 3 as well as from Category 1.

The measurement of non-HDL-cholesterol is preferred for monitoring of response to lipid lowering therapy as assessment of response to treatment as recommended in the NICE Lipid Modification guideline CG181 for reasons explained in the Full Guideline. This states that *"The measurement of cholesterol, cholesterol sub-fractions and triglycerides are necessary to ensure treatment is appropriate. The GDG discussed that the Friedewald equation for calculation of LDL-cholesterol as commonly used for risk assessment requires a fasting sample and triglycerides below 4.5 mmol/litre. It is derived from a small number of patients (130) and the original study included very few patients with diabetes (<30). The GDG were aware that a recent very large database analysis had revealed excess variance and bias in the calculation of LDL cholesterol such that a complicated table of correction factors would have to be applied by clinical laboratories.[160] The formula was also limited in its utility at low LDL-cholesterol levels as seen with high-intensity statin treatment.[159] The use of direct LDL-cholesterol measurement is limited by cost and availability in the NHS. Meta-analyses of CVD outcomes in relation to lipid fractions by the Emerging Risk Factors collaboration and others have consistently shown the superior predictive value of non-HDL cholesterol (that is, the difference between total and HDL cholesterol) on CV events.[73] Non-HDL cholesterol does not require a fasting blood sample. The GDG decided that the use of non-HDL cholesterol was preferable to calculated or measured LDL cholesterol given its greater practicality"*. The equivalent non-HDL-cholesterol of 5 mmol/L was suggested after careful consideration by the RCPath, on the basis that the (non-HDL-cholesterol – LDL-cholesterol) difference of 1 mmol/L equates to the Friedewald calculated VLDL-cholesterol at a fasting triglyceride value of 2.2 mmol/L. This is likely to be more slightly more difficult to achieve than the corresponding LDL-C threshold and is not likely to affect the numbers of patients being considered eligible, except due to greater practicability of sample collection.

The RCPath recommends therefore that this treatment should be an option for patients with
-primary non-familial hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic cardiovascular disease (CVD)
-primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic CVD
-severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD,

with pre-treatment LDL-C concentrations above 8.0 mmol/litre
be considered for treatment if they have:
-persistently high non-high density lipoprotein cholesterol (LDL-C) concentrations above 5.0 mmol/litre and/or low-density lipoprotein cholesterol (LDL-C) concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy
-or initial statin therapy is contraindicated
-or statin therapy is not tolerated
-or statin dose titration is limited by intolerance

The RCPath would like to see some guidance regarding frequency of monitoring as required to detect loss of response (which might potentially occur due to development of neutralizing antibodies). A three month interval for lipid monitoring in the first year, perhaps with less frequent monitoring in the second and subsequent years, would seem appropriate. Where there is secondary loss of response, access for clinicians to measurements of drug and anti-drug antibodies would of great value, and would be essential for investigation of suspected antibody mediated adverse reactions. The manufacturer should support the provision of such an analytical service.

MSD Response to NICE ACD for evolocumab

MSD welcomes the opportunity to comment on the appraisal consultation document (ACD) for evolocumab.

MSD has comments on the following areas in the ACD recommendation, which are outlined in more detail below:

- Misleading and inconsistent use of terminology between recommendation and NICE Lipid Modification Guideline (CG181)
- Relevance of the patient access scheme to the recommendation

Misleading and inconsistent use of terminology between recommendation and NICE Lipid Modification Guideline (CG181)

- **'Lipid lowering therapies' & 'lipid lowering therapy'**

  In section 1.1, these terms are used interchangeably to encompass either a statin and ezetimibe (the only non-statin lipid lowering therapy recommended in CG181) or ezetimibe (the only non-statin lipid lowering therapy recommended in CG181). MSD is concerned this exchangeability of terms may cause confusion in the recommendations interpretation.

  This is compounded when referring to *'maximal tolerated lipid-lowering therapy*' where following language from CG181 we assume that the committee is talking about ezetimibe but the use of *'maximal tolerated'* suggests a statin also, as ezetimibe is only available as one dose (10mg).

  For consistency, MSD suggests the removal of the term *'lipid lowering therapies'* and that where the term '*other lipid lowering therapy*' is used it refers only to ezetimibe and statins be mentioned separately to the term – this would be in line with terminology used in CG181 and be clear to readers. Consequently, MSD would also request the removal of '*maximal tolerated*' if '*lipid lowering therapy'* refers to ezetimibe only.

Relevance of the patient access scheme to the recommendation

The following comments are made on the assumption that a positive recommendation would not have been made in the absence of the patient access scheme.

The text of the guidance document discusses a potential challenge around the applicability of the patient access scheme in relation to prescribing potentially occurring in primary care where the patient access scheme would not apply. The text of the document also is clear that it is expected that prescribing should only occur in secondary care.

It is suggested that the recommendation 1.1, as currently worded, does not reflect the discussion and intention recorded in the document. A potential remedy for this would be to explicitly state in section 1 that, initial and repeat prescribing should occur only in a secondary care setting.

We would also note that in section 1.1 of the ACD, there is the statement making recommendations for:

> *"Severe primary heterozygous-familial hypercholesterolaemia or mixed dyslipidaemia without CVD, with pre-treatment LDL-C concentrations above 8.0 mmol/litre"*

MSD suggests the term severe is superfluous in this sentence.

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Thank you for the opportunity to review the updated ACD on evolucumab.

I agree with the document's strategy and suggested patient pathway.

There are a couple of minor points of wording and clarification that need to be addressed.

1.1a This would be better phrased as

the person has:
□ primary non-familial hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic cardiovascular disease (CVD), and persistently high low-density lipoprotein cholesterol (LDL-C) concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy **and**
□ high potency high dose statin therapy is not tolerated (as defined in NICE's guideline on familial hypercholesterolaemia: identification and management)

This includes a tautology. NICE CG71relies on the prescription of high potency high dose statins. This clarifies the indication as high residual LDL-C despite highest tolerated dose of any statin.

1.1b This would be better phrased as
primary ~~heterozygous-familial~~ hypercholesterolaemia or mixed dyslipidaemia with progressive, symptomatic CVD, and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy

This differentiates 1.1.b from 1.1a. There is a small population of individuals who do not have genetically proven familial hypercholesterolaemia but do have severe hypercholesterolaemia or mixed hyperlipidaemia of polygenic origin who cannot reach even population average lipid levels despite second-line agents due to partial or total statin intolerance. They often have aggressive coronary heart disease with no other treatment option except apheresis and evolucumab would be clinically indicated in this group.

1.1C
severe primary heterozygous-familial hypercholesterolaemia ~~or mixed dyslipidaemia~~ without CVD, with pre-treatment LDL-C concentrations above 8.0 mmol/litre and persistently high LDL-C concentrations above 4.0 mmol/litre despite maximal tolerated lipid-lowering therapy **and**

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□ statin therapy is not tolerated (as defined in NICE's guideline on familial hypercholesterolaemia: identification and management) **or**

□ initial statin therapy is contraindicated

The indication here is, I believe, meant to reflect primary prevention in patients with familial hypercholesterolaemia with severe disease (90th centile). Mixed dyslipidaemia should be excluded as no studies have evaluated the efficacy of evolucumab or any other PCSK-9 in patients with triglycerides >4.5mmol/L. There is a group of patients with other genetic disorders of lipid metabolism who can have high levels of triglycerides and total cholesterol and in whom inappropriate calculation (as opposed to measurement) of LDL-C may give rise to a 'high ' LDL-C- many of whom will have remnant hyperlipidaemias. Use of evolocumab in this patient group has never been studied and should not be recommended at this time.

Yours Sincerely

[redacted]

Anthony S. Wierzbicki