National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (review of TA132)

Response to consultee and commentator comments on the draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Merck Sharp & Dohme	In paragraph three, prevalence and epidemiological data is presented for primary hypercholesterolaemia. This looks to be an underestimate of primary non-familial hypercholesterolaemia in England. In the Use of NICE appraised medicines in the NHS in England – 2010 and 2011, Experimental statistics[1] report published by the Health & Social Care Information Centre (HSCIC) in October 2012, the prevalence of primary (familial or non-familial) hypercholesterolaemia was estimated at 6.94% of a population of 51,438,821. Familial hypercholesterolaemia affects 1 in 500, 103,000 or 0.2%. Therefore, according to H&SCIC's calculation, primary non-familial hypercholesterolaemia affects 6.92%, approximately 3.5 million people in England. Additionally, in the same H&SCIC report it states that 32% of patients receive lipid-modifying treatment, not 460,000 out of 600,000 (77%) as stated in the draft scope. MSD request that NICE use accurate data to reflect epidemiological data and provide a reference to substantiate this. In addition please reference the source for the statistics for approximate deaths attributed to CVD in 2011 in paragraph four. Ref 1: H&SCIC (2012) Use of NICE appraised medicines in the NHS in England – 2010 and 2011, Experimental statistics. [online] available from: http://www.hscic.gov.uk/catalogue/PUB07985/use-nice-app-med-nhs-exp-stat-eng-10-11-rep.pdf accessed March 19th 2015.	Comment noted. The background section of a scope is intended to provide a brief overview of the condition and is aligned with previous scopes for the same condition. No change to the scope required.
	Merck Sharp &	On page 2, first paragraph, please update the text around lipid-regulating drugs	Comment noted. NICE clinical

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	Dohme	to reflect NICE guideline CG181. The current text states that "fibrates, nicotinic acid derivatives or bile acid sequestrants may also be used." This is inaccurate as CG181 does not recommend fibrates, nicotinic acid derivatives, bile acid sequestrants or omega-3 fatty acid compounds (please see CG181, sections 1.3.45 to 1.3.50).	guidelines are not mandatory, which is why the draft scope stated that they *may* be used and included a question for consultation about their use. Following feedback at consultation, these treatments have been removed from the background section of the scope.
	Merck Sharp & Dohme	The second paragraph on page two that describes the recommendations from TA132 is not complete. TA132 recommends ezetimibe for primary heterozygous-familial and non-familial hypercholesterolaemia not just heterozygous familial hypercholesterolaemia. Please amend the text to: "NICE technology appraisal 132 recommends ezetimibe as an option for treating primary (heterozygous-familial and non-familial) hypercholesterolaemia, as a monotherapy when statins are contraindicated or not tolerated and in combination with statins when initial statin therapy does not provide appropriate control of LDL-cholesterol"	Comment noted. The scope has been amended to specify that the recommendations in NICE technology appraisal guidance 132 apply to primary (heterozygous familial or non-familial) hypercholesterolaemia.
	Royal College of Pathologists	Heteterozygous FH may be also caused by mutations in the APOB and PCSK9 genes	Comment noted.
The technology/ intervention	Merck Sharp & Dohme	The description is accurate.	Comment noted.
	Royal College of Pathologists	Ezetimibe blocks NCP1L1, inactivating genetic mutations of which have recently been shown to be associated with reduced cardiovascular disease risk.	Comment noted.
Population	Merck Sharp & Dohme	MSD considers that the population from the draft scope should be amended slightly. CG181 describes the appropriate options for lipid modification, and ezetimibe has a particular place in the treatment pathway. The population	Comment noted. Ezetimibe will be appraised within its marketing authorisation:

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		should be defined as: "People with primary heterozygous familial or non-familial hypercholesterolaemia: • Co-administered with statin: people whose condition is not appropriately controlled with a statin alone, either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance **or** • Monotherapy: patients in whom a statin is considered inappropriate or is contraindicated or not tolerated."	• co-administered with statin in people with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone • as monotherapy in people with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated. This will be achieved by considering the intervention as well as the population as presented in the scope. No change to the scope required.
	Royal College of Pathologists	Patients with CKD and diabetes are at higher risk and may behave differently, so should be considered separately.	Comment noted. The company has advised that, if evidence allows, it will present a ranges of subgroups in its evidence submission, including people with CKD and diabetes.
Comparators	Merck Sharp & Dohme	MSD considers that the comparators from the draft scope should be amended slightly. CG181 describes the appropriate options for lipid modification, and ezetimibe has a particular place in the treatment pathway, which dictates the appropriate comparators. The comparators should be defined as:	Comment noted. The Committee will consider the definition of optimal statin therapy during the course of

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		"For people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone: • Optimal statin therapy (maximum tolerated dose) For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is contraindicated or not tolerated: • No treatment" In the second scenario other lipid regulating drugs has been removed and replaced with no treatment. After initial statin therapy only ezetimibe is recommended by NICE as an option for lipid modification.	the appraisal with input from various stakeholders. It is not appropriate to restrict it to maximum tolerated dose in the scope. 'Guide to methods of technology appraisal' advises that treatments used in established NHS practice in England should be included as comparators, and that the scope should be inclusive. Other consultation responses indicated that alternative treatment was used in this patient group. No changes to the scope required.
	Royal College of Pathologists	Bile Acid Sequestrants are an appropriate comparator for FH. Other lipid regulating are not recommended for non-FH in CG181 Yes. Optimal statin therapy is regarded as the standard care; there is no established 'best alternative'.	Comment noted. No change to the scope required.
Outcomes	Merck Sharp & Dohme	These outcome measures are appropriate. MSD considers that to effectively assess the full license indication for ezetimibe change in LDL-c is the most important outcome to allow modelling of CV events using CTT collaboration meta-analysis.	Comment noted.

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	Royal College of Pathologists	Change in non-HDL-C should be added in line with CG181	Non-HDL cholesterol has been added to the list of outcomes in the scope.
Economic analysis	Merck Sharp & Dohme	No comment.	Comment noted.
	Royal College of Pathologists	A 5 year time horizon would be appropriate. Ezetimibe is likely to come off patent in 2018/9	Comment noted. The NICE reference case states that the time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. Generally a lifetime time horizon is adopted for chronic conditions. In a single technology appraisal like this one, it will ultimately be the company's choice in preparing its evidence submission and the Appraisal Committee's decision in what it considers acceptable.
Equality and Diversity	Merck Sharp & Dohme	No comment.	Comment noted.
	Royal College of Pathologists	No comments.	Comment noted.
Other considerations	Merck Sharp & Dohme	The other considerations box in the draft scope states that: "Appropriate control of cholesterol concentrations should be based on individualised risk assessment in line with NICE clinical guideline 71."	Comment noted. The request regarding appropriate control of cholesterol concentrations

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		This should be amended to: "Appropriate control of cholesterol concentrations should be based on individualised risk assessment in line with NICE clinical guideline 181."	individualised risk assessment has been removed from the scope, in line with other recent scopes in this therapy area.
	Royal College of Pathologists	Ezetimibe is considered of value in sitosterolaemia, are rare condition characterised by excessive absorption/retention of this phytosterol.	Comment noted. The technology will be appraised according to its marketing authorisation. No change to the scope required.
Questions for consultation	Merck Sharp & Dohme	*Is it appropriate to review the guidance on ezetimibe (NICE technology appraisal guidance 132) based on this new evidence or should the guidance be moved to the static list?* It is appropriate to review the guidance on ezetimibe through the STA process. The results from the IMPROVE-IT study evaluating the effect of adding ezetimibe to simvastatin 40 mg on CV endpoints has recently completed. In addition, NICE clinical guideline CG181 was published in July 2014, therefore a review of ezetimibe is appropriate to align with current clinical practice.	Comment noted.
	Merck Sharp & Dohme	*Have all the relevant comparators for ezetimibe been included in the scope?* For people with primary heterozygous familial or non-familial hypercholesterolaemia whose condition is not appropriately controlled with a statin alone: • Only statin therapy (atorvastatin, simvastatin, pravastatin and fluvastatin) is a comparator. Statins in combination with fibrates, bile acid sequestrants, nicotinic acid and omega-3 fatty acid compounds are not recommended by NICE. • Rosuvastatin is not recommended within the guideline CG181. The full guideline states 'Given the considerably higher cost of using rosuvastatin, it would need to be considerably more effective than atorvastatin for there to be a possibility that its use could be cost effective. In the absence of trial evidence of greater effectiveness the	Comments noted. Specific statins have not been listed in the scope. 'Guide to methods of technology appraisal' advises that treatments used in established NHS practice in England should be included as comparators, and that the scope should be inclusive. Other consultation responses indicated that alternative

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		guideline development group are therefore unable to recommend the use of rosuvastatin'. For people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated: • Only no treatment is a comparator. Fibrates, bile acid sequestrants, nicotinic acid and omega-3 fatty acid compounds are not recommended by NICE.	treatment was used in people with primary heterozygous familial or non-familial hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated. No changes to the scope required.
	Merck Sharp & Dohme	*Are there any subgroups of people in whom ezetimibe is expected to be more clinically effective and cost effective or other groups that should be examined separately?* MSD anticipate analysis of the following sub-groups, dependant on data being available: • Primary prevention • Primary prevention with diabetes • People with CKD • Secondary prevention • Heterozygous-familial hypercholesterolaemia	Comment noted.
	Merck Sharp & Dohme	*Where do you consider ezetimibe will fit into the existing NICE pathway, familial hypercholesterolaemia?* MSD consider that for primary heterozygous non-familial hypercholesterolaemia ezetimibe fits into the pathway according to CG181. For heterozygous-familial hypercholesterolaemia ezetimibe fits into the pathway according to CG71.	Comment noted.
	Royal College of Pathologists	In view of the new evidence which is available, it is appropriate to review the guidance	Comment noted.
	Royal College of Pathologists	Other lipid regulating drug comparators previously considered are no longer recommended for non-FH in CG181	Comment noted.

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		Bile acid sequestrants are an appropriate comparator for FH only. Relevant comparators for ezetimibe have been included in the scope.	
	Royal College of Pathologists	Potential subgroups of people in whom ezetimibe is expected to be more clinically effective and cost effective or other groups that should be examined separately include: i. Secondary CVD event prevention ii. Diabetes iii. Metabolic syndrome / fatty liver iv. CKD	Comment noted.
	Royal College of Pathologists	In the NICE FH pathway, ezetimibe fits in if optimal statin therapy is not effective (in reducing LDL-C by >50%) or is not tolerated; in the latter situation ezetimibe may be used with a reduced dose of statin, or exceptionally, as monotherapy. Ezetimibe is considered the current "standard of care" for statin intolerant patients, particularly those with myopathy.	Comment noted.
	Royal College of Pathologists	Ezetimibe is well tolerated and has an established role in lipid management. It is a unique drug but no longer considered innovative, nor a step change in management.	Comment noted.
Additional comments on the draft scope.	Merck Sharp & Dohme	Please change the remit to better reflect the positioning for ezetimibe: "To appraise the clinical and cost effectiveness of ezetimibe within its licensed indication for treating primary heterozygous-familial and non-familial hypercholesterolaemia in adults."	Comment noted. The remit is received from the Department of Health and should not be changed by NICE.
	Royal College of Pathologists	No.	Comment noted.

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Remove Genetic Alliance	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. Remove Genetic Alliance has not been included in the matrix of consultees and commentators

2.	Remove Weight Centres	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. Remove Weight Centres has not been included in the matrix of consultees and commentators
3.	National Obesity Forum	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. National Obesity Forum has not been included in the matrix of consultees and commentators

4.	Stroke Association	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. Stroke Association has not been included in the matrix of consultees and commentators
5.	Weight Concern	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. Remove Weight Centres has not been included in the matrix of consultees and commentators

6.	Coronary Prevention Group	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Coronary Prevention Group has been added to the matrix of consultees and commentators under 'patient/carer groups'.