National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Daiichi Sankyo UK	Yes	Comment noted. No action required.
	British Cardiovascular Society	Yes. Its generic for known drugs approved for LDL lowering. So statins, MAbs, eztemibe. Stains and ezetemibe are generic. Note Bempedoic acid is available in combination with eztemibe which would mean depending upon pricing that part is free.	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Wording	Daiichi Sankyo UK	Yes	Comment noted. No action required.

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	British Cardiovascular Society	The wording does not reflect the population need. Despite the clear benefit of statins and the low cost, media scare stories have impacted on statin uptake or adherence, reported side effects. PCSK9 inhibitors are cost effective and the NICE thresholds of 3.5 (very high ASCVD), 4.0 (high risk CVD) and 5 mmol/L (heFH primary prevention) for different scenarios for Mabs mean many patients remain at LDL-C levels at much higher levels than desirable so there is an urgent need to find cheaper alternatives to reduce this inequity in NICE guidelines at present. Also Mabs are not approved by NICE for primary prevention and DM primary prevention.	Comment noted. Bempedoic acid will be appraised within its marketing authorisation.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Timing Issues	Daiichi Sankyo UK	If referred by the Department of Health, Daiichi Sankyo consider the proposed NICE Single Technology Appraisal (STA) process is appropriate to ensure timely guidance to the NHS	Comment noted. No action required.
	British Cardiovascular Society	Normal	Comment noted. No action required.
	Royal College of Pathologists	Not urgent	Comment noted. No action required.

Comment 2: the draft scope

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Background information	Daiichi Sankyo UK	Page 1:"*Primary hypercholesterolaemia is associated with an underlying genetic cause, which may be caused by a single genetic defect (familial), or more commonly, by the interaction of several genes with dietary and other factors such as smoking or physical inactivity (non-familial).*" Smoking and physical inactivity lead to heart disease but do not cause high cholesterol. Suggest rewording to aid clarity. Page 1-2: "*Primary non-familial hypercholesterolaemia affects about 4% of the adult population, totalling approximately 1.5 million people in England, of whom an estimated 600,000 are diagnosed and 460,000 are receiving treatment. Primary heterozygous familial hypercholesterolaemia affects an estimated 1 in 500 people, totalling 106,000 in England (although only 15–17% are diagnosed).*" This is considered to be an underestimate of primary non-familial hypercholesterolaemia in England based on published literature. 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%. In the current NICE clinical guideline 'Familial hypercholesterolaemia: identification and management' (https://www.nice.org.uk/guidance/cg71), the prevalence of heterozygous familial hypercholesterolaemia in the UK population is estimated to be somewhere between 1 in 250 and 1 in 500, which means that between approximately 130,000 and 260,000 people are affected. Further, the guideline states that the clinical community recognises that familial hypercholesterolaemia is underdiagnosed, with prevalence more likely to be approximately 1 in 250. Ref 1: H&SCIC (2012) Use of NICE appraised medicines in the NHS in England – 2010 and 2011, Experimental statistics. [online] available from:	Thank you for your comments. The background section of the scope has been updated.

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		https://files.digital.nhs.uk/publicationimport/pub13xxx/pub13413/use-nice-app-med-nhs-exp-stat-eng-12-rep.pdf; (last accessed 01/03/2019)	
	British Cardiovascular Society	Yes but scale of issues with people intolerant of statins and burden of LDL in UK missing for contextualise need.	Comment noted. The background section of the scope is only intended to briefly describe the disease, prognosis associated with the condition, epidemiology and treatments currently used in the NHS.
	Royal College of Pathologists	The description of mutations causing FH is not entirely accurate. The dose of alirocumab is incorrect.	Comments noted. The background section has been updated.
The technology/ intervention	Daiichi Sankyo UK	Page 2: Bempedoic acid (brand name unknown, Esperion Therapeutics) – please add: commercialisation by Daiichi Sankyo in EU/UK Page 2: "is a pro-drug that is activated in the liver." We recommend to add that this liver specific mode of action has the potential to avoid the muscle related ADRs associated with statin therapy.	Comment noted. The technology section has been updated to reflect Daiichi Sankyo's involvement in the commercialisation of bempedoic acid in the UK. With regard to the liver-specific mode of action, the company can expand on the benefits of this in its evidence submission if

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			referred for a technology appraisal.
	British Cardiovascular Society	Yes	Comment noted. No action required.
	Royal College of Pathologists	Unknown to me	Comment noted. No action required.
Population	Daiichi Sankyo UK	Yes, see also comment in comparator section	Comment noted. No action required.
	British Cardiovascular Society	Yes	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Comparators	Daiichi Sankyo UK	Page 2-3: We recommend to replace “optimised statin therapy” with “when maximum tolerated statin dose” does not appropriately control LDL-C as a more accurate description. Page 3: between the 2 mentioned populations we recommend to add the following to have more complete/accurate description of potentially relevant populations: - When LDL-C is not adequately controlled with the maximum tolerated statin dose in combination with ezetimibe: - Evolocumab in combination with ezetimibe and a statin - Alirocumab in combination with ezetimibe and a statin	Comment noted. The comparator section has been updated following further discussion with the company at the decision problem meeting. Additional comparators include: When statins are contraindicated or not tolerated, and ezetimibe

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			does not appropriately control LDL-C: • Ezetimibe (when evolocumab and alirocumab are not appropriate) • Evolocumab (with or without another lipid-lowering therapy) • Alirocumab (with or without another lipid-lowering therapy) When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: • Ezetimibe with a statin (when evolocumab and alirocumab are not appropriate) • Evolocumab with a statin

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			(with or without another lipid-lowering therapy) • Alirocumab with a statin (with or without another lipid-lowering therapy)
	British Cardiovascular Society	Yes	Comment noted. No action required.
	Royal College of Pathologists	Yes, along with lifestyle modification	Comment noted. No action required.
Outcomes	Daiichi Sankyo UK	We would like to add high-sensitivity C-reactive protein (hsCRP) level as a clinically relevant outcome.	Comment noted. Clinical outcomes that reflect survival or health-related quality of life are preferred over surrogate outcomes in technology appraisals. If surrogate outcomes are used to model the effect of treatment on mortality and/or health-related quality of life, the relationship between the surrogate

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			and final outcome should be explained and justified, and this would be associated with some degree of uncertainty. Please see Guide to the methods of technology appraisal (2013) for further details. No changes required.
	British Cardiovascular Society	Inappropriate as there are no data on adverse cardiovascular events, mortality, apharesis etc. The outcomes studied are LDL-C reduction, Non-HDL-C or apo B. All causal all atherogenic. Lp(a) whilst likely causal is irrelevant as no therapies are approved for lp(a) lowering and CVD reduction. The CVOT trials are ongoing.	Comment noted. Clinical outcomes that reflect survival or health-related quality of life are preferred over surrogate outcomes in technology appraisals. If surrogate outcomes are used to model the effect of treatment on mortality and/or health-related quality of life, the relationship between the surrogate and final outcome should be explained and justified, and this would be associated

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			with some degree of uncertainty. Please see Guide to the methods of technology appraisal (2013) for further details. No changes required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Economic analysis	British Cardiovascular Society	Yes	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Equality and Diversity	British Cardiovascular Society	See comments above. Because NICE has approved PCSK9 MAbs at a higher LDL-C threshold based on cost effectiveness they have created inequalities for people say in the 1.8-3.5, or 1.8-4, or 1.8 to 5 mmol/L range who have limited options for add on therapy as they are ineligible for a Mab. Also for diabetes and primary prevention patients NICE does not approve MAbs so there is a inequality at present as many if they can't tolerate statins only have eztemibe and despite that may still have high LDL levels.	Thank you for your comments. If this topic is referred as an appraisal, the appraisal committee will take into account potential equality issues relevant to its recommendations. No changes to the scope are needed.

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	Royal College of Pathologists	No	Comment noted. No action required.
Other considerations	British Cardiovascular Society	As mentioned above and below	Comment noted. No action required.
	Royal College of Pathologists	Patients with diabetes and children with FH might be other groups to consider	Thank you for your comment. Subgroups may be included in the company's submission if evidence allows. Treatment in children may be considered if included in the marketing authorisation for bempedoic acid.
Innovation	Daiichi Sankyo UK	Bempedoic acid's mode of action – with potential to avoid muscle side effects - in combination with its convenient oral administration provides potential for a step-change in the treatment of primary hypercholesterolemia and mixed dyslipidemia: Bempedoic acid's mechanism of action is similar to that of statins: it inhibits cholesterol synthesis and upregulates LDL receptors on liver cells and lowers LDL-C. However, unlike statins, bempedoic acid does not inhibit the cholesterol biosynthesis pathway in skeletal muscle, nor promote the associated cytotoxicity believed to lead to muscle-related side effects. It is differentiated in one key way: bempedoic acid is inactive until it enters the liver where it is converted to its active form by the enzyme, ACSVL1, an enzyme not found in skeletal muscle cells.	Comment noted. The committee would consider the innovative nature of bempedoic acid during the course of an appraisal.

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		[Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis, Stephen L. Pinkosky and all ; https://www.nature.com/articles/ncomms13457]	
	British Cardiovascular Society	First in class. Novel mechanism of action . Drug is a pro drug. Works through the same pathway as statins, genetics suggest per mmol/L same benefit as a per mmol/L lowering with statins. Because the drug is activated in the liver and once that happens cannot leave the hepatocyte the common muscle related side effects should be limited . This is one of the biggest barriers to statin uptake and adherence/ discontinuation.	Comment noted. The committee would consider the innovative nature of bempedoic acid during the course of an appraisal.
	Royal College of Pathologists	Potentially	Comment noted. The committee would consider the innovative nature of bempedoic acid during the course of an appraisal.
Questions for consultation	Daiichi Sankyo UK	If referred by the Department of Health, Daiichi Sankyo consider the proposed NICE STA process is appropriate to ensure timely guidance to the NHS.	Comment noted. No action required.
	British Cardiovascular Society	A key consideration is what to do re statin intolerance for patients with LDL below the NICE reimbursement threshold of MAbs . They are currently left at higher levels. As this drug lowers LDL by around 30% and 50% with eztemibe in patients with say an LDl of 3mmol/L below a reimbursed PCSK9i and intolerant of statins the absolute LDL reduction would be 1.5 mmol/L or about a 32% RRR over 5 years which could be applied to their 10 y risk to calculate ARR. This portion of the population is not inconsequential.	Comment noted. No action required.

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Additional comments on the draft scope	British Cardiovascular Society	See above details. Safety data has been provided at 1 y in 2200 people in press next week. Combination therapy with Ezetemibe gives 50% reduction in LDL , addition to statins gives 18% LDL reduction. Good safety profile and CVOT ongoing. Its at the same stage Eze, MAbs were when they were approved for LDL lowering by NICE.	Comment noted. All relevant evidence submitted by consultees will be considered by the appraisal committee.

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

Amgen

Department of Health and Social Care