National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia ID1647

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Heart UK	The majority of individuals diagnosed with a primary dyslipidaemia will require lifelong treatment with cholesterol lowering medication in order to reduce their chances of early and avoidable death from coronary heart disease. These patients are often highly motivated to make changes to their diet and lifestyle and to maintain regular medication.	Thank you for your comment. No change to scope.
	British Cardiovascular Society	Yes [it would be appropriate to refer this topic to NICE for appraisal]	Thank you for your comment. No change to scope.
	Novartis Pharmaceuticals UK Ltd	We consider it appropriate to refer this topic to NICE for appraisal.	Thank you for your comment. No change to scope.
Wording	British Cardiovascular Society	Yes [the wording of the remit reflects the issue(s) of clinical- and cost-effectiveness about this technology that NICE should consider]	Thank you for your comment. No change to scope.

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	Novartis Pharmaceuticals UK Ltd	We consider the proposed wording [of the remit] appropriate.	Thank you for your comment. No change to scope.
Timing Issues	British Cardiovascular Society	It is important to assess interventions which might lower cardiovascular morbidity and mortality in a timely manner. Clinical outcome data from randomised controlled trials for this drug are not yet available. However, low density lipoprotein cholesterol (LDL-C) is an established causal factor for cardiovascular disease (CVD), LDL-C lowering is an accepted indication for treatment by the FDA and EMEA, and is often considered before indications for CVD prevention (usually from parallel ongoing trials). UK general practice data show that many patients do not reach target LDL-C levels using standard therapies - the average LDL-C in such patients is about 2.5 mmol/L on statin therapy. Use of ezetimibe is low at about 10% and the cost and pathway to PCSK9 monoclonal antibodies (currently reserved for high risk patients who have LDL> 3.5 or 4 mmol/L) has limited their uptake to a few thousand people nationally. So the bulk of higher risk patients are in the 1.8 -3.5 mmol/L range. Doubling the dose of statins achieves 6% lowering of LDL-C, use of ezetimibe achieves 20-25% LDL-C lowering, hence even if statins are optimised and ezetimibe used more frequently, LDL-C levels will remain above 1.4 mmol/L for many high risk patients. There is, therefore, a large population of patients who might benefit from cost effective, safe, convenient, potent therapies which lower LDL-C. A suitably priced therapy which reduces LDL-C by 50% would significantly improve the population distribution of LDL-C to the left, targeting this middle group of patients.	Thank you for your comment. No change to scope.
	Novartis Pharmaceuticals UK Ltd	Inclisiran offers a novel, durable and first-in-class treatment to reduce low-density lipoprotein cholesterol (LDL-C) levels, which could improve long-term cardiovascular outcomes in patients with atherosclerotic cardiovascular disease (ASCVD), ASCVD-risk equivalents, heterozygous familial	Thank you for your comment. No change to scope.

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		hypercholesterolemia (HeFH) and mixed dyslipidaemia. Its twice-yearly injection regimen offers the potential for patients to reach their LDL-C goals with minimal burden on the healthcare system, as well as the potential to reduce existing adherence concerns. This is a clear concern for NICE and NHS England since current medicines are limited by poor adherence and persistence,[1] with a reported high levels of non-adherence in the range of 33%-50%.[2-3] On 13th January 2020, Novartis announced its plans to collaborate with NHS England to tackle the burden of cardiovascular disease in the UK and, subject to approval of the marketing authorisation and NICE reimbursement, provide inclisiran to secondary prevention ASCVD patients through a population-level type agreement. We therefore believe that inclisiran should be reviewed promptly by NICE to enable timely implementation of the population health agreement. *1 Nieuwlaat R, et al. Interventions for enhancing medication adherence. Cochrane Systematic Review - Intervention Version published: 20 November 2014* *2 NICE CG76* *3 Khatib R, et al. Adherence to coronary artery disease secondary prevention medicines: exploring modifiable barriers*	
Additional comments on the draft remit	Novartis Pharmaceuticals UK Ltd	No comments.	No change to scope.

Comment 2: the draft scope

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Background information	British Cardiovascular Society	The background is well written. It might be worth including a comment about the benefits achieved with statins and the potential problems with them – if they were fully effective and caused no problems, there would be no need for this technology appraisal! In addition, there is clear evidence, as described in the ESC/EAS 2019 guidelines, that those at highest risk benefit from LDL-C lowering to around 1.4 mmol/L. This is more than can be achieved with monotherapy for many patients.	Thank you for your comment. The background section is intended to provide a brief overview of the disease and its management. No change to scope.
	Novartis Pharmaceuticals UK Ltd	No comments.	No change to scope.
The technology/ intervention	British Cardiovascular Society	Yes [the description of the technology is accurate].	Thank you for your comment. No change to scope.
	Novartis Pharmaceuticals UK Ltd	No comments.	No change to scope.
Population	British Cardiovascular Society	Appropriate [i.e., the population is defined appropriately]	Thank you for your comment. No change to scope.
	Novartis Pharmaceuticals UK Ltd	The population broadly captures the anticipated licensed indication for inclisiran which is for:	Thank you for your comment. No change to scope.

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		[redacted]	
	Sanofi Aventis	Would be good to clarify if the population referred to was that for primary prevention or for secondary prevention.	Thank you for your comment. The population has been kept broad to cover both primary and secondary prevention, in line with previous scopes in the therapy area (TA393, TA394, ID1515). No change to scope.
Comparators	British Cardiovascular Society	Statins are the standard of care for primary hypercholesterolaemia. However, they may not lower LDL-cholesterol concentration sufficiently by themselves and require add-on therapy, or they may be contraindicated or not tolerated. Comparators should include placebo, Ezetimibe, (monoclonal antibody) PCSK9 inhibitors. Consider Bempenoic acid/Ezetimibe fixed dose combination therapy as a comparator.	Thank you for your comment. Statins have been added to the scope to keep the comparator section inclusive. Bempedoic acid has been added as a comparator, subject to ongoing NICE appraisal. Homozygous

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		Lomitapide is a relevant comparator for homozygous familial hypercholesterolaemia.	FH is not in scope, so lomitapide is not a relevant comparator.
	Novartis Pharmaceuticals UK Ltd	Novartis suggests to consider patients who are intolerant to statins or for whom statins are contraindicated as a subgroup of the main population: when maximally tolerated statin dose does not appropriately control LDL-C. This is because the maximally tolerated statin dose can be zero i.e. patient intolerant to statins. Novartis suggests the comparator section is re-written as follows: • standard of care i.e. maximally tolerated statin dose (with or without another lipid-lowering therapy) For people eligible for proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i's): • evolocumab with maximally tolerated statin dose with or without another lipid-lowering therapy • alirocumab with maximally tolerated statin dose with or without another lipid-lowering therapy We consider ezetimibe as a component of standard of care (and not a standalone comparator) for the following reasons: • The anticipated marketing authorisation for inclisiran will not preclude the use of inclisiran in addition to ezetimibe. • Ezetimibe is not sufficient for patients with higher baseline LDL-C to reach their targets which could explain the low use of ezetimibe in clinical practice (2-10% of patients with FH, ASCVD and ASCVD risk-equivalents treated with a lipid lowering therapy in England [1-5], and as such inclisiran is unlikely to displace the use of ezetimibe.	Thank you for your comment. Maximally tolerated statins have been added to the scope, and ezetimibe monotherapy remains in scope, to keep the scope inclusive.

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		1 *Bellows BK, et al. Identification of Patients with Statin Intolerance in a Managed Care Plan: A Comparison of 2 Claims-Based Algorithms. Journal of Managed Care & Specialty Pharmacy. 2017;23(9):926-34*. 2 *Steen DL, Ray KK, et al. Retrospective examination of lipid-lowering treatment patterns in a real-world high-risk cohort in the UK in 2014: comparison with the National Institute for Health and Care Excellence (NICE) 2014 lipid modification guidelines. BMJ Open. 2017;7(2):e013255.* *3 Decision Resources Group. Dyslipidemia Disease Landscape & Forecast Report 2018-2028 (Market-Forecast-Assumptions)* *4 IQVIA: Patient equivalent numbers derived from historical IQVIA RxA C10 unit sales data* *5 Novartis Advisory board*	
Outcomes	British Cardiovascular Society	Currently cardiovascular outcomes data are not available. However, as LDL-C concentration is causally and cumulatively related to cardiovascular outcomes, the clinical benefits can be estimated based on its absolute lowering and years of treatment. Nevertheless, the results of clinical outcome trials remain key to understanding the importance of this drug.	Thank you for your comment. No change to scope.
	Novartis Pharmaceuticals UK Ltd	We consider the outcomes specified to be broadly appropriate. However, apheresis is generally prescribed for homozygous familial hypercholesterolaemia, which is not part of the targeted population, and used very infrequently in England.	Thank you for your comment. NICE CG71 recommends that in exceptional circumstances LDL apheresis can be offered to people with HeFH. No change to scope.

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Economic analysis	British Cardiovascular Society	Any economic analysis is likely to underestimate the true benefit as this treatment has the potential to overcome the major problem of adherence to long-term daily oral lipid lowering treatment or to the more frequently required PCSK9 monoclonal antibodies. Current poor adherence to statins and suboptimal prescribing accounts for about 23 cases of cardiovascular disease per 1000 per year compared to optimal adherence and prescribing.	Thank you for your comment. The economic benefits will be considered as part of the full appraisal process. No change to scope.
	Novartis Pharmaceuticals UK Ltd	No comments.	No change to scope.
Equality and Diversity	British Cardiovascular Society	No equality issues identified.	Thank you for your comment. No change to scope.
	Novartis Pharmaceuticals UK Ltd	No equality issues have been identified.	Thank you for your comment. No change to scope.
Other considerations	British Cardiovascular Society	This is a treatment which could be initiated in primary care. Currently many patients who meet criteria for more aggressive lipid lowering add-on therapies and are not referred to clinics in secondary care where such therapies might be initiated. Consideration of how this therapy might be administered in primary care is important.	Thank you for your comment. No change to scope.
	Novartis Pharmaceuticals UK Ltd	No comments.	No change to scope.

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Innovation	British Cardiovascular Society	This treatment is potentially practice-changing. Cardiovascular outcomes are related to lipid lowering treatment intensity and adherence. It offers the potential to improve population health by achieving annualised reductions in LDL-cholesterol of over 50% with two injections. It potentially overcomes the issues of poor adherence. (Khunti et al 2018 JAMA network Open)	Thank you for your comment. No change to scope.
	Novartis Pharmaceuticals UK Ltd	We consider inclisiran to be innovative as it is the first and only cholesterol-lowering small interfering ribonucleic acid (siRNA) that inhibits the synthesis of PCSK9 inside the cell, representing a step-change in the management of LDL-C levels (and consequently CV event risk) in patients with HeFH, ASCVD, and ASCVD risk-equivalents. The combination of inclisiran efficacy and twice-yearly injection regimen means that the treatment offers the potential to help patients reach their LDL-C goals with minimal administration requirements for the healthcare system as well as a potential for better adherence. For example, limited adherence to statins, which now dominate the market, in the range of 33%–50%, suggests a lack of persistence which is known to be strongly associated with poor outcomes.[1] *1 Khunti K, et al. Association of a Combined Measure of Adherence and Treatment Intensity With Cardiovascular Outcomes in Patients With Atherosclerosis or Other Cardiovascular Risk Factors Treated With Statins and/or Ezetimibe. December 7, 2018. JAMA Netw Open. 2018;1(8):e185554*	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No change to scope.
Questions for consultation	Novartis Pharmaceuticals UK Ltd	Have all relevant comparators for inclisiran been included in the scope? *Novartis: See comments in comparators section above.* Which treatments are considered to be established clinical practice in the NHS for primary hypercholesterolaemia and mixed dyslipidaemia? Is lomitapide a relevant comparator?	Thank you for your comments. No change to scope.

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		Novartis: We believe that that established clinical practice treatments for primary hypercholesterolaemia and mixed dyslipidaemia are lifestyle modifications (including dietary changes, exercise and smoking cessation) and lipid modification therapies, primarily high intensity statins. If desired reductions in LDL-C levels are not achieved with statins, additional options for treatment include the cholesterol absorption inhibitor ezetimibe, then PCSK9 inhibitors alirocumab and evolocumab. *We consider lomitapide not to be a relavant comparator since it is prescribed for homozygous familial hypercholesterolaemia, which is not part of the targeted population.* Are the outcomes listed appropriate? *Novartis: See comments in outcomes section above.* Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom inclisiran is expected to be more clinically effective and cost effective or other groups that should be examined separately? *Novartis: Subgroups are appropriate.* Where do you consider inclisiran will fit into the existing NICE pathways, cardiovascular disease prevention and familial hypercholesterolaemia? *Novartis: In the cardiovascular disease prevention pathway, we would expect inclisiran to be positioned in secondary prevention after statin with or without other lipid lowering therapy for patients who are uncontrolled despite receiving their maximally tolerated statin dose, and in primary prevention for*	

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		risk-equivalent patients who are uncontrolled despite receiving their maximally tolerated statin dose. *In the familial hypercholesterolaemia, we would expect inclisiran to be positioned for patients who are uncontrolled despite receiving their maximally tolerated statin dose.* NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which inclisiran will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. *Novartis: We understand that tackling health inequalities is at the forefront of the NHS' priorities and the proposed delivery model of inclisiran in primary care could enable easier access to all.*[1]	

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		1 Phase 3 letter to Chief executives of all NHS trusts and foundation trusts. 31 July 20 Do you consider inclisiran to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? *Novartis: See comments in Innovation section above.* Do you consider that the use of inclisiran can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. *Novartis: We believe that the potential improved adherence associated to the twice-yearly regimen of inclisiran compared to a daily oral molecule will not be captured as part of the QALY calculation.* To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. *Novartis: We believe that there will be no barriers to adoption of this technology, which will be facilitated by the collaboration with NHS England. It is anticipated that inclisiran will be managed in primary care reducing the need for secondary care referrals and thus costs associated with providing hypercholesterolaemmia services within the NHS.* NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of	

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		appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). *Novartis:* [redacted]. NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. • Would it be appropriate to use the cost comparison methodology for this topic? • Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? • Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? • Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? *Novartis: We do not believe that this topic will be appropriate for a cost comparison.*	
Additional comments on the draft scope	British Cardiovascular Society	It was noted that the Cardiac Care Partnership is included in the list of stakeholders, which we believe is appropriate since it is important to offer	Thank you for your comment. No change to scope.

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		patient groups the opportunity to provide input to consultations such as this one.	
	Novartis Pharmaceuticals UK Ltd	We believe that the Accelerated Access Collaborative should be added as a stakeholder.	Thank you for your comment. The Accelerated Access Collaborative (AAC) is made up of multiple organisations in the healthcare economy, and is not a legal entity. It is not the role of the AAC to engage in the assessment of a product by NICE. The AAC are therefore not relevant to include as a stakeholder.

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