NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of inclisiran within its marketing authorisation for treating primary hypercholesterolaemia or mixed dyslipidaemia.

Background

Dyslipidaemia is a broad term describing a number of conditions, including hypercholesterolaemia, hyperlipidaemia and mixed dyslipidaemia, in which disturbances in fat metabolism lead to changes in the concentrations of lipids in the blood. Mixed dyslipidaemia is defined as elevations in LDL cholesterol and triglyceride levels that are often accompanied by low levels of high-density lipoprotein (HDL) cholesterol.

Hypercholesterolaemia is the presence of high concentrations of cholesterol in the blood, typically including elevated low-density lipoprotein (LDL) cholesterol. 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 (non-familial). There are 2 forms of familial hypercholesterolaemia (FH): heterozygous and homozygous. Homozygous FH is much less common than heterozygous FH and is more severe. In homozygous FH, the inherited gene mutations affecting LDL are from both parents (so the individual has two genetic mutations)[2]. In heterozygous FH, the inherited gene mutations are from a single parent.

Most people with hypercholesterolaemia have cholesterol concentrations that are only mildly or moderately elevated, and show no clinical symptoms. Severe hypercholesterolaemia, however, can cause xanthomas (lesions on the skin containing cholesterol and fats) and arcus corneae (cholesterol deposits in the eyes).

People with hypercholesterolaemia are at increased risk of cardiovascular disease (CVD) because long-term elevations of cholesterol accelerate the build-up of fatty deposits in the arteries (atherosclerosis). The narrowed arteries can cause diseases such as angina, myocardial infarction and stroke, particularly in familial hypercholesterolaemia. CVD is a common cause of death in England, accounting for approximately 136,317 deaths in 2018[1], and it is a major cause of disability and reduced quality of life.

48% of all adults in England had raised cholesterol (greater than or equal to 5mmol/litre) in 2017, equating to around 21 million people[3]. Approximately 7% of the population in England were diagnosed with primary (familial and non-familial) hypercholesterolaemia in 2009, totalling approximately 3.5 million people, of whom about a third are receiving lipid-modifying treatment[4]. Primary heterozygous familial hypercholesterolaemia is estimated to affect between 1 in 250 and 1 in 500 people[5,6], totalling around 113,000 to 225,000 people in England[7] (although it is thought to remain widely underdiagnosed[8]).

Managing primary hypercholesterolaemia and mixed dyslipidaemia involves dietary and lifestyle changes such as smoking cessation, weight loss and increased physical activity. NICE clinical guideline 181 (CG181) for lipid modification to prevent cardiovascular disease and NICE clinical guideline 71 (CG71) for familial hypercholesterolaemia recommend initial treatment with statins. NICE technology appraisal 385 (TA385) recommends ezetimibe as an option for treating primary 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. NICE technology appraisals 393 (TA393) and 394 (TA394) recommend alirocumab and evolocumab, respectively, as options for treating primary hypercholesterolaemia and mixed dyslipidaemia, depending on LDL concentrations. LDL apheresis (a process similar to dialysis which removes LDL from the blood stream) may be considered in exceptional instances for people with heterozygous familial hypercholesterolaemia.

The technology

Inclisiran (brand name unknown, Novartis Pharmaceuticals) is a small interfering RNA molecule that inhibits production of PCSK9 in the liver. It is administered as a subcutaneous injection.

Inclisiran does not currently have a marketing authorisation in the UK for treating primary hypercholesterolaemia or mixed dyslipidaemia. It has been studied in clinical trials alone or with a statin, with or without other lipid-lowering therapy, compared with placebo in people with familial hypercholesterolaemia, or those with a history of atherosclerotic cardiovascular disease.

Intervention(s)	Inclisiran, alone or with a statin, with or without other lipid-lowering therapy
Population(s)	People with primary hypercholesterolaemia or mixed dyslipidaemia
Comparators	When statins are contraindicated or not tolerated: • Ezetimibe • Evolocumab (with or without another lipid-lowering therapy) • Alirocumab (with or without another lipid-lowering therapy) When maximally tolerated statin dose does not appropriately control LDL-C: • Ezetimibe with a statin • Evolocumab with a statin (with or without another lipid-lowering therapy) • Alirocumab with a statin (with or without another lipid-lowering therapy)

Outcomes	The outcome measures to be considered include: • plasma lipid and lipoprotein levels, including LDL-cholesterol, non-HDL cholesterol, apolipoprotein B and lipoprotein a • requirement of procedures including LDL apheresis and revascularisation • fatal and non-fatal cardiovascular events • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.
Other considerations	If the evidence allows the following subgroups will be considered: • Presence or risk of cardiovascular disease • People with heterozygous familial hypercholesterolaemia • People with statin intolerance • Severity of hypercholesterolaemia. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	Related Technology Appraisals:

and NICE Pathways	Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (2016). NICE technology appraisal 393. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (2016). NICE technology appraisal 394. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (2016). NICE technology appraisal 385. Appraisals in development (including suspended appraisals) Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia. NICE technology appraisals guidance [ID1515]. Publication date to be confirmed. Mipomersen for the prevention of cardiovascular events in people with homozygous or severe heterozygous familial hypercholesterolaemia. NICE technology appraisals guidance [ID524]. Suspended indefinitely. Related Guidelines: Cardiovascular disease: risk assessment and reduction, including lipid modification (2014). NICE guideline CG181. Reviewed 2018 - update to be scheduled. Familial hypercholesterolaemia: identification and management (2008, updated 2019). NICE guideline CG71. Related Quality Standards: Cardiovascular risk assessment and lipid modification (2015). NICE quality standard 100. Familial hypercholesterolaemia (2013). NICE quality standard 41. Related NICE Pathways: Cardiovascular disease prevention (2017) NICE Pathway Familial hypercholesterolaemia (2017) NICE Pathway.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018) Manual for prescribed specialised services 2018/19 Chapter 7 section C Inherited Cardiac Condition Services Department of Health and Social Care (2016) NHS Outcomes Framework 2016-2017: Domains 1 and 2. NHS England (2018/2019)

Questions for consultation

Have all relevant comparators for inclisiran been included in the scope? Which treatments are considered to be established clinical practice in the NHS for primary hypercholesterolaemia and mixed dyslipidaemia? Is lomitapide a relevant comparator?

Are the outcomes listed appropriate?

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?

Where do you consider inclisiran will fit into the existing NICE pathways, cardiovascular disease prevention and familial hypercholesterolaemia?

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.

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)?

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.

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.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of 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).

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?

References

1. British Heart Foundation. England Factsheet, December 2019. Accessed June 2020
2. National Organization for Rare Diseases. Familial Hypercholesterolemia (2019). Accessed June 2020.
3. British Heart Foundation. Heart and Circulatory Disease Statistics 2019, Chapter 5. Accessed June 2020
4. NHS Digital. Use of NICE appraised medicines in the NHS in England – 2010 and 2011, Experimental statistics: Report (2012). Accessed June 2020
5. Akioyamen L et al. (2017) Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open 7(9):e016461
6. Bhatnager D et al. (2008) Hypercholesterolaemia and Its Management. BMJ 337:a993
7. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland, provisional: mid-2019. Accessed June 2020
8. Barbir M et al. (2019) Diagnosis, management and prognosis of familial hypercholesterolaemia in a UK tertiary cardiac centre. Clinical Lipidology and Metabolic Disorder 14(1), 1-10