

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia

1 Recommendations

- 1.1 Inclisiran is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if:
- there is a history of any of the following cardiovascular events:
 - acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
 - coronary or other arterial revascularisation procedures
 - coronary heart disease
 - ischaemic stroke or
 - peripheral arterial disease, and
 - low-density lipoprotein cholesterol (LDL-C) concentrations are persistently 2.6 mmol/l or more, despite maximum tolerated lipid-lowering therapy, and
 - the company provides inclisiran according to the commercial arrangement (see section 2).
- 1.2 Inclisiran is recommended only in research for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in adults who have no history of cardiovascular events. This research is in the form of a clinical trial currently in development.
- 1.3 These recommendations are not intended to affect treatment with inclisiran that was started in the NHS before this guidance was published.

People having treatment outside these recommendations may continue

without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia includes statins for lowering LDL-C levels. Ezetimibe and either alirocumab or evolocumab may be added when a person's LDL-C levels are not lowered enough with the maximum tolerated dose of statins. Inclisiran would be used when statins or other lipid-lowering therapies do not control LDL-C well enough or when people cannot have statins.

Clinical trial evidence shows that inclisiran can lower LDL-C levels when statins or other lipid-lowering therapies have not reduced them enough. But, there is no data directly comparing inclisiran with ezetimibe, alirocumab or evolocumab. There is also no long-term evidence on whether inclisiran reduces cardiovascular events. This means the clinical evidence and the cost-effectiveness estimates are very uncertain.

But, despite the uncertainties, inclisiran is still considered cost effective in people who have previously had a cardiovascular event and have persistently high LDL-C levels (2.6 mmol/l or more) despite maximum lipid-lowering therapy. Therefore, inclisiran is recommended as an option in this population.

In people who have never had a cardiovascular event, the cost-effectiveness estimates were very uncertain and likely to be above what NICE considers an acceptable use of NHS resources. But, a clinical trial is planned that will look at inclisiran's effect on cardiovascular events in this population. So in this population, inclisiran is recommended only in research.

2 Information about inclisiran

Marketing authorisation indication

- 2.1 Inclisiran (Leqvio, Novartis) is 'indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
 - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated'.

Dosage in the marketing authorisation

- 2.2 The dosage schedule for inclisiran is available in the [summary of product characteristics](#).

Price

- 2.3 Inclisiran costs £1,987.36 per 284-mg dose pack (company submission). The company has a commercial arrangement (commercial access agreement). This makes inclisiran available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The [appraisal committee](#) considered evidence from a number of sources. See the [committee papers](#) for full details of the evidence.

Clinical pathway

People with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia will welcome a new treatment option

- 3.1 The clinical experts stated that the aim of treatment is to lower, and reduce long-term exposure to, low-density lipoprotein cholesterol (LDL-C) and that statins are the first treatment offered. The clinical experts explained that if people's LDL-C levels remain too high, then ezetimibe may also be offered and, if they are eligible, alirocumab and evolocumab are also options. The patient expert explained that people with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia are at increased risk of cardiovascular events and that the conditions are treated inconsistently across the NHS. They highlighted that it can be difficult to access testing for high cholesterol and that treatments like alirocumab and evolocumab are only offered to people with higher levels of LDL-C. They added that a large proportion of people who are eligible for these treatments are not referred to secondary care to have them. The clinical and patient experts also highlighted that many people do not receive testing for heterozygous familial hypercholesterolaemia. The patient expert stated that inclisiran offers a twice-yearly treatment option, compared with more frequent dosing of currently available treatments, and this would likely increase treatment adherence. The clinical experts explained that it is difficult to reach LDL-C target levels with currently available oral treatments (statins and ezetimibe). The committee concluded that people with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia would welcome a new treatment option.

The appropriate position of inclisiran in the treatment pathway is after maximum tolerated statins alone or with ezetimibe

3.2 The NICE scope outlined 3 separate positions for inclisiran in the treatment pathway:

- compared with maximum tolerated statins
- when maximum tolerated statins do not appropriately control LDL-C, and
- when maximum tolerated statins with ezetimibe do not appropriately control LDL-C.

The NICE scope also requested analyses for when statins are contraindicated or not tolerated. The company positioned inclisiran as a treatment option if LDL-C levels were too high after standard of care treatment. The company defined standard of care as a mix of maximum tolerated statins and other lipid-lowering therapy, including a small proportion of ezetimibe use based on the placebo arm of the ORION trials (see sections 3.5 and 3.7). The clinical experts stated that inclisiran could be used after maximum tolerated statins, or after maximum tolerated statins and ezetimibe. The committee noted that this was in line with the treatment pathway defined by inclisiran's marketing authorisation, which allows its use after maximum tolerated statins or maximum tolerated statins and other lipid-lowering therapies. The committee concluded that the appropriate position of inclisiran in the treatment pathway is after maximum tolerated statins or after maximum tolerated statins with ezetimibe.

Inclisiran is likely to be used in a primary care setting

3.3 The company proposes that inclisiran would be given by a nurse in a primary care setting. After an initial dose, it would be given again after 3 months and then twice a year. The committee was aware that other currently available treatments, such as alirocumab and evolocumab, are usually prescribed in secondary care. The clinical experts stated that the

primary care setting could be appropriate, although it would need some changes in how the condition is currently managed. The committee noted that, in general, the responses to technical engagement from professional organisations supported the use of inclisiran in a primary care setting. These responses also noted that primary care can be used to identify and provide treatment for people who would be eligible for inclisiran. The committee noted that there were some concerns in submissions received surrounding the implementation of inclisiran in a primary care setting but noted that the Accelerated Access Collaborative and NHS England had plans to support the implementation of inclisiran within a primary care setting. The committee was also aware of an ongoing implementation research project (SPIRIT) that aims to assess the feasibility of delivering inclisiran within a primary care setting in England. The committee noted that this trial was due to complete in 2022 and considered that it could provide some relevant information on how inclisiran can be delivered in a primary care setting. The committee accepted that inclisiran is likely to be used in a primary care setting.

Population

The populations included in the company's submission are clinically relevant but are narrower than inclisiran's marketing authorisation and trial data

3.4 The marketing authorisation for inclisiran does not specify a minimum LDL-C level before beginning treatment. The company presented analysis by 3 populations:

- secondary prevention: people who have had a previous cardiovascular event, including acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke or peripheral arterial disease. The committee noted that [NICE's technology appraisal guidance on alirocumab](#) and

[evolocumab](#) defined this population as having a high risk of cardiovascular disease.

- primary prevention with elevated risk: people who have not had a cardiovascular event and have type 2 diabetes or heterozygous familial hypercholesterolaemia, or who have a 10-year cardiovascular disease risk of 20% or more based on Framingham risk score or equivalent
- primary prevention with heterozygous familial hypercholesterolaemia

In each of the 3 populations, the company submitted evidence based on a minimum LDL-C level of 2.6 mmol/l. This was narrower than the marketing authorisation in all 3 populations and narrower than the clinical trial data for the secondary prevention population (see section 3.7). The company stated that a minimum LDL-C level of 2.6 mmol/l was selected because a greater clinical benefit was observed in the ODYSSEY OUTCOMES trial (alirocumab compared with placebo after acute coronary syndrome) in people with a baseline LDL-C of 2.6 mmol/l or more. The company also highlighted that an LDL-C of 2.6 mmol/l was close to the mean baseline LDL-C in the ORION clinical trials and the company's clinical experts supported the use of this threshold. The clinical experts at the meeting highlighted that the use of a 2.6 mmol/l threshold meant that inclisiran, if approved, would enable more people to access a treatment that could significantly reduce LDL-C levels, meaning that they were more likely to reach LDL-C goals. The clinical experts noted that the ORION-11 trial used a 10-year cardiovascular disease risk of 20% or higher, based on Framingham risk score or equivalent, as part of its criteria for the primary prevention with elevated risk population. They explained that NHS practice uses the QRISK score to identify risk and this measure would be used instead and adjusted to identify this population. The evidence review group (ERG) highlighted that a lack of genetic testing for all people with suspected heterozygous familial hypercholesterolaemia may result in cases either being missed or

being incorrectly classified as other population groups (see section 3.1). The committee concluded that the populations included in the company's submission are clinically relevant but are narrower than inclisiran's marketing authorisation and the clinical trial data.

Comparators

The appropriate comparators are ezetimibe, alirocumab, evolocumab and maximum tolerated statins

3.5 NICE technology appraisal guidance recommends ezetimibe, alirocumab and evolocumab as treatment options in the same part of the treatment pathway as inclisiran (see section 3.2). The company did not consider ezetimibe to be a relevant comparator. Instead, the company included a small amount of ezetimibe use as part of standard of care, based on the placebo arms of the ORION clinical trial programme (see section 3.7), and did not include the efficacy of ezetimibe as estimated by the network meta-analysis (NMA; see section 3.8). The company highlighted that ezetimibe use in the NHS was low and that [NICE's guideline on cardiovascular disease: risk assessment and reduction](#) includes ezetimibe only as an option and not a required pathway step before further treatment. The ERG believed that ezetimibe should be a distinct comparator and their base case used the efficacy from the company's NMA for ezetimibe, rather than comparing with the company's definition of standard of care, which was assumed to provide no reduction in baseline LDL-C (see section 3.2). The ERG had been informed by its clinical experts that if LDL-C is too high after maximum tolerated statins, then there is a clinical decision to either switch to rosuvastatin (another statin, which is not yet generic) or add ezetimibe. The ERG also highlighted that, unlike for treatment with alirocumab or evolocumab, there are no minimum LDL-C thresholds needed for treatment with ezetimibe (see section 3.6). It also noted that ezetimibe is now available as a generic treatment, which means its cost is low, and highlighted that ezetimibe was considered a relevant comparator in each of NICE's previous technology

appraisals in this condition. The ERG also highlighted that hypercholesterolemia is undertreated, and this applies to all treatments. The committee agreed with the ERG that ezetimibe should be considered as a relevant comparator. The committee also agreed that it would not eliminate the company's definition of standard of care from its decision-making, noting that this was a mix of predominately maximum tolerated statins, with low amounts of ezetimibe use (but with no efficacy assumed), based on the placebo arm in ORION trials. The committee concluded that the appropriate comparators are ezetimibe, alirocumab, evolocumab and maximum tolerated statins (when inclisiran is given in combination with statins).

The relevant comparators are dependent on alirocumab or evolocumab eligibility

3.6 The committee noted that the populations in the company submission included people with a minimum LDL-C level of 2.6 mmol/l (see section 3.4). Therefore, a proportion of people would be eligible for alirocumab or evolocumab based on recommendations in [NICE's technology appraisal guidance on alirocumab](#) and [evolocumab](#). This includes people in:

- secondary prevention, if their LDL-C levels are persistently above 4 mmol/l and they have a high risk of cardiovascular disease, defined as any history of:
 - acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation)
 - coronary or other arterial revascularisation procedures,
 - coronary heart disease,
 - ischaemic stroke,
 - peripheral arterial disease
- secondary prevention who have a very high risk for cardiovascular disease (defined as recurrent cardiovascular events or cardiovascular

events in more than one vascular bed [that is, polyvascular disease]), only if LDL-C levels are persistently above 3.5 mmol/l

- secondary prevention with heterozygous familial hypercholesterolaemia, only if LDL-C levels are persistently above 3.5 mmol/l, and
- primary prevention with heterozygous familial hypercholesterolaemia, only if LDL-C levels are persistently above 5 mmol/l.

The committee was also aware that there are populations in the company's submission who would not be eligible for alirocumab or evolocumab as outlined by previous NICE recommendations, specifically people in:

- secondary prevention who have a high risk for cardiovascular disease and an LDL-C level between 2.6 mmol/l and 4.0 mmol/l
- secondary prevention who have a very high risk for cardiovascular disease and an LDL-C level between 2.6 mmol/l and 3.5 mmol/l
- secondary prevention with heterozygous familial hypercholesterolaemia and an LDL-C level between 2.6 mmol/l and 3.5 mmol/l
- primary prevention with elevated risk (excluding heterozygous familial hypercholesterolaemia) with an LDL-C level of 2.6 mmol/l or more
- primary prevention with heterozygous familial hypercholesterolaemia and an LDL-C above 5.0 mmol/l.

The committee noted that, based on [NICE's technology appraisal guidance on ezetimibe](#), ezetimibe was available as an option in all populations and also a relevant comparator in all populations included in the company's submission (see sections 3.4 and 3.5). The committee considered that for people who are ineligible for alirocumab or evolocumab, ezetimibe was the only relevant NICE-recommended comparator. But, it acknowledged that maximum tolerated statins was also a treatment option and a relevant comparator in this population (see section 3.5). For people who are eligible for alirocumab or

evolocumab, the committee agreed that ezetimibe, alirocumab, evolocumab and maximum tolerated statins are relevant comparators. The committee were aware that mean baseline LDL-C would be lower in the population ineligible for alirocumab or evolocumab compared with people who are eligible. The committee concluded that the relevant comparators are dependent on alirocumab or evolocumab eligibility.

Clinical evidence

Results from ORION-9, ORION-10 and ORION-11 show inclisiran reduces LDL-C levels and are generalisable to people with primary hypercholesterolaemia or mixed dyslipidaemia in the NHS

3.7 The clinical trial evidence in the company submission came from 3 randomised 18-month trials comparing inclisiran with placebo:

- ORION-9 included people with heterozygous familial hypercholesterolaemia and elevated LDL-C levels (2.6 mmol/l or more)
- ORION-10 included people with atherosclerotic cardiovascular disease (secondary prevention) and elevated LDL-C levels (1.8 mmol/l or more)
- ORION-11 included people with atherosclerotic cardiovascular disease (secondary prevention) and elevated LDL-C levels (1.8 mmol/l or more) and people who had not had a cardiovascular event (primary prevention) but had elevated risks of atherosclerotic cardiovascular disease and LDL-C levels (2.6 mmol/l or more)

The trials included people on lipid-lowering therapies (such as statins or ezetimibe or both). The ERG noted that the proportion of people in the ORION trials receiving ezetimibe was 51% in ORION-9, 11% in ORION-10 and 9% in ORION-11. In the trials, people who were on a statin were on their maximum tolerated dose. The trials also included

people who had documented evidence of statin intolerance. All 3 trials had co-primary endpoints of mean LDL-C percentage change from baseline to 510 days and time-adjusted LDL-C percentage change by day 90 and up to day 540. The results showed that inclisiran compared with placebo significantly reduced levels of LDL-C. From baseline to day 510, LDL-C was reduced by 47.9% (95% confidence interval [CI] 53.5 to 42.3), 52.3% (95% CI 55.7 to 48.8) and 49.9% (95% CI 53.1 to 46.6) in ORION-9, ORION-10 and ORION-11 respectively. Similar results were also seen in the co-primary end point of time-adjusted LDL-C percentage change from day 90 to day 540. The committee was aware that the clinical trials were mostly carried out in the US but noted that the clinical expert submissions stated that the trial results were generalisable to the NHS. The clinical trial results also showed that rates of adverse events were similar for people treated with inclisiran compared with placebo, with the exception of injection site reactions, which were more common in people treated with inclisiran (8.2% compared with 1.8% in those treated with placebo). The committee concluded that results from ORION-9, ORION-10 and ORION-11 show that inclisiran reduces LDL-C levels compared with placebo and these results are generalisable to people with primary hypercholesterolaemia or mixed dyslipidaemia seen in NHS clinical practice.

Indirect treatment comparison

The network meta-analyses used by the company are appropriate but are associated with some uncertainties

3.8 Because the ORION trials only included a placebo comparator, the company undertook NMAs to indirectly compare inclisiran with alirocumab, evolocumab and ezetimibe. The company produced 3 NMAs for different populations, based on a common placebo comparator:

- secondary prevention or primary prevention with elevated risk on maximum tolerated statins

- secondary prevention or primary prevention with elevated risk and statin intolerance
- heterozygous familial hypercholesterolaemia on maximum tolerated statins.

The company used a 24-week timepoint in its NMAs. The company explained that this choice reflected the longest available timepoint for which data was available from comparator treatment trials included in the NMAs. The results from the random-effects model showed that inclisiran was associated with a greater LDL-C reduction compared with ezetimibe and compared with placebo. The NMAs estimated that inclisiran was associated with an LDL-C reduction that was marginally less than with alirocumab or evolocumab, although this result was not statistically significant. The company explained that it could not provide effectiveness estimates for ezetimibe in the heterozygous familial hypercholesterolaemia on maximum tolerated statins NMA, as no trials were identified for ezetimibe in that population. The ERG agreed that the methods used by the company to undertake the NMA were appropriate. But they noted that the NMAs included trials with high levels of heterogeneity and that some trials in the NMAs were inconsistent in their definitions of cardiovascular risks. The committee noted that the 24-week timepoint used in the NMA added some uncertainty to the clinical outcomes as there was limited evidence of whether LDL-C reduction achieved at 24 weeks would be maintained over a lifetime, as assumed in the model (see section 3.10). The committee was also aware that the estimates from the NMA were more favourable for inclisiran than the co-primary endpoints from the clinical trials. The committee concluded that the network meta-analyses used by the company are appropriate but are associated with some uncertainties.

Long-term treatment effect of inclisiran

The effect of inclisiran on cardiovascular event risk is uncertain as there is a lack of long-term evidence

3.9 The completed ORION clinical trials (see section 3.7) were unable to provide enough data on the effectiveness of inclisiran in reducing cardiovascular events and mortality. This was because the follow up of 18 months was not long enough to provide these outcomes. The company used the reduction in LDL-C from the indirect treatment comparison (see section 3.8) to estimate the assumed reduction in cardiovascular events. The company used the Cholesterol Treatment Trialist Collaboration (CTT) meta-analyses, which reported change in cardiovascular event risk per 1 mmol/l reduction in LDL-C by statin use. The ERG agreed that these analyses were appropriate and noted that earlier versions of this source were used in past NICE technology appraisals in this disease area ([NICE technology appraisal guidance on ezetimibe](#), [alirocumab](#), [evolocumab](#) and [bempedoic acid with ezetimibe](#)). The committee expressed a concern that the link between changes in LDL-C levels and cardiovascular outcomes used in the company model, may not be appropriate for inclisiran because the mechanism of action is different to that of statins. The clinical experts stated that the CTT meta-analyses were appropriate and that a similar relationship between LDL-C lowering and a reduction in cardiovascular event risk as seen with statin use could be expected with inclisiran. The committee was aware that longer-term trial evidence was available for alirocumab (ODYSSEY OUTCOMES) and evolocumab (FOURIER) but noted that the follow-up period of these trials may not have been long enough to estimate the full effect on cardiovascular outcomes. The committee also noted that the ODYSSEY OUTCOMES trial was restricted to people who had had a recent cardiovascular event. The committee was also aware that an ongoing UK clinical trial, ORION-4, would provide outcome data on cardiovascular events with a median follow up of 5 years for inclisiran compared with placebo in people who have already had a

cardiovascular event. The committee noted, however, that this trial would not report until 2026. The company explained that a global clinical trial with a similar design was in development. The company also confirmed that it is planning a clinical trial (ORION-17) to collect data on cardiovascular outcomes of inclisiran compared with placebo, in people who have not experienced a cardiovascular event. The committee considered that the lack of data on inclisiran's effect on cardiovascular outcomes was a key uncertainty in the appraisal and was a major driver of the cost-effectiveness results. The committee concluded that the effect of inclisiran on cardiovascular event risk is uncertain as there is a lack of long-term evidence.

The assumptions of no treatment effect waning, and no treatment discontinuation may be appropriate but adds uncertainty

3.10 The company's economic model assumed that the treatment effect as estimated by the NMA at 24 weeks (see section 3.8) would be maintained at the same level over a lifetime. The company stated that this assumption was based on previous NICE technology appraisals of alirocumab and evolocumab in the same condition. The ERG noted that given the lack of long-term trial evidence beyond 18 months to support this assumption, the company could have provided a scenario in which inclisiran's effectiveness is assumed to reduce over time. The clinical experts stated that inclisiran would likely be used over the course of a lifetime, as LDL-C levels would be expected to return to baseline if discontinued. The company highlighted that the assumption of no treatment discontinuation was also based on previous NICE technology appraisals of alirocumab and evolocumab and stated that the treatment discontinuation rate for inclisiran in the ORION clinical trials was low (annual discontinuation rate of 1.7% in ORION-9 and 3.2% in ORION-10 and ORION-11). The committee noted that there was a lack of long-term data for inclisiran to support this assumption. The committee concluded that assumptions of no waning of treatment effect and no treatment discontinuation may be appropriate but add uncertainty.

Innovation

Inclisiran is innovative, however all relevant benefits are likely to be captured in the quality-adjusted life year calculations

3.11 The company highlighted that inclisiran was the first cholesterol-lowering small interfering RNA (siRNA) and has the potential to be a step change in how the condition is managed. The company, clinical and patient experts highlighted that treatment with inclisiran had the potential to increase treatment adherence, because of its twice-yearly dosing schedule (see section 3.1). The committee considered the potential additional benefits inclisiran might provide but concluded that there was no evidence of additional gains in health-related quality of life over those already included in the quality-adjusted life year (QALY) calculations. The committee concluded that inclisiran is innovative, however all relevant benefits are likely to be captured in the QALY calculations.

Cost-effectiveness estimates

The ERG's base case includes the committee's preferred assumptions

3.12 The ERG's base-case analyses included ezetimibe as a separate comparator and also included comparisons with maximum tolerated statins. Therefore, it differed from the company's base case, which included a small amount of ezetimibe use as part of standard care (see section 3.5). The committee was aware that the ERG's base-case analyses was otherwise the same as the company's. This included using the company's NMA estimate for treatment efficacy (see section 3.8) and no treatment waning or treatment discontinuation (see section 3.10). The committee concluded that it preferred the ERG base case but would take the company analyses into account in its decision making.

Because of the uncertainty the acceptable incremental cost-effectiveness ratios are £20,000 per QALY gained and above £30,000 per QALY lost

3.13 [NICE's guide to the methods of technology appraisal](#) notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee also needs to be increasingly certain of the cost effectiveness of a technology as the impact of its adoption on NHS resources increases and may need more robust evidence for technologies that are expected to have a larger impact. Therefore, because of the high level of uncertainty in the clinical and economic evidence, primarily caused by the lack of outcome data on inclisiran's effect on cardiovascular events (see section 3.9), the NMA clinical effectiveness estimates (see section 3.8) and long-term treatment effects and discontinuation assumptions (see section 3.10), the committee agreed that an acceptable ICER would be no higher than £20,000 per QALY gained or above £30,000 per QALY lost when considering each of the population groups and their respective LDL-C ranges (see section 3.6).

Inclisiran is cost effective for secondary prevention in people who are eligible for alirocumab and evolocumab

3.14 The cost-effectiveness results for the secondary prevention population who are eligible for alirocumab or evolocumab were assessed by calculating net monetary benefit. This was because inclisiran was estimated to provide marginally fewer incremental QALYs compared with alirocumab or evolocumab (see section 3.8). The incremental net monetary benefit of inclisiran was compared with alirocumab or evolocumab, at threshold values of £30,000 saved per QALY lost using the committee preferred assumptions (see sections 3.12 and 3.13). This

resulted in a positive incremental net monetary benefit at that threshold value, meaning that the amount of lost QALYs associated with inclisiran compared with alirocumab or evolocumab was acceptable when considering the differences in costs between these treatments. The committee considered that net monetary benefit was appropriate for decision making as it was likely that any differences in QALYs between inclisiran and alirocumab or evolocumab are small. This confirmed that inclisiran is cost effective compared with alirocumab and evolocumab in the following secondary prevention populations in which alirocumab and evolocumab are available:

- secondary prevention with a high risk for cardiovascular disease, only if LDL-C levels are persistently above 4 mmol/l
- secondary prevention with a very high risk for cardiovascular disease, only if LDL-C levels are persistently above 3.5 mmol/l
- secondary prevention with heterozygous familial hypercholesterolaemia, only if LDL-C levels are persistently above 3.5 mmol/l

Inclisiran was associated with an ICER of below £20,000 per QALY gained compared with either ezetimibe or maximum tolerated statins in the populations eligible for treatment with alirocumab and evolocumab described above. The committee concluded that inclisiran is cost effective in these populations for both pairwise and fully incremental analysis. Because of the confidential discount for inclisiran, the exact ICERs have not been reported here.

Inclisiran is cost effective for secondary prevention in people who are not eligible for alirocumab or evolocumab

3.15 Using the committee's preferred assumptions (see section 3.12) the most plausible ICERs for inclisiran compared with ezetimibe or maximum tolerated statins for the secondary prevention population who are not eligible for alirocumab or evolocumab (see section 3.6), were likely to be

around or below £20,000 per QALY gained in pairwise and fully incremental analysis. Therefore, the committee concluded that inclisiran is cost effective in this population. Because of the confidential discount for inclisiran, the exact ICERs cannot be reported here.

Inclisiran is not cost effective in the primary prevention population with elevated risk

3.16 Using the committee's preferred assumptions (see section 3.12) the most plausible ICERs for inclisiran in the primary prevention with elevated risk population and an LDL-C of at least 2.6 mmol/l, were likely to be above £20,000 per QALY gained. This was based on considering comparisons with ezetimibe or maximum tolerated statins in pairwise and fully incremental analysis. Therefore, the committee concluded that inclisiran is not cost effective in the primary prevention population with elevated risk.

Inclisiran is recommended only in research in the primary prevention population

3.17 The committee considered that the cost-effectiveness estimates were highly uncertain for the primary prevention with elevated risk population. The committee highlighted that smaller numbers from ORION-11 informed the cost-effectiveness estimates for this population (see section 3.9). The committee also noted that the budget impact for inclisiran was estimated to be high in the primary prevention population. The committee was aware that [NICE's guide to the methods of technology appraisal](#) notes, in general, that the committee will want to be increasingly certain of the cost effectiveness of a technology as the impact of its adoption on NHS resources increases. The committee was also aware that the company is developing a UK clinical trial (ORION-17) to evaluate the effect of inclisiran compared with placebo on cardiovascular outcomes in people who have not had a cardiovascular event. The committee therefore recommended that inclisiran is used only in the context of research in this population.

Inclisiran is not cost effective in the primary prevention with heterozygous familial hypercholesterolaemia population

3.18 Using the committee's preferred assumptions (see section 3.12) the most plausible ICERs for the primary prevention with heterozygous familial hypercholesterolaemia populations were as follows:

- In people who are not eligible for alirocumab or evolocumab (LDL-C levels between 2.6 mmol/l and 5 mmol/l; see section 3.6) the ICERs were significantly above £20,000 per QALY gained when compared with maximum tolerated statins.
- In people who are eligible for alirocumab or evolocumab (LDL-C levels of at least 5 mmol/l; see section 3.6), the ICER was below £20,000 per QALY gained when compared with maximum tolerated statins. The incremental net monetary benefit of inclisiran was compared with alirocumab or evolocumab, at threshold values of £30,000 saved per QALY lost (see section 3.13) in this population. This resulted in a positive incremental net monetary benefit for inclisiran compared with these treatments.

The committee noted that the company did not provide cost-effectiveness results for inclisiran compared with ezetimibe in the heterozygous familial hypercholesterolaemia populations. Comparisons with ezetimibe were part of the committee's preferred base case (see section 3.12). This was because there was no clinical trial data for ezetimibe in these populations to inform the NMA (see section 3.8). For the alirocumab- or evolocumab-eligible and -ineligible populations, the committee considered that the ICERs for inclisiran compared with ezetimibe would be higher than the ICERs comparing inclisiran with maximum tolerated statins and would be significantly above £20,000 per QALY gained if incorporated into a pairwise and fully incremental analyses. The committee concluded that inclisiran is not cost effective

in the primary prevention with heterozygous familial hypercholesterolaemia population.

Inclisiran is recommended only in research in the primary prevention with heterozygous familial hypercholesterolaemia population

3.19 The committee considered that the cost-effectiveness estimates were highly uncertain for the primary prevention with heterozygous familial hypercholesterolaemia population. The committee also noted that many people do not receive testing for heterozygous familial hypercholesterolaemia. This means cases may either be missed or classified as other population groups (see sections 3.1 and 3.4). The committee was also aware that the company is developing a UK clinical trial (ORION-17) to evaluate the effect of inclisiran compared with placebo on cardiovascular outcomes in people who have not had a cardiovascular event. The committee therefore recommended that inclisiran is used only in the context of research in this population

Other factors

There are no equalities issues that can be addressed in this appraisal

3.20 A number of potential equality issues were raised during the appraisal. These included the higher prevalence of cardiovascular conditions in more deprived areas and in some specific populations (such as minority ethnic groups or people with severe mental health conditions or learning disabilities). The committee also heard that the treatments provided could vary across the NHS depending on region and availability of specialist care, and that there may be difficulties in accessing treatment for older people. The committee concluded that its recommendations for inclisiran would apply to all patients and that the recommendation would not affect people protected by the equality legislation any differently. The committee also considered that further evidence should be collected to assess whether the implementation of inclisiran into the treatment pathway would reduce health inequalities in this condition (see section 5.4).

Conclusion

Inclisiran is recommended for people with a history of cardiovascular events (secondary prevention) if LDL-C levels are at least 2.6 mmol/l

3.21 The committee was concerned that there was a lack of long-term data on cardiovascular outcomes from the clinical trials that compared inclisiran with placebo. However, it noted that ongoing clinical trials would provide more data on these outcomes. The cost-effectiveness results based on the committee's preferred modelling assumptions with a commercial arrangement for inclisiran, represent a cost-effective use of NHS resources for adults with a history of cardiovascular events and persistent LDL-C levels of at least 2.6 mmol/l despite having the maximum tolerated lipid-lowering therapy. The committee therefore concluded that inclisiran is recommended for this group.

Inclisiran is recommended only in research for people who do not have a history of cardiovascular events (primary prevention)

3.22 The cost-effectiveness results for both the primary prevention with elevated risk, and primary prevention with heterozygous familial hypercholesterolaemia were highly uncertain and the ICERs for these populations were likely above £20,000 per QALY gained. The committee considered that inclisiran had the potential to be cost effective in these populations. Based on the information it had heard about ORION-17, it considered that it was likely that the research needed would be commissioned and successfully report, and that its potential value to the NHS would likely represent good value in the context of limited research resources. It therefore recommended inclisiran only in the context of research in this group.

4 Implementation

4.1 [Section 7 of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information](#)

[Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within a specified period. For the purpose of this appraisal, the time period is 30 days after the date of publication, as agreed with NHS England.

- 4.2 NHS England & NHS Improvement will make interim funding for inclisiran available from release of positive draft guidance or from launch in the UK, whichever is later. Further information about funding arrangements will be provided by NHS England.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document. Queries should be directed to Pharmacyand.PrescribingBranch@gov.wales.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia and a history of cardiovascular disease with persistent LDL-C levels of at least 2.6 mmol/l despite having the maximum tolerated lipid-lowering therapy and the doctor responsible for their care thinks that inclisiran is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Recommendations for research and data collection

- 5.1 The company confirmed to the committee that it was developing a randomised controlled trial (ORION-17) of the effectiveness of inclisiran compared with placebo. This will be a UK-based trial in people who have

not previously had a cardiovascular event (primary prevention). The main outcomes of interest are cardiovascular events and mortality.

- 5.2 The committee was also aware that ORION-4, an ongoing randomised controlled UK trial of inclisiran compared with placebo in people with a history of cardiovascular disease (secondary prevention), is due to complete in 2026. In addition, the company stated that an additional global trial of a similar design was also in development. The main outcomes of interest in these trials are also cardiovascular events and mortality.
- 5.3 The committee noted that there was an ongoing trial that aimed to compare inclisiran with or without behavioural support, lipid-lowering medication with behavioural support, and lipid-lowering medication without inclisiran (SPIRIT). This trial will also assess the feasibility of delivering inclisiran within a primary care setting in England and is due to complete in 2022. The committee considered that this evidence was also of interest.
- 5.4 The committee also recommended that additional evidence collection should be carried out. Mindful of the issues raised concerning equality (see section 3.19), the committee strongly encouraged the collection of data to assess whether implementing inclisiran into the treatment pathway leads to a reduction in health inequalities. This should include real-world evidence on assessing inclisiran uptake in areas of high deprivation and across various population groups, as well as data on treatment adherence. The committee encouraged the collection of this data as it would be of interest in a review of this guidance.

6 Review of guidance

- 6.1 The committee strongly recommended that a review of this guidance should be considered once more mature cardiovascular outcome data is available. This would validate whether LDL-C reduction was an appropriate surrogate outcome for inclisiran. The committee was aware

that a population-based health approach had been agreed between NHS

England and the company, and would strongly welcome real-world evidence to feed into the review.

The guidance on this technology will be considered for review once cardiovascular event data becomes available from ORION-4 (secondary prevention population), which is expected in 2026. The guidance on this technology for both the primary prevention with elevated risk, and primary prevention with heterozygous familial hypercholesterolaemia populations will be considered for review once data from ORION-17 becomes available. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Stephen O'Brien
Chair, appraisal committee
August 2021

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Alan Moore

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