



inclisiran 284mg solution for injection in pre-filled syringe (Leqvio[®])

Novartis Pharmaceuticals UK Limited

09 July 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows

ADVICE: following a full submission

inclisiran (Leqvio[®]) is accepted for use restricted use within NHSScotland.

Indication under review: for 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 who are 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.

SMC restriction: for specialist use only in patients at high cardiovascular risk as follows:

- patients with heterozygous familial hypercholesterolaemia (HeFH) and LDL-C ≥ 5.0 mmol/L, for primary prevention of cardiovascular events or,
- patients with HeFH and LDL-C ≥ 3.5 mmol/L, for secondary prevention of cardiovascular events or,
- patients with high risk due to previous cardiovascular events and LDL-C ≥ 4.0 mmol/L or,
- patients with recurrent/polyvascular disease and LDL-C ≥ 3.5 mmol/L.

In three phase III studies, both the percentage reduction in LDL-C to day 510 and the time-adjusted percentage in LDL-C from day 90 to day 540 were significantly larger with inclisiran compared with placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

For 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 who are 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.¹

Dosing Information

Inclisiran 284mg administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months.

Inclisiran is for subcutaneous injection into the abdomen; alternative injection sites include the upper arm or thigh. Injections should not be given into areas of active skin disease or injury such as sunburns, skin rashes, inflammation or skin infections.

Inclisiran is intended for administration by a healthcare professional.¹

Product availability date

July 2021

Summary of evidence on comparative efficacy

Inclisiran is a new injectable lipid-lowering medicine. It is the first of a new class of small interfering ribonucleic acid (siRNA) that is conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes where it inhibits the production of proprotein convertase subtilisin/kexin type 9 (PCSK9). This increases LDL-C receptor recycling and expression on the hepatocyte cell surface which increases LDL-C uptake and lowers circulation LDL-C levels.^{1, 2}

The evidence for the use of inclisiran to treat primary hypercholesterolaemia comes from three double-blind, placebo-controlled, phase III studies which were of similar design. ORION-9 recruited 482 patients with HeFH and LDL-C ≥ 2.6 mmol/L; ORION-10 recruited 1,561 patients with ASCVD and LDL-C ≥ 1.8 mmol/L and ORION-11, 1,617 patients with ASCVD and LDL-C ≥ 1.8 mmol/L or an ASCVD risk equivalent (reflecting the PPER population) and LDL-C ≥ 2.6 mmol/L. The studies included patients aged ≥ 18 year who were receiving a statin at maximally tolerated dose or had documented evidence of intolerance to all doses of at least two different statins. Eligible patients were randomised equally to receive inclisiran 284mg or placebo by subcutaneous injection on days 1, 90, 270 and 450. Randomisation was stratified according to country (except in ORION-10 which was performed in United States only) and by current use of statins or other lipid-modifying therapies. Patients were allowed to continue on stable doses of lipid-lowering medicines, such as statins with or without ezetimibe, but were not allowed PCSK9 inhibitors.²⁻⁴

All three studies had the same two primary outcomes: percent change in LDL-C level from baseline to day 510 and time-adjusted percent change in LDL-C from baseline after day 90 and to day 540. The key secondary outcomes included absolute change in LDL-C from baseline to day 510; time-adjusted absolute change in LDL-C from baseline after day 90 to day 540; percentage change from baseline to day 510 in PCSK9, total cholesterol, apolipoprotein B and non-high-density lipoprotein cholesterol (non-HDL-C). Efficacy was assessed in the intention-to-treat (ITT) populations which included all randomised patients. A hierarchical statistical testing strategy was applied in each of the studies to the two primary and key secondary outcomes with no formal testing of outcomes after the first non-significant outcome in the hierarchy.²⁻⁴

In all three studies, inclisiran significantly reduced both the mean percentage change in LDL-C from baseline to day 510 and the time-adjusted percentage change in LDL-C from day 90 to day 540, compared with placebo, as well as the key secondary outcomes.²⁻⁴ Detailed results are presented in table 1.

Table 1: Results for the two primary and key secondary outcomes of the ORION-9, ORION-10 and ORION-11 studies (ITT population)²⁻⁴

	ORION-9		ORION-10		ORION-11	
	Inclisiran (n=242)	Placebo (n=240)	Inclisiran (n=781)	Placebo (n=780)	Inclisiran (n=810)	Placebo (n=807)
Primary outcomes						
Mean baseline LDL-C, mg/dL	151.4 (3.9mmol/L)	154.7 (4.0mmol/L)	104.5 (2.7mmol/L)	104.8 (2.7mmol/L)	107.2 (2.8mmol/L)	103.7 (2.7mmol/L)
% change in LDL-C to day 510 ^A	-40%	8.2%	-51%	1.0%	-46%	4.0%
Difference (95% CI), p-value	-48% (-54 to -42), p<0.001		-52% (-56 to -49), p<0.001		-50% (-53 to -47), p<0.001	
Time-adjusted % change in LDL-C between day 90 and day 540	-38%	6.2%	-51%	2.5%	-46%	3.4%
Difference (95% CI), p-value	-44% (-48 to -40), p<0.001		-54% (-56 to -51), p<0.001		-49% (-52 to -47), p<0.001	
Key secondary outcomes						
Absolute change in LDL-C to day 510, mg/dL ^A	-59.0 (-1.5mmol/L)	9.9 (0.26mmol/L)	-56.2 (-1.5mmol/L)	-2.1 (-0.05mmol/L)	-50.9 (-1.3mmol/L)	1.0 (0.03mmol/L)
Difference (95% CI),	-68.9 (-77.1 to -60.7), p<0.001		-54.1 (-57.4 to -50.9), p<0.001		-51.9 (-55.0 to -48.7), p<0.001	

mg/dL, p-value						
Time-adjusted absolute change in LDL-C between day 90 and day 540, mg/dL	-56.9 (-1.5mmol/L)	5.8 (0.15mmol/L)	-53.7 (-1.4mmol/L)	-0.4 (-0.01mmol/L)	-48.6 (-1.3mmol/L)	0.3 (0.008mmol/L)
Difference (95% CI), mg/dL, p-value	-62.6 (-69.0 to -56.5), p<0.001		-53.3 (-55.8 to -50.8), p<0.001		-48.9 (-51.4 to -46.5), p<0.001	
% change to day 510 in PCSK9 ^A	-61%	18%	-70%	14%	-64%	16%
Difference (95% CI), p-value	-78% (-84 to -73), p<0.001		-83% (-89 to -77), p<0.001		-79% (-82 to -77), p<0.001	
% change to day 510 in total cholesterol ^A	-25%	6.7%	-34%	-0.4%	-28%	1.8%
Difference (95% CI), p-value	-32% (-36 to -28), p<0.001		-33% (-37 to -33), p<0.001		-30% (-32 to -28), p<0.001	
% change to day 510 in apoprotein B ^A	-33%	2.9%	-45%	-1.7%	-38%	0.8%
Difference (95% CI), p-value	-36% (-40 to -32), p<0.001		-43% (-46 to -41), p<0.001		-39% (-41 to -37), p<0.001	
% change to day 510 in non-HDL-C ^A	-35%	7.4%	-47%	-0.1%	-41%	2.2%
Difference (95% CI), p-value	-42% (-47 to 37), p<0.001		-47% (-50 to -44), p<0.001		-43% (-46 to -41), p<0.001	

^A = from baseline; LDL-C=low-density lipoprotein cholesterol; CI=confidence interval; PCSK9= proprotein convertase subtilisin-kexin type 9; HDL-C=high-density lipoprotein cholesterol

A secondary outcome of mean LDL-C reduction of $\geq 50\%$ from baseline to day 510 was achieved by 38% of inclisiran and 0.8% of placebo patients in ORION-9, 73% and 2.6% of patients respectively in ORION-10 and 58% and 2.3% of patients in ORION-11.^{3,4}

A major adverse cardiovascular event (MACE; defined as cardiovascular death, non-fatal myocardial infarction, resuscitated cardiac arrest and non-fatal stroke) was not a pre-specified efficacy or adjudicated outcome in the three studies. However this exploratory outcome of MACE

occurred in 4.1%, 7.4% and 7.8% of inclisiran-treated patients in ORION-9, ORION-10 and ORION-11 and in 4.2%, 10% and 10% of placebo-treated patients respectively.²⁻⁴

Health-related quality of life was not assessed during ORION-9, ORION-10 and ORION-11.

ORION-9 enrolled patients with HeFH and a LDL-C ≥ 2.6 mmol/L (≥ 100 mg/dL) and provides evidence to support the primary and secondary prevention in these patients. For the subgroup of patients with HeFH receiving primary prevention (n=350), the LS mean percentage difference in LDL-C at day 510 between inclisiran and placebo was -47% (95% CI: -54% to -41%); for the secondary prevention subgroup (n=132), this was -54% (95% CI: -65% to -42%). Post hoc analysis performed in the PPER subgroup of patients from ORION-11 (13%) were consistent with those in the ITT population, however patient numbers were small. The majority of patients in all three studies were also receiving maximum tolerated statins and no further subgroup analysis was presented to support those on maximum tolerated statins.²⁻⁵

A recently published, pre-specified, pooled analysis of the three key studies found a difference in percentage change in LDL-C from baseline to day 510 of -51% (95% CI: -53 to -48) and in time adjusted percentage change in LDL-C from baseline after day 90 to day 540 of -50% (95% CI: -52 to -49) with inclisiran compared with placebo.^{2, 6}

The submitting company presented Bayesian network meta-analyses (NMAs) to compare inclisiran with alirocumab and evolocumab in three patient populations with inadequately controlled LDL-C: (i) patients with ASCVD or risk equivalent who were receiving maximum tolerated doses of statins; (ii) patients with ASCVD or risk equivalent who were statin intolerant and (iii) patients with HeFH who were receiving maximum tolerated doses of statins. Due to a lack of relevant comparator studies, the company noted that it was not possible to perform an NMA in patients with HeFH who were statin intolerant. The outcome used in the base case economic analysis was the percentage change in LDL-C from baseline to week 24.

[*Other data were also assessed but remain confidential.**](#)

Summary of evidence on comparative safety

The European Public Assessment Report (EPAR) notes that during the key phase III studies, the type and incidence of adverse events were comparable between the inclisiran and placebo groups with the exception of injection site reactions but these were mainly mild in severity, transient and resolved without sequelae.²

Pooled safety analysis of the three ORION studies reported that 78% (1,430/1,833) of inclisiran and 77% (1,409/1,822) of placebo patients had at least one treatment-emergent adverse event. The most frequently reported treatment-emergent AEs of any grade in the pooled inclisiran and placebo groups respectively were: diabetes mellitus (12% versus 11%), nasopharyngitis (7.6% versus 7.4%), upper respiratory tract infection (5.7% versus 5.7%), hypertension (5.7% versus 5.7%), arthralgia (5.0% versus 4.0%), back pain (4.5% versus 4.2%), urinary tract infection (4.4% versus 3.6%), diarrhoea (3.9% versus 3.5%) and bronchitis (4.3% versus 2.7%). Injection-site

reactions were more common in the inclisiran than placebo group (3.1% versus 0.1%), as was injection site pain (2.2% versus 0.5%).^{2, 6}

Summary of clinical effectiveness issues

Hypercholesterolaemia is associated with an increased risk of cardiovascular disease because the long-term raised cholesterol levels increase the development of atherosclerosis. Cardiovascular disease is a leading cause of morbidity and mortality and there are various treatment recommendations for primary and secondary prevention. Initial management of hypercholesterolaemia involves dietary and lifestyle changes including smoking cessation, weight loss and increased physical activity. Statins are the treatment of choice for patients with hypercholesterolaemia. However, a proportion of patients fail to achieve adequate LDL-C control despite maximum tolerated doses of statins and require additional lipid-lowering therapy. In addition, a further proportion of patients have contra-indications to or are unable to tolerate statins and, therefore, require alternative lipid lowering therapy to reduce LDL-C. For these groups of patients, current treatment options include ezetimibe and for a smaller number of higher risk patients the PCSK9 inhibitors.⁷⁻⁹ Bempedoic acid has also recently been accepted for restricted use in combination with ezetimibe in patients who are statin intolerant or in whom statins are contraindicated where LDL-C levels are not controlled on ezetimibe alone and PCSK9 inhibitors are not appropriate (SMC2363).¹⁰ Inclisiran is the first in class siRNA.

The clinical evidence from the three key studies in patients with ASCVD, ASCVD risk equivalent (reflecting the PPER population) and / or HeFH requiring additional LDL-C reduction despite maximally tolerated statins, found that inclisiran compared with placebo significantly reduced the percentage change in LDL-C from baseline to day 510 (by 48% to 52%) and time-adjusted percentage change in LDL-C from baseline after day 90 to day 540 (by 44% to 54%). These results were considered clinically relevant by the European Medicines Agency. More inclisiran-treated patients than placebo-treated patients achieved LDL-C thresholds and a $\geq 50\%$ reduction in LDL-C from baseline. This was supported by the key secondary outcomes, including absolute change from baseline to day 510 (reductions of 51.9mg/dL to 68.9 mg/dL compared with placebo) and other relevant parameters of the cholesterol profile. The treatment effect of inclisiran on LDL-C was consistent across subgroups, including baseline LDL-C and intensity of statin treatment and other lipid-lowering therapy. These clinical benefits were achieved with minimal side effects.²⁻⁴

The outcomes were assessed after approximately 18 months of study treatment which was considered sufficient to determine the maximal stable treatment effects on LDL-C. However, the duration of treatment was not sufficient to determine long term efficacy and safety and included only four doses of inclisiran, which is of particular importance given that many patients will require life-long lipid-lowering treatment. An ongoing extension study, ORION-8, will assess efficacy and safety over an additional 4 years. Although the reduction in LDL-C is an accepted surrogate outcome for cardiovascular morbidity and mortality, the impact of inclisiran on cardiovascular outcomes has not yet been confirmed. The ORION studies included an exploratory outcome evaluating MACE but this was not independently adjudicated and the studies were not powered

for this outcome. A clinical outcome study, ORION-4, is recruiting patients to assess the effect of inclisiran on MACE in over 15,000 patients and results are expected in December 2024.^{2-4, 11}

Primary and secondary prevention in the HeFH population is supported by subgroup analysis of ORION-9 according to ASCVD disease at baseline. In ORION-11, 13% of patients had ASCVD risk equivalent and were receiving primary prevention; post hoc analyses in these patients supported primary prevention. These analyses should be treated with caution since they were not planned or powered for but resulted in similar reductions in LDL-C to the ITT populations. In addition each of these analyses did not consider use or intolerance of statins.

There are a number of limitations which may affect the generalisability of ORION study results to clinical practice in Scotland. Apart from the HeFH population of ORION-9, few study patients were receiving study treatment as primary prevention (no patients in ORION-10 and 13% of patients in ORION-11). The EMA noted that the inclusion criteria for studies ORION-10 and ORION-11, with ASCVD or risk equivalent, represents a population with increased cardiovascular risk and increased LDL-C levels, eligible for lipid lowering therapy in line with European guidelines. However this may not reflect clinical practice in Scotland, particularly in patients eligible for primary prevention. The LDL-C thresholds in the ORION studies may not reflect treatment thresholds used in practice and are lower than the various LDL-C thresholds defined by SMC to restrict the use of alirocumab and evolocumab.

ORION study patients included those on maximum tolerated statins and those with statin intolerance. The majority of study patients (92%) were receiving maximum tolerated statins, defined as the maximum dose that could be taken regularly without intolerable adverse events; 74% were receiving high-intensity statins. In ORION-9, >50% of patients were also receiving ezetimibe; as were 9.9% and 7.1% in ORION-10 and ORION-11. The amount of available evidence in patients who were intolerant to statins (defined as documented evidence of intolerance to all doses of at least two different statins) was more limited. Partially or completely intolerant to statins was noted in 25% of ORION-9 study patients, 22% of ORION-10 study patients and 11% of ORION-11 study patients.²⁻⁴ No further subgroup analyses were presented in patients on maximum tolerated statins or with statin intolerance.

The key ORION studies have only compared inclisiran with placebo and there is a lack of direct evidence with alirocumab and evolocumab. The use of alirocumab and evolocumab in Scotland is restricted to high risk patients with LDL-C ≥ 5.0 mmol/L for primary prevention, and ≥ 3.5 mmol/L for secondary prevention with in patients with HeFH and patients with recurrent/polyvascular disease, and ≥ 4.0 mmol/L in patients at high risk due to previous cardiovascular events.^{12, 13} The majority of patients eligible for inclusion in the ORION studies may not be eligible for treatment with the PCSK9 inhibitors in practice due to the restrictions on LDL-C levels.

The NMAs presented by the company had number of limitations including heterogeneity across the studies, patient populations, background treatment and timing of assessment of percentage change in LDL-C. In addition the NMAs were performed in a broader patient population than those eligible for alirocumab and evolocumab in clinical practice according to SMC restrictions.

The introduction of inclisiran would offer an additional injectable lipid lowering treatment. This may further reduce LDL-C in patients who are already receiving the maximum tolerated dose of

statin or offer an alternative treatment option for patients who cannot tolerate or have contraindications to statins. After two initial doses, inclisiran is administered by subcutaneous injection at a maintenance dose of once every 6 months by a healthcare professional. This may improve treatment compliance in patients; alirocumab and evolocumab require subcutaneous injection every 2 to 4 weeks. Clinical experts consulted by SMC considered that the reduced administration was a therapeutic advancement.

[Other data were also assessed but remain confidential.](#)*

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of inclisiran as an adjunct to statins and/or ezetimibe (standard of care, SoC) versus SoC alone for the treatment of adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet. Additionally, using the same results, the company further compared inclisiran with two PCSK9 inhibitors (alirocumab and evolocumab) which are accepted by SMC for restricted use within NHS Scotland (SMC 1147/16 and 1148/16). The company requested SMC consider inclisiran for use in two key groups of patients:

- Adults with ASCVD (including HeFH) and LDL-C ≥ 2.6 mmol/L despite maximally tolerated statins
- Adults who require primary prevention due to elevated risk (PPER) with LDL-C ≥ 4.0 mmol/L despite maximally tolerated statins

The company used a Markov model with the structure based on the model for alirocumab submitted to NICE TA393 and SMC 1147/16. As per the model, patients enter in an initial state of having raised LDL-C and over time they can either stay in this state, experience a non-fatal cardiovascular event and move to a subsequent health state, or die (from CV or non-CV causes). Time dependency has been built into these health states to capture the fact that after a recent cardiac event there is an increased risk of another event within 1 year. The model has a lifetime time horizon.

The model effect was worked through using LDL-C as a surrogate outcome measure linked to cardiovascular events, where reducing LDL-C is predicted to reduce CV events in the future. In the model, this relationship in terms of treatment efficacy was based on the evidence from a NMA that demonstrated no statistically significant differences in treatment efficacy between either alirocumab or evolocumab and inclisiran. The outcome selected for efficacy was the percent change in LDL-C at 24 weeks in all patient populations.

Baseline annual CV event probabilities (MACE events and non-CV mortality) were based on real world data using the Clinical Practice Research Database (CPRD).¹⁴ ASCVD-risk equivalent (ASCVD-RE) patients within the CPRD analysis were used to inform the risks for the PPER population and due to some inconsistencies found in CPRD analysis, a separate published study (Mohrschladt et al. 2004) was used to inform the CVD event and mortality risk in secondary prevention HeFH patients.¹⁵ Kaplan Meier survival analysis was used to estimate the probability of occurrence of

each primary outcome (revascularisation, unstable angina), non-fatal myocardial infarction (NF-MI), non-fatal stroke, cardiovascular and non-cardiovascular death) within twelve months. Thereafter, annual event probabilities from the CPRD analysis are assigned to health states based on the starting cohort being modelled and their event history upon reaching a given state.

CV risks over time were adjusted for age with a 3% and 5% increase in risk each year for non-fatal CV events and CV death respectively. The model sets a minimum LDL-C level of 2.6 mmol/L and then applies the average LDL-C value for patients within their respective groups obtained in the ORION clinical studies. Lastly, the company chose the Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis to estimate the rate ratios i.e. rate at which the risk of a cardiovascular event declines with the absolute reduction in LDL-C levels.¹⁶ The CTTC meta-analysis has been previously accepted in related health technology assessment (HTA) submissions to inform this relationship.

No health-related quality of life data were collected in the inclisiran clinical studies. As such, the baseline utility values were informed by a study by Ara & Brazier which estimated age- and gender-adjusted utilities for people with no history of CV disease. Utility multipliers were then applied to account for disutilities associated with CV events and derive baseline utility values for each starting cohort.

Drug acquisition, and resource use costs associated with managing both acute CV events and post-CV events were included in the analysis. Drug administration costs were only accounted for inclisiran and assumed to be zero for all comparators. All estimates were sourced from standard and robust data sources. The cost associated with adverse events were not included in the analysis as the company assumed them to be similar across all treatments.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price of inclisiran. The company's main economic results are given in tables 2 and 3 using list prices.

PAS discounts are in place for evolocumab and alirocumab and these were included in the results used for decision-making by using estimates of the comparator PAS price. The results presented do not take account of the PAS for evolocumab or alirocumab or the PAS for inclisiran but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for evolocumab and alirocumab due to commercial confidentiality and competition law issues.

Table 2: Base-case results ASCVD (deterministic) - List prices for all medicines

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	£5,563	10.069	7.016	-	-	-	-	-
Inclisiran+SoC	£50,669	11.245	7.893	£45,106	1.176	0.877	£51,408	£51,408
Alirocumab+SoC	£53,093	11.245	7.893	£47,530	1.176	0.877	£54,171	Dominated
Evolocumab+SoC	£53,707	11.245	7.893	£48,144	1.176	0.877	£54,871	Dominated

Table 3: Base-case results PPER(deterministic) - List prices for all medicines

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	£3,695	13.156	10.300	-	-	-	-	-
Inclisiran+SoC	£61,788	14.597	11.482	£58,093	1.441	1.182	£49,137	£49,137
Alirocumab+SoC	£65,495	14.597	11.482	£61,800	1.441	1.182	£52,272	Dominated
Evolocumab+SoC	£66,292	14.597	11.482	£62,597	1.441	1.182	£52,946	Dominated

Deterministic sensitivity analysis submitted by the company showed that results were most sensitive to RR per mmol/L change in LDL-C for CV death and stroke followed by baseline utility multipliers for CHD and rates of CV death. Rates of CV events was also a key driver for primary prevention HeFH population. On request, the company provided a probabilistic sensitivity analysis which showed the probability of inclisiran being cost-effective at different LDL-C thresholds using willingness to pay thresholds of £20,000 or £30,000 per QALY. As expected, the probability of inclisiran being cost-effective increased with increase in LDL-C thresholds.

Subgroup analysis in the populations where alirocumab and evolocumab are accepted for restricted use by SMC are presented in Tables 4-6.

Tables 7 presents the company's key scenario analysis with list prices. These show that any difference in treatment efficacy or removing the first year of treatment from the calculation of rate ratios for CV events affect the inclisiran ICER. The list price results do not take account of the patient access scheme (PAS) for any medicine.

Table 4: Results for patients with ASCVD and serum LDL-C ≥4.0 mmol/L- list prices for all medicines

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	£6,937	9.301	6.423	-	-	-	-	-
Inclisiran+SoC	£50,494	11.109	7.774	£43,557	1.808	1.352	£32,220	£32,220
Alirocumab+SoC	£52,866	11.109	7.774	£45,929	1.808	1.352	£33,975	Dominated
Evolocumab+SoC	£53,472	11.109	7.774	£46,536	1.808	1.352	£34,423	Dominated

Table 5: Results for patients with very high risk of CVD[†] and serum LDL-C ≥3.5mmol/L- list prices for all medicines

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	£4,713	9.143	6.996	-	-	-	-	-
Inclisiran+SoC	£48,087	10.818	8.366	£43,374	1.675	1.370	£31,649	£31,649
Alirocumab+SoC	£50,347	10.818	8.366	£45,634	1.675	1.370	£33,297	Dominated
Evolocumab+SoC	£50,937	10.818	8.366	£46,224	1.675	1.370	£33,728	Dominated

[†]Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).

Table 6: Results for patients with primary prevention HeFH and serum LDL-C \geq 5.0 mmol/L- list prices for all medicines

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	£3,128	17.358	14.058	-	-	-	-	-
Inclisiran+SoC	£75,950	18.235	14.825	£72,822	0.877	0.766	£95,020	£95,020
Alirocumab+SoC	£81,059	18.235	14.825	£77,931	0.877	0.766	£101,685	Dominated
Evolocumab+SoC	£82,054	18.235	14.825	£78,926	0.877	0.766	£102,984	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio, LYG, life year gained; QALY, quality-adjusted life year; SoC, standard-of-care.

Table 7: Key scenario analysis- List prices for all medicines

Scenario	ASCVD (ICER)*	PPER (ICER)*
Base case	Inclisiran + SoC dominant (£51,408)	Inclisiran + SoC dominant (£49,137)
Differential efficacy- using point estimates from NMAs for PCSK9is	Evolocumab + SoC extended dominance (£49,180)	Evolocumab + SoC extended dominance (£48,535)
Efficacy for inclisiran taken from the clinical trials	Inclisiran + SoC dominant (£56,298)	Inclisiran + SoC dominant (£52,918)
Adjusting rate ratios for CV events- by removing the first year of treatment from the calculation of rate ratios for CV events (as per Collins et al)	Inclisiran + SoC dominant (£45,127)	Inclisiran + SoC dominant (£43,942)
Discontinuation scenario 1: rates taken from the ORION trials for inclisiran, from ODDYSEY Outcomes for alirocumab and from FOURIER for evolocumab	Inclisiran + SoC extended dominance (£51,297)	Inclisiran + SoC extended dominance (£49,693)
Discontinuation scenario 2: patients discontinue inclisiran, alirocumab and evolocumab at the same rate	Inclisiran + SoC dominant (£51,244)	Inclisiran + SoC dominant (£50,022)

*ICER presented is for the most cost-effective treatment option vs SoC

Weaknesses in the economic analysis were as follows:

- For the comparisons with alirocumab and evolocumab, as the ITC showed no difference in efficacy between these treatments and inclisiran, a cost-minimisation analysis was provided. SMC considered this to be a relevant analysis but also discussed the limitations of this approach due to differences between the SMC restricted patient populations for evolocumab and alirocumab compared to the patient groups included in the inclisiran model. Concerns were raised about the broadening of the patient populations beyond the patient populations covered by the SMC restricted advice for evolocumab and alirocumab, particularly given the lack of final outcome data for inclisiran. In addition, the committee considered the ICER for inclisiran vs SoC in the ASCVD population may be underestimated as it included all patients with LDL-C \geq 2.6 mmol/L including patients with higher LDL-C levels where alirocumab and evolocumab, not SoC, would be the relevant comparator. Given these issues, SMC concluded it would be more appropriate to consider inclisiran in the restricted patient populations for which alirocumab and evolocumab are accepted.
- The model is based on assuming that inclisiran, by lowering LDL-C, will prevent CV events.

Although this relationship is acceptable given previous HTAs in the same disease area, general consensus is that the absolute effect is greater in high risk patients. This is confirmed by the cost-effectiveness being better in the high-risk patients than in the PPER and HeFH primary prevention groups.

- There is uncertainty regarding the size/magnitude of the reduction in CV events for a given change in LDL-C. However, this has been minimized since the analysis used rate ratios from the CTT meta-analysis which can be considered a robust source.
- The model assumes that the treatment effect is sustained over the lifetime of the model across all sub-groups with the ASCVD and HeFH populations. When questioned about this assumption, the company stated that lifetime treatment is assumed for all treatments unless patients discontinue treatment. The company has presented two treatment discontinuation scenarios, both of which show inclisiran to be more cost-effective than SoC and the active comparators.
- The NMA used to inform the model has some uncertainty, however, overall it demonstrated that there was no significant difference in treatment efficacy between inclisiran, alirocumab and evolocumab. Nevertheless, as seen in scenario analysis, any change in comparative efficacy does influence the inclisiran ICER and creates uncertainty in the conclusion obtained.

Despite the limitations outlined above, the economic case was demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Heart UK – The Cholesterol Charity, which is a registered charity.
- Heart UK - The Cholesterol Charity has received 36% pharmaceutical company funding in the past two years, including from the submitting company.
- Most people with hypercholesterolaemia show no symptoms. In some people with familial hypercholesterolaemia (FH), it can cause xanthomas, raised, pale, yellowish patches around the eyes and on the eyelids. CVD is a particular concern in Scotland and access to long term treatment remains very poor.
- Long term adherence to lipid lowering therapies is very poor. Often patients are reluctant to express doubts and concerns about medicines and frequently will stop taking medicine without exploring all additional alternatives. Those at high CVD risk who are intolerant to high intensity statin treatment may be offered a lower dose statin, an alternative statin or be advised to stop taking statins for 4 – 6 weeks before ezetimibe. This pathway may not always be completed by many patients because it is time consuming. PCSK9 inhibitors are under used by 60-70% and depend on meeting strict criteria.

- Inclisiran would offer a convenient treatment option as it is only given twice yearly. The reduced burden of administration would help promote adherence. A more convenient treatment option will ensure patients can better manage their risk of CVD and will be beneficial for family and carers, practically and psychologically

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published publication on risk estimation and the prevention of cardiovascular disease includes recommendations on lipid lowering in June 2017.⁹ This recommends atorvastatin 20mg/day is recommended as primary prevention in adults assessed as being at high cardiovascular risk, but with no established CVD, following an informed discussion on risks and benefits. In patients with established atherosclerotic cardiovascular disease, atorvastatin 80mg/day is recommended, with a lower dose considered for patients at increased risk of adverse events or drug interactions. Patients reporting statin intolerance can be rechallenged, if willing, initially with the same dose of the same statin unless they have significant creatine kinase elevation. An alternative statin should be offered if statin intolerance persists. People with familial hypercholesterolaemia should be offered statin therapy regardless of their calculated cardiovascular risk and may be considered for combination therapy with ezetimibe where LDL-C lowering is inadequate on maximally tolerated statin therapy, or for monotherapy when statins are contra-indicated. Patients with heterozygous familial hypercholesterolaemia and elevated LDL-C despite statin monotherapy or statin/ezetimibe combination therapy should be considered for a PCSK9 inhibitor. Ezetimibe and bile acid sequestrant therapy should only be considered for primary prevention in patients at elevated CVD risk in whom statin therapy is contraindicated, and in patients with familial hypercholesterolaemia. Ezetimibe and bile acid sequestrant therapy should be considered for secondary prevention in combination with maximum tolerated statin therapy if LDL cholesterol is considered to be inadequately controlled. Fibrates are not routinely recommended for primary or secondary prevention of cardiovascular disease.

The National Institute for Health and Care Excellence (NICE) published a clinical guideline (CG181) on cardiovascular disease risk assessment and reduction, including lipid modification in July 2014 and this was last updated in September 2016.⁷ NICE recommend atorvastatin 20mg daily for primary prevention of cardiovascular disease in the following groups:

- $\geq 10\%$ ten year risk of developing CVD (QRISK2 tool)
- Type I diabetes who are over the age of 40, have had diabetes >10 years, have established neuropathy or have other CVD factors
- Type II diabetes who have $\geq 10\%$ ten year risk of developing CVD (QRISK2 tool)
- Chronic kidney disease

NICE also recommends that atorvastatin 20mg may also be considered in:

- People ≥ 85 years old (possible reduction in non-fatal MI)

- All adults with type I diabetes

In patients with established CVD, including acute coronary syndrome, statins are recommended at the maximum tolerable dose (atorvastatin 80mg).

Specialist advice should be sought when patients with a high risk of CVD (primary or secondary) are intolerant to three different statins. Fibrates, nicotinic acid, bile sequestrants and omega-3 fatty compounds are not recommended as monotherapy or in combination with a statin for people being treated for primary or secondary CVD, those with CKD or type I or type II diabetes.

In people with primary (heterozygous-familial and non-familial) hypercholesterolaemia, ezetimibe can be taken as monotherapy when statins are contraindicated or not tolerated, or in combination with the person's usual statin when cholesterol target levels have not been met despite increased statin dose or where increased statin dose is intolerable.

NICE published a clinical guideline (CG71) on the identification and management of familial hypercholesterolaemia in August 2008 and this was last updated in October 2019.⁸ The guideline recommend life-long lipid lowering treatment. A high-intensity statin with the lowest acquisition cost treatment is the recommended initial treatment for all adults with familial hypercholesterolaemia. The maximum licensed/tolerated dose of statin should be considered to achieve a >50% reduction in LDL-C concentration from baseline. Ezetimibe monotherapy is recommended as an option for patients with primary heterozygous familial hypercholesterolaemia who have a contra-indication or cannot tolerate to statins. Ezetimibe, co-administered with initial statin therapy, is recommended as an option for the treatment of adults with primary heterozygous familial hypercholesterolaemia who have been initiated on statin therapy when serum total cholesterol or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy, and consideration is being given to changing from initial statin therapy to an alternative statin.

NICE recommends that adults with familial hypercholesterolaemia should be offered a referral to a specialist when

- the recommended reduction in LDL-C concentration of >50% from baseline has not been achieved despite maximum tolerated dose of a high intensity statin and ezetimibe or
- the patient has been assessed as being at very high risk for of a coronary event (established coronary heart disease, family history or premature coronary heart disease or two or more other cardiovascular risk factors) or
- statin or ezetimibe therapy is contraindicated or not tolerated

Treatment with a bile acid sequestrant, nicotinic acid or a fibrate may be considered when statins or ezetimibe are contraindicated or not tolerated; the decision to offer these treatments should be made by specialists in familial hypercholesterolaemia.

The Joint British Societies produced consensus recommendations for the prevention of cardiovascular disease in 2014 (JBS3).¹⁷ Cholesterol lowering therapy is recommended in the following individuals:

- established cardiovascular disease
- high risk of cardiovascular disease: diabetes age >40 years, chronic kidney disease stages 3 to 5, or familial hypercholesterolaemia
- high 10-year cardiovascular disease risk (threshold to be defined by NICE guidance)
- high lifetime cardiovascular disease risk (JBS3 calculator) where lifestyle changes are insufficient

In all patients with familial hypercholesterolaemia, lifetime lowering of LDL-C is recommended to reduce CVD outcomes. Familial combined hyperlipidaemia cases should be managed by a lipid specialist. Statins are recommended as a highly effective treatment and, with benefits evident at 2mmol/L LDL-C levels, intensive therapy is encouraged. JBS3 advises a ‘lower is better’ approach, supporting strategies to achieve non-HDL-C of <2.5mmol/L (equivalent to LDL of <1.8mmol/L) in those at high risk of cardiovascular events. Combination therapy with the addition of a bile sequestrant, ezetimibe or possibly nicotinic acid to statin therapy are suggested when increased statin dose is not tolerated. However, specialist lipid advice should be sought if there is a failure to establish statin therapy in patients with established CVD or with suspected FH, or if there is a rise in creatine kinase >5× upper limit of normal on a statin.

These guidelines predates the availability of bempedoic acid and inclisiran.

Additional information: comparators

Alirocumab and evolocumab

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)	
inclisiran	284mg by subcutaneous injection initially, 3 months later and then every 6 months	Year 1:	5,962
		Subsequent years:	3,975

Costs from Dictionary of Medicines and Devices Browser on 10 May 2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

References

1. Novartis Pharmaceuticals UK Ltd. Inclisiran solution for injection in pre-filled syringe (Leqvio®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated: 29.01.2021.
2. European Medicines Agency (EMA). European Public Assessment Report. Inclisiran (Leqvio®). 06/01/2021, EMEA/H/C/005333/0000.
3. Raal FJ, Kallend D, Ray KK, Turner T, Koenig W, Wright RS, *et al.* Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *New England Journal of Medicine.* 2020;382(16):1520-30.
4. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, *et al.* Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *New England Journal of Medicine.* 2020;382(16):1507-19.
5. Data on file. Novartis Pharmaceuticals UK Ltd.
6. Wright RS, Ray KK, Raal FJ, Kallend DG, Jaros M *et al.* Pooled patient-level analysis of inclisiran trials in patients with familial hypercholesterolaemia or atherosclerosis. *J Am Coll Cardiol* 2021;77:1182-93.
7. National Institute for H, Care E. CG181: Cardiovascular disease: risk assessment and reduction, including lipid modification. Available at: <https://www.nice.org.uk/guidance/cg181> (last accessed 9th April 2020). 2016.
8. National Institute for H, Care E. CG71: Familial hypercholesterolaemia: identification and management. Available at: <https://www.nice.org.uk/guidance/cg71> (last accessed 9th April 2020). 2019.
9. Scottish Intercollegiate Guidelines Network (SIGN). Risk estimation and the prevention of cardiovascular disease. 2017 [cited 2021 Feb 23]; Available from: <https://www.sign.ac.uk/our-guidelines/risk-estimation-and-the-prevention-of-cardiovascular-disease/>.
10. Daiichi Sankyo UK Ltd. Bempedoic acid film-coated tablets (Nilemdo®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated: 04.09.2020.
11. ClinicalTrials.gov. A randomized trial assessing the effects of inclisiran on clinical outcomes among people with cardiovascular disease (ORION-4). Available from: <https://clinicaltrials.gov>.
12. Scottish Medicines C. Detailed advice document: alirocumab 75mg and 150mg solution for injection in pre-filled pen (Praluent®); SMC No. 1147/16. Available at: https://www.scottishmedicines.org.uk/media/1228/alirocumab_praluent_final_july_2016_amended_040816_for_website.pdf (last accessed 18th December 2020). 2016.
13. Scottish Medicines C. Detailed advice document: evolocumab 140mg solution for injection in pre-filled pen (Repatha® Sureclick) or pre-filled syringe (Repatha® PFS); SMC No. 1148/16. Available at: https://www.scottishmedicines.org.uk/media/1701/evolocumab_repatha_resubmission_final_jan_2017_for_website.pdf (last accessed 18th December 2020). 2016.
14. Clinical Practice Research D. Primary care data for public health research: CPRD Gold. Available at: <https://cprd.com/primary-care%20> (last accessed 28 Jan 2021).
15. Mohrschladt MF, Westendorp RGJ, Gevers Leuven JA, Smelt AHM. Cardiovascular disease and mortality in statin-treated patients with familial hypercholesterolemia. *Atherosclerosis.* 2004;172(2):329-35.
16. Cholesterol Treatment Trialists C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *The Lancet.* 2012;380(9841):581-90.
17. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart.* 2014;100 Suppl 2:ii1-ii67.

This assessment is based on data submitted by the applicant company up to and including 11 June 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.