Medicines Optimisation Pack for INCLISIRAN

Contents

Purpose of the pack

The overall purpose of this document is to support the rapid decision making required to enable inclisiran prescribing and funding within 30 days of the date of publication of a positive NICE Final Appraisal Document (FAD). Specifically, this document provides the following:

- Information to Medicines Optimisation Teams and Area Prescribing and Formulary Committees on the NHS England and Improvement Population Health Management (PHM) approach to using inclisiran in the lipid management pathway.
- Information about inclisiran including the efficacy and safety data, and positioning for prescribing in primary care, to support listing within the local formulary and allocation of funding from the medicines budget.
- Explanation of the nationally agreed reimbursement and funding structure for inclisiran.

Background

The NHS Long Term Plan (LTP)[1] identifies cardiovascular disease (CVD) as a clinical priority and the single biggest area where lives can be saved over the next 10 years. It sets out a major ambition to prevent 150,000 strokes, heart attacks and dementia cases.[1] Low density lipoprotein cholesterol (LDL-C) is a proven risk factor for patients with CVD, and the NICE FAD for inclisiran highlights that hypercholesterolemia is undertreated.[2]

Inclisiran is a novel potent therapy that reduces LDL-C and, after an initial dose and another at 3 months, is maintained by two doses a year by subcutaneous injection.

Inclisiran has been identified by NHS England and Improvement as a medicine that it wishes to adopt systematically and at scale to help address sub-optimal lipid management in high-risk patient populations.[3]

Prior to the license for inclisiran, there were four classes of lipid-lowering medicines available in the lipid management pathway, for patients with atherosclerotic cardiovascular disease (ASCVD):

- High intensity statins (HISTs) currently available as generic medicines which can be prescribed in primary care[4]
- Ezetimibe for use as an adjunct when statin monotherapy is ineffective, or as monotherapy for those patients that are intolerant to statins[4]
- PCSK9 inhibitors (alirocumab, evolocumab) for use either alone or in combination with statins or ezetimibe (NICE TA393[5] 394[6])
- Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet in adults (NICE TA694[7])

The introduction of inclisiran into the lipid management pathway is seen as an opportunity to address a current gap in the range of treatment options available for people with ASCVD* in whom lipid targets cannot be met on maximum tolerated statins alone or with ezetimibe.[2]

Inclisiran uses the small interfering RNA (siRNA) mechanism of action to lower LDL-C[8,9] by blocking the production of the PCSK9 enzyme. The normal role of the PCSK9 enzyme is to block LDL- C receptors and prevent them from binding to LDL-C in the blood stream, leading to higher LDL-C levels. By “silencing” or switching off the gene responsible for the production of the PCSK9 enzyme or protein, LDL-C receptors are no longer blocked, and can clear LDL-C from the bloodstream. The numbers of LDL-C receptors on the surface of liver cells can also increase again. This results in lower LDL-C levels in the blood.

In January 2020, under a PHM framework to help improve outcomes in CVD, NHS England and Improvement announced a partnership with Novartis Pharmaceuticals UK, to launch inclisiran in England.[3] This agreement ensures affordability of inclisiran at a highly cost effective price and enables access to treatment in primary care for high-risk ASCVD patients unable to reach their LDL-C target on statins alone. There are 3 core components to the collaboration:

1. A commercial component: the population health implementation of inclisiran into the lipid management treatment pathway for secondary prevention of ASCVD including an implementation research project in primary care based in Greater Manchester.
2. A clinical trial in the primary prevention of ASCVD and
3. A manufacturing development consortium to improve scale-efficiency of oligonucleotides

*For the ASCVD population covered by the NICE recommendation, see section titled 'What is the NICE guidance for prescribing inclisiran?'

To achieve the scale and volumes required to positively improve lipid management in England requires that the majority of inclisiran initiation and management be carried out within the primary care setting. This is where, predominantly, this patient population is currently managed.[10] To that end, a novel PHM approach to lower LDL levels in the large at-risk patient populations with ASCVD was created.

About the PHM approach to lipid management

NHS England and Improvement have negotiated a commercial agreement with Novartis and set up a funding mechanism which supports prescribing of inclisiran in primary care and promotes a PHM approach to lipid management. The goal of the PHM approach is to implement a large-scale intervention in lipid management, with patients proactively identified and their lipid management optimised in primary care.

Work has been undertaken by the Accelerated Access Collaborative (AAC) and Academic Health Science Networks (AHSNs) to assess the burden of ASCVD in England and the size of the population at risk, and to develop a data-driven and targeted approach to secondary prevention, which can help address health inequalities and demonstrate the benefits of implementing inclisiran within the lipid optimisation pathway for patients with CVD in England.

Based on the NICE submission for inclisiran, there are approximately 4 million patients with ASCVD in England and the likely size of the population that will benefit from inclisiran treatment is estimated at around 300,000 by year 3.

As all AHSNs are working on a 3-year national lipid management programme with the aim of improving patient care and outcomes by effectively treating patients with hypercholesterolaemia, AHSNs were identified as the delivery partner to work with local healthcare systems to adapt lipid management pathways. AHSN managers will be responsible for managing the roll-out of inclisiran in primary care by working with local leaders and stakeholders to formulate local implementation plans. Please contact your local AHSN CVD Programme Lead if you have any questions about this programme.

Health Innovation Manchester (HInM) is the lead AHSN for the Implementation Science Research which will help to inform the adoption of inclisiran. Since 2015, HInM has been working to truncate the timeline for getting new innovations to the frontline using inclisiran as a model. The implementation research study based in Greater Manchester will look at the impact of a PHM approach on cholesterol services.[11] The study will run in parallel to the AHSN activities on implementation of inclisiran into the local lipid pathway.

Your role within the PHM approach to lipid management

We are asking you to implement the NICE FAD and comply with the 30-day funding directive through:

- Rapid convening of local area prescribing committees to review and adopt inclisiran. You should find the majority of information that you need to review inclisiran contained in this pack.
- Listing inclisiran within the local formulary in line with draft NICE guidance set out in the FAD. Details of the NICE FAD are provided in this pack
- Listing inclisiran with a green status on your local formulary to allow prescribing by GPs and independent prescribers in the primary care team.
- Allocation of funding to GP prescribing budgets to fund inclisiran prescriptions in line with anticipated uptake

About inclisiran

What is the presentation?

Drug Name: Inclisiran

Brand Name: Leqvio®

Drug Form: Solution for injection in pre-filled syringes

Drug Strength: 284 mg (equivalent to 300 mg inclisiran sodium)

Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution

What are the licensing details?

Inclisiran (Leqvio®) 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.

Drug dose: The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months.[12]

Intended Duration of Use: Long-term

Is this drug a black triangle drug (▼)? Yes

The Commission on Human Medicines and the Medicines & Healthcare products Regulatory Agency (MHRA) encourages the reporting of all suspected reactions to newer drugs and vaccines. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.[12]

Intended setting for prescribing

Inclisiran initiation and management is intended to be carried out within the primary care setting where most patients with ASCVD are currently managed. The cost of inclisiran in primary care will be predominantly funded by NHS England and Improvement, based on prescribing data, to facilitate and support proactive prescribing in primary care. Although there is an option to initiate in a secondary care setting, inclisiran is not on the excluded drugs list and the confidential commercial agreement price would be funded by the trust. Please refer to the section 'How will inclisiran be reimbursed?' for more information.

What is the evidence of efficacy?

Inclisiran has been studied in three Phase III trials including over 3,457 patients.[13,14]

Patients in ORION-10 (n=1,561) had established ASCVD (defined as coronary heart disease, cerebrovascular disease or peripheral arterial disease).[13] Patients in ORION-11 (n= 1,617) had either established ASCVD or ASCVD-risk equivalents (i.e. type 2 diabetes mellitus, familial hypercholesterolaemia, or 10-year risk of ≥20% of having a cardiovascular event assessed by Framingham Risk Score or equivalent).[13] ORION-9 recruited patients with familial hypercholesterolaemia (FH) only.[14]

In ORION-10 and ORION-11, subjects had to be taking a maximally tolerated dose of a statin, with or without other lipid modifying therapy, but still not achieving their LDL cholesterol target (i.e. serum LDL-C ≥1.8 mmol/L (≥70 mg/dL) for ASCVD subjects or ≥2.6 mmol/L (≥100 mg/dL) for ASCVD-risk equivalent subjects).[15]

Study inclusion criteria are shown in table 1. A full list of inclusion and exclusion criteria can be found in the study protocols.[15]

Table 1: Study inclusion criteria for ORION-10 and ORION-11[15]

ORION-10[15]	ORION-11[15]
• Patients ≥ 18 years • History of ASCVD, which was defined as CHD, CVD, or PAD • LDL-C ≥1.8 mmol/L (≥ 70 mg/dL) • Fasting triglyceride <4.52 mmol/L (<400 mg/dL) • Lipid-lowering therapies: statin and/or ezetimibe • If on statin, patient must have been receiving the maximally tolerated dose • If not already on a statin, patient must have shown intolerance to all doses of ≥ 2 statins • Relevant exclusion criteria: Any major CV event ≤ 3 months before study, uncontrolled severe hypertension (>180/110) despite treatment, PCSK9 inhibitor treatment	• Patients ≥ 18 years • History of ASCVD, which was defined as CHD, CVD, or PAD • ASCVD-risk equivalents: Type 2 Diabetes (T2DM), FH, and patients with a 10-year risk of a CV event (Framingham Risk) • LDL-C ≥1.8 mmol/L (≥ 70 mg/dL) or ≥2.6 mmol/L (≥100 mg/dL) for ASCVD-risk equivalent subjects • Fasting triglyceride <4.52 mmol/L (<400 mg/dL) • Lipid-lowering therapies: statin and/or ezetimibe • If on statin, patient must have been receiving the maximally tolerated dose • If not already on a statin, patient must have shown intolerance to all doses of ≥ 2 statins • Relevant exclusion criteria: Any major CV event ≤ 3 months before study, uncontrolled severe hypertension (>180/110) despite treatment, PCSK9 inhibitor treatment

ORION-10 was conducted in the USA and ORION-11 in Europe and South Africa.[13] Randomisation was stratified according to background use of statins in both trials and also according to country in the ORION-11 trial. Patients were assigned to receive either inclisiran (284 mg) or placebo, both administered as a 1.5 ml subcutaneous injection under blinded conditions.[13] Each patient received four injections of inclisiran or placebo. After the first injection (day 1), patients returned on day 90, day 270, and day 450 to receive subsequent doses of inclisiran or placebo. Patients attended for follow-up and limited laboratory assessments on days 30, 150, 330, 510 and 540.[13]

Co-primary endpoints

The co-primary endpoints in each trial were changes in LDL-C level from baseline to day 510 compared to placebo and the time-adjusted percentage change in LDL-C level from baseline after day 90 and up to day 540 (to allow for peaks and troughs with different measurements over time). Assessment of efficacy was made on the intention to treat principle.[13]

Secondary endpoints

The key secondary endpoints included:[13]

- Absolute change in LDL-C level from baseline to day 510
- The time-adjusted absolute change in LDL-C level from baseline after day 90 and up to day 540
- The percentage change from baseline to day 510 in levels of:
  - PCSK9
  - total cholesterol
  - apoliprotein B
  - non–high-density lipoprotein (HDL) cholesterol

The study designs are summarised in table 2 below.

Table 2: Study design, patient population and endpoints for the inclisiran phase III studies[13]

	ORION-10	ORION-11
Study Design	Multicentre, double-blind, randomised, placebo-controlled 18-month trial. Patients were randomised to receive inclisiran or placebo. Patients were taking a maximally tolerated dose of statin with/without other lipid modifying therapy.	
Study Size	N=1561	N=1617
Patient Population	Established ASCVD	Patients had either established ASCVD or ASCVD-risk equivalents
Co-Primary Endpoint 1	% change in LDL-C from baseline to Day 510 (month 17) relative to placebo	
Co-Primary Endpoint 2	Time adjusted % change in LDL-C from baseline after Day 90 (3 months) and up to Day 540 (month 18)	
Secondary Endpoint 1	Several, including % of patients who achieved LDL-C target < 70 mg/dL Day 510 (month 17)	
Secondary Endpoint 2	Several, including % of patients who achieved LDL-C target < 50 mg/dL Day 510 (month 17)	

ORION-10 and ORION-11: Population characteristics[12,13]

Population characteristics of the in ORION-10 and ORION-11 were similar (see table 3) with respect to age and the proportion of men enrolled. ORION-10 trial enrolled fewer white patients but a higher proportion of patients with diabetes, hypertension, and heterozygous FH.[13] Both trials enrolled patients with ASCVD. The ORION-11 trial also enrolled 203 patients (12.6%) in the risk-equivalent category, of whom 132 (65.0%) had diabetes, 30 (14.8%) had heterozygous FH, and 41 (20.2%) had a 10-year predicted risk of CVD of 20% or greater.[13]

The mean (±SD) LDL cholesterol level at baseline was 2.71±0.99 mmol/L (104.7±38.3 mg/dL) and 2.73±1.01 mmol/L (105.5±39.1 mg/dL) in the respective trials (Table 3).[13]

Table 3 Population characteristics at study baseline[12,13]

Population characteristics	ORION-10 n=1,561	ORION-11 n=1,617
Mean Age at Baseline (years)	66 (range: 35 to 90)	65 (range: 20 to 88)
% were ≥65 years old (%)	60	55
Women (%)	31	28
White (%)	86	98
Black (%)	13	1
Asian (%)	1	1
Hispanic or Latino ethnicity (%)	14	1
Mean LDL-C mmol/L (mg/dL)	2.71 (104.7)	2.73 (105.5)
High-intensity statins (%)	69	78
Medium-intensity statins (%)	19	16
Low-intensity statins (%)	1	0.4
Not on a statin (%)	11	5
On either ezetimibe alone or in combination with a statin (%)	9.9	7.1
Stable doses of statin treatment (defined as 30 days of use before study entry) (%)	89.2	94.7
Most commonly administered statins	atorvastatin and rosuvastatin	atorvastatin and rosuvastatin

Data in this table are taken from both the SmPC[12] and Ray KK et al.[13]

ORION-10 and ORION-11: Results[12,13]

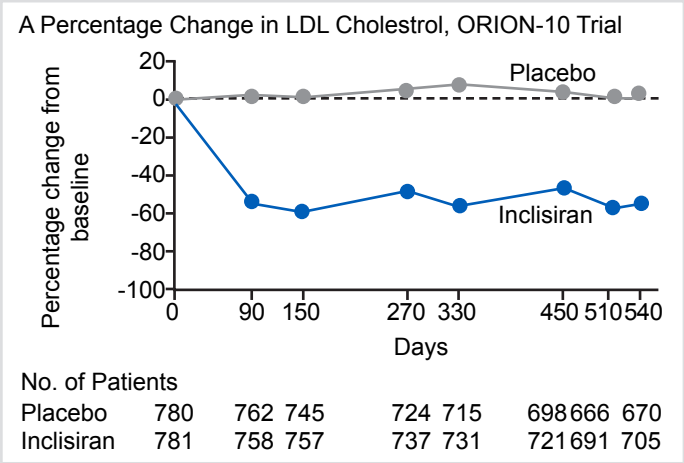
ORION-10: Inclisiran significantly reduced LDL-C from baseline to day 510 (Month 17) by 52% (95% CI: -56%, -49%; p <0.0001) compared to placebo (figure 1).[13]

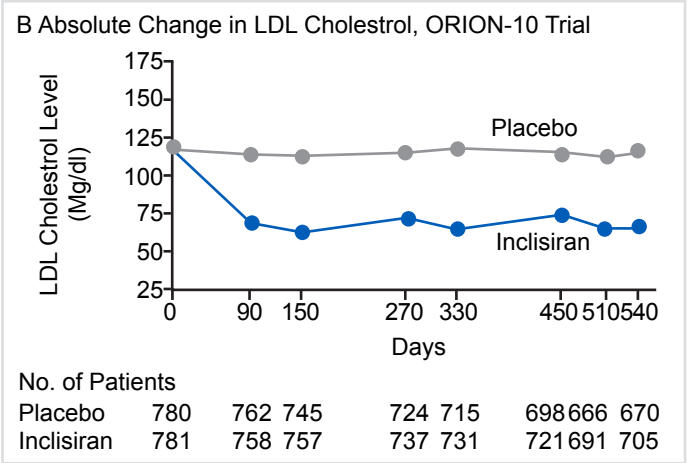
The time-adjusted reduction in LDL-C level by inclisiran after day 90 (Month 3) and up to day 540 (Month 18) as compared with baseline (co-primary endpoint) was 54% (95% CI: -56%, -51%; p <0.0001) when compared to placebo (figure 1).[12]

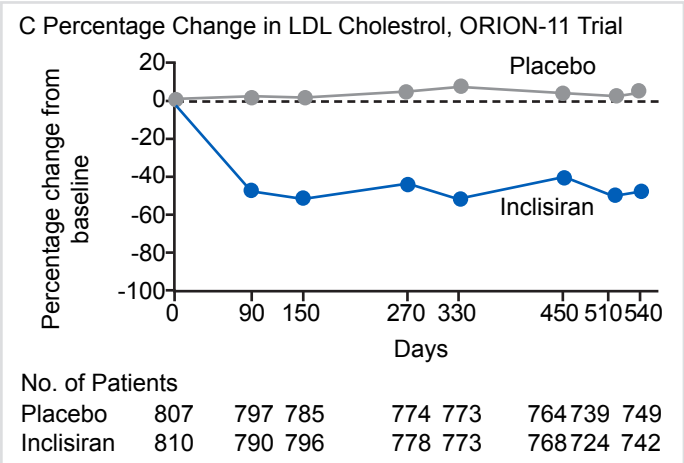
ORION-11: Inclisiran significantly reduced LDL-C from baseline to day 510 (Month 17) by 50% (95% CI: -53%, -47%; p <0.0001) compared to placebo (figure 1).[13]

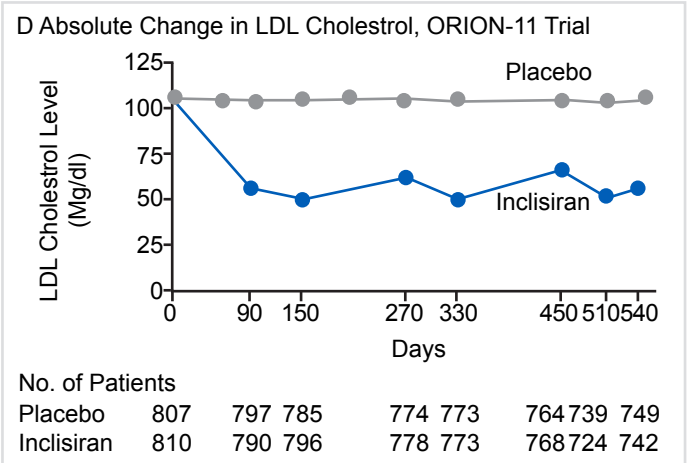
The time-adjusted reduction in LDL-C level by inclisiran after day 90 (Month 3) and up to day 540 (Month 18) as compared with baseline (co-primary endpoint) was 49% (95% CI: -52%, -47%; p <0.0001) when compared to placebo (figure 1).[12]

Figure 1. Efficacy of inclisiran or placebo in lowering LDL cholesterol over the 540-day trial period (Intention-to-Treat Population).[13] Inclisiran injections were given at 0, 90 days (month 3), 270 days (month 9), 450 days (month 15)









Secondary endpoints

The absolute reductions in LDL-cholesterol and percentage changes in PCSK9 as compared with baseline for both studies are shown in table 4.[13]

Table 4: Changes in the secondary endpoints: absolute change in LDL-C and percentage change in PCSK9

ORION-10[13]	ORION-11[13]
Absolute change in LDL-C at Month 17: −1.40 mmol/L relative to placebo (95% CI: −1.48 to −1.32; P<0.001)	**Absolute change in LDL-C at Month 17:** −1.34 mmol/L relative to placebo (95% CI: −1.42 to −1.26; P<0.001)
Percentage change in PCSK9 at Month 17: −83.3% relative to placebo (95% CI: −89.3 to −77.3; P<0.001)	**Percentage change in PCSK9 at Month 17:** −79.3% relative to placebo (95% CI: −82.0 to −76.6; P<0.001)

In both studies, inclisiran showed improvement compared to placebo in other key secondary end points at day 510 as compared placebo (table 5).[16]

Table 5: ORION-10 and ORION-11 - Change in lipid parameters at day 510[16]

	ORION-10				ORION-11			
Parameter	Inclisiran (n=781)	Placebo (n=780)	Placebo adjusted	P value	Inclisiran (n=810)	Placebo (n=807)	Placebo adjusted	P value
Total cholesterol	-33.6%	+0.4%	-33.1%	< 0.001	-28.0%	+1.8%	-29.8%	< 0.001
ApoB	-44.8%	-1.7%	-43.1%	< 0.001	-38.2%	+0.8%	-38.9%	< 0.001
Non-HDL-C	-47.4%	-0.1%	-47.4%	< 0.001	-41.2%	+2.2%	-43.3%	< 0.001
Triglyceride (median)	-14.9%	-2.3%	-12.6%		-12.0%	-5.0%	-7.0%	
Lp (a)* (median)	-21.9%	+3.7%	-25.6%		-18.6%	+0.0	-18.6%	
HDL-C	+7.5%	+2.4%	+5.1%		+10.2%	+4.1%	+6.1%	

*Day 540 sampling time point

ApoB: Apolipoprotein B; Non-HDL-C: Non-high density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; Lp (a): Lipoprotein (a)

At day 510, inclisiran lowered triglycerides and lipoprotein(a) levels and increased HDL cholesterol levels.

In both studies, the proportion of patients likely to have a 50% reduction in LDL-C was higher in the inclisiran group.[13] The effect of inclisiran on LDL-C levels at day 510 in both trials was consistent across subgroups (e.g. age, sex, ethnicity, kidney function, baseline statin, and intensity of statin).[13]

The studies were not powered to show patient oriented outcomes such as cardiovascular events or death. Overall death rates were similar to placebo in both studies. The pre-specified cardiovascular composite end point occurred at a lower frequency with inclisiran (7.4-7.8%) versus placebo (10.2-10.3%) but the numbers were too small to draw any conclusion. A further study ORION-4 is underway in approximately 15,000 ASCVD subjects, to measure the benefit of inclisiran on cardiovascular outcomes.[8]

What is the safety evidence?

Inclisiran was generally well tolerated, with a safety profile similar to placebo.[13] Injection-site adverse reactions were more frequent with inclisiran than placebo (ORION-10: 2.6% v 0.9%) (ORION-11: 4.7% v 0.5%).[13] Adverse reactions at the injection site resulted in discontinuation in 0.2% (inclisiran) and 0.0% (placebo) of patients. Adverse reactions were mild or moderate in severity, transient and resolved without sequelae. The majority of these reactions were mild, with none being severe or persistent. The most frequently occurring adverse reactions at the injection site in patients treated with inclisiran were injection site reaction (3.1%), injection site pain (2.2%), injection site erythema (1.6%), and injection site rash (0.7%).[12]

Serious adverse events are shown in table 6. There were no differences in cancer-related deaths and new, worsening, or recurrent cancer between patients receiving inclisiran and placebo. Laboratory results were also similar in the inclisiran and placebo groups in each trial.[13]

Table 6: Serious adverse events, deaths and prespecified CV endpoints in ORION-10 and ORION-11[13]

Variable	ORION-10 Trial			ORION-11 Trial		
	Inclisiran (N=781)	Placebo (N=778)	Risk Ratio (95% CI)	Inclisiran (N=811)	Placebo (N=804)	Risk Ratio (95% CI)
	No. of patients (%)			No. of patients (%)		
≥1 Serious adverse event	175 (22.4)	205 (26.3)	0.9 (0.7-1.0)	181 (22.3)	181 (22.5)	1.0 (0.8-1.2)
Death any cause	12 (1.5)	11 (1.4)	1.1 (0.5-2.4)	14 (1.7)	15 (1.9)	0.9 (0.4-1.9)
Prespecified exploratory CV endpoint	58 (7.4)	79 (10.2)	0.7 (0.5-1.0)	63 (7.8)	83 (10.3)	0.8 (0.6-1.0)

In ORION-10, 89% inclisiran and 87% placebo participants completed the study. In ORION-11, 95% completed the study in both inclisiran and placebo groups.[16]

Elderly

In the clinical trials, no differences in safety were shown between older (65 years of age or older) and younger subjects.[12,13]

Body weight, gender and ethnicity

Body weight, gender and race were not found to significantly influence the pharmacodynamics of inclisiran.[12] No dose adjustments are recommended for patients with these demographics.[12]

Hepatic and renal function

Compared to patients with normal renal function inclisiran C_{max} is increased by approximately 2.3, 2.0 and 3.3-fold and inclisiran AUC increases by approximately 1.6, 1.8 and 2.3-fold, in patients with mild, moderate and severe renal impairment, respectively.[12] The reduction in LDL-C was similar across all groups of renal function. The manufacturer recommends that no dose adjustment is necessary in patients with mild, moderate or severe renal impairment.

The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after dosing.[12]

Compared to patients with normal hepatic function inclisiran C_{max} is increased by approximately 1.1 and 2.1-fold, and inclisiran AUC increases by approximately 1.3 and 2.0-fold, respectively, in patients with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment. The reductions in LDL-C were similar between the groups of patients administered inclisiran with normal hepatic function and mild hepatic impairment.[10] No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Inclisiran has not been studied in patients with severe hepatic impairment.[12]

Pregnancy

There is no safety data on using inclisiran during pregnancy. For this reason, inclisiran is best avoided during pregnancy.[12]

Breastfeeding

It is unknown whether inclisiran is excreted in human milk. Pharmacodynamic/toxicological data in animals have shown excretion of inclisiran in milk. A risk to newborns/infants cannot be excluded. A risk benefit decision needs to be made with the mother as to whether to discontinue/abstain from inclisiran therapy or to discontinue breastfeeding.[12]

Drug interactions

Inclisiran is not expected to have clinically significant interactions with other medicinal products. This is because inclisiran is not a substrate for common drug transporters and it is not anticipated to be a substrate for cytochrome P450. Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters.[12] However as this is a new drug, prescribers should be aware of anything they suspect to be an interaction with another drug.

Product storage and administration

Inclisiran does not require any special storage conditions. It should not be frozen.[12]

Inclisiran has a 2-year shelf life.

Inclisiran does not require any special storage conditions but should not be frozen.

Inclisiran solution should be clear, colourless to pale yellow and essentially free of particulates. If the solution contains visible particulate matter, the solution should not be used.

What is the NICE guidance for prescribing inclisiran?

National Institute for Health and Care Excellence (NICE) Final Appraisal Document (FAD) “Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia” states[2]:

- *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.*

- *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.*
- *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.*

Population data

The data in table 7 is taken from the NICE submission used to assess the cost effectiveness of inclisiran. It is provided to support the assessment of the size of the local population that would benefit from lipid treatment optimisation and potential treatment with inclisiran.

Table 7: ASCVD prevalence estimations

	Patient numbers	Assumption & Source
UK diagnosed ASCVD prevalent cases *(**secondary prevention** population)*	~4,759,500	2020 estimate of 4,712,748 with 1.01% growth applied. Data on File. Decision Resources Group. ASCVD *Epidemiology, 2020.* Prepared exclusively for Novartis. April 30th 2020
England diagnosed ASCVD prevalent cases *(**secondary prevention** population)*	~3,998,000	Assuming 84% of UK population are in England (https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2020)
On lipid lowering therapy currently or historically	~3,650,000	Assuming 91.3% of ASCVD patients are on lipid-lowering therapy (81%) or have been previously (54% of remaining 19%) *Steen DL, Khan I, Ansell D, Sanchez RJ, Ray KK. Retrospective examination of lipid-lowering treatment patterns in a real-world high-risk cohort in the UK in 2014: comparison with the National Institute for Health and Care Excellence (NICE) 2014 lipid modification guidelines. BMJ open. 2017 Feb 1;7(2):e013255.*
With LDL-C ≥ 2.6 mmol/L	~1,314,000	Assuming 36% of those treated with lipid-lowering therapy have LDL-C > 2.6 mmol/L *Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA, Simes RJ, Keech AC. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. Journal of the American College of Cardiology. 2014 Aug 5;64(5):485-94.*
Patients on inclisiran by year 3	300,000	22.8% uptake is targeted, given this is an AAC priority, to drive implementation via NHS England and the AHSNs with appropriate incentives for primary care delivery.

The number given for the uptake of inclisiran in year 3 builds on the ASCVD population data above and has been generated by the collaboration.

Table 8 provides an estimate of the expected uptake of inclisiran at a national level for the following three financial years.

Table 8: Anticipated national uptake of inclisiran by NHS financial year[11]

NHS financial year:	2021/22	2022/23	2023/24
The approximate size of the population that will benefit from inclisiran treatment (per 100,000 ASCVD population)	~1,400	~6,500	~9,200

Where in the clinical pathway should inclisiran be prescribed?

Within the PHM approach, inclisiran is intended for patients with established ASCVD and lipid levels that have not been maximised with current treatment prior to referral to secondary care.
NICE FAD[2] states:

- *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.*
- *The appropriate position of inclisiran in the treatment pathway is after maximum tolerated statins alone or with ezetimibe.*
- *The committee accepted that inclisiran is likely to be used in a primary care setting.*

If, following inclisiran treatment, the patients LDL-C remains persistently above 2.6 mmol/L, consider referral to a cardiologist or lipid specialist.

How should inclisiran be categorised on the local formulary traffic light system?

The PHM approach being implemented is intended to identify and treat patients in primary care and at scale. The formulary traffic light position should therefore be green to allow prescribing by GPs and independent prescribers in the general practice team.

There may be instances where a specialist wants to initiate inclisiran in an inpatient setting e.g. following an MI and where cholesterol management is sub-optimal. The standardised CVD discharge protocol would be used to inform general practitioners how to continue CVD treatments including inclisiran.[17]

Specialists in an outpatients setting would be expected to advise the general practitioner to initiate treatment and not initiate themselves in an outpatient setting.

Which healthcare professionals can prescribe inclisiran?

Inclisiran is a prescription only medicine and can be prescribed by all independent prescribers in accordance with The Human Medicines Regulations 2012.[18]

How is inclisiran administered?

The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months.

Inclisiran is given by 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.[12]

What monitoring is required?

Reporting suspected adverse reactions is important as it allows continued monitoring of the benefit/risk balance. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.[12]
There are no additional monitoring requirements for inclisiran for patients with reduced renal or hepatic function. Following initiation, cholesterol monitoring and adherence to medication should be in line with local lipid management guidelines.

How will patients be identified for lipid optimisation?

NHS Digital are developing a case finding tool / business rule set for integration into GP systems, e.g. EMIS. This aims to be live in the autumn and will create 'in-session alerts' to support patient identification for secondary prevention of ASCVD at GP practice level.

How will inclisiran be reimbursed?

Primary Care

The NHS will fund inclisiran centrally from a national NHS budget in order that local finances are not a barrier to the local uptake of inclisiran. To enable primary care providers (GP surgeries or pharmacies) to be able to purchase inclisiran directly from the national wholesaler for the medicine, a 'nominal' price (charge) has been agreed at which local primary care providers will be able to purchase the medicine.

Inclisiran will be available in primary care as a personally administered item via an FP34D form or on an FP10 prescription, and will be listed in the Drug Tariff at a reimbursed price of £55 per injection. After an initial dose and another at 3 months, inclisiran is maintained by two doses a year by subcutaneous injection.
Inclisiran will be available from the wholesaler (AAH) at £45, which is payable 30 days from the end of that month.
Inclisiran is listed in the Drug Tariff as a "zero discount" item (no clawback applicable).

The cost to the CCG and primary care prescribing budget will be the Drug Tariff price. As the Drug Tariff price is set at a nominal price, a separate payment will be made to Novartis from a central NHS budget for the difference between the commercial agreement price and the drug tariff price.

Hospitals

When ordering stock of inclisiran, the trust will be charged the confidential commercial agreement price.

How is stock ordered and supplied?

Primary care

The preference is for primary care to purchase stock from the wholesaler (AAH), and then to make a claim on the monthly submitted FP34D. Typically, there would be no patient prescription charge via this method.

Inclisiran can also be supplied by the FP10 route, with the patient bringing the injection to the surgery for administration. If issued via FP10, patients would pay the prescription charge, if they normally do so.

Hospitals

In the hospital setting, stock is ordered from the Novartis customer care team. It is delivered by a company called Alloga. If prescribed and administered in hospital, patients do not have to pay a prescription fee. Alternatively, the

specialist could ask primary care to initiate and continue the prescribing and administration of inclisiran.

Disclaimer

NHS England and Improvement is working with Novartis Pharmaceuticals UK Ltd as part of a collaboration which includes resources in the form of funding, skills, expertise, project management and administrative support. Ownership of this document is the responsibility of NHS England and Improvement. Novartis has had no input into this document but it has checked this document for factual accuracy.

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