Prescribing Support Guide

Inclisiran (Leqvio®) for treating primary hypercholesterolaemia or mixed dyslipidaemia

- Inclisiran is a cholesterol- lowering, double- stranded, small interfering ribonucleic acid. In hepatocytes it utilises the RNA interference mechanism to increase LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation (typically by around 50%).
- It is recommended for restricted use as an option for the treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet in adults with a history of specified cardiovascular events in line with the recommendations in TA 733 (see below). It is not currently recommended for prescribing for adults who have no history of cardiovascular events.
- Amber Initiation Status - for specialist initiation (prescribing, administration and monitoring for first 2 injections) with prescribing, administration and monitoring continued by primary care in patients responding to and tolerating treatment.
- Inclisiran is intended for healthcare professional administration. The recommended dose is 284mg as a subcutaneous injection: initially, again at 3 months, then every 6 months.
- Studies are ongoing to investigate the long-term cardiovascular outcomes of inclisiran.

This Prescribing support guide has been developed to provide prescribing, administration & monitoring guidance. It should be read in conjunction with the Specialist's clinic correspondence, the SPC, BNF and HMMC decision document.

Recommendation

Inclisiran (Leqvio®) is classified as **Amber Initiation status** and **RECOMMENDED FOR RESTRICTED USE** as an option in certain adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet following initiation and initial management by a specialist in line with NICE TA733 criteria below:

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, that is:
  - maximum tolerated statins with or without other lipid-lowering therapies or,
  - other lipid-lowering therapies when statins are not tolerated or are contraindicated, and
- the company provides inclisiran according to the commercial arrangement.

Inclisiran is recommended only in research for treating primary hypercholesterolaemia 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.

Amber Initiation Status

- Initiation by chemical pathologists, endocrinologists, and cardiologists with a special interest in lipid management.
- Specialist to initiate, prescribe, arrange administration and monitor for the first 2 injections until patient is responding to and tolerating treatment. Following this if ongoing treatment is indicated prescribing, administration and monitoring may be undertaken in primary care under the Prescribing Support Guide.

Licensed indication

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.

Dosage and Administration

- Inclisiran is intended for healthcare professional administration, and is not licensed for self administration.
- The recommended dose is 284mg as a subcutaneous injection: initially, again at 3 months, then every 6 months. Inclisiran is for subcutaneous injection into the abdomen; alternative injection sites include the upper arm or thigh. Each 284 mg dose is administered using a single pre-filled syringe.
- Injections should not be given into areas of active skin disease or injury such as sunburns, skins rashes, inflammation, or skin infections.

Hepatic impairment

- No dose adjustments are necessary for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.
- Inclisiran should be used with caution in patients with severe hepatic impairment (Child-Pugh class C).

Renal impairment

- No dose adjustments are necessary for patients with mild, moderate, or severe renal impairment or patients with end-stage renal disease, however:
- there is limited experience with inclisiran in patients with severe renal impairment. Inclisiran should be used with caution in these patients.

Elderly population

- No dosage adjustment is necessary.

Cautions And Contra-indications

- Caution in severe hepatic and renal impairment
- Hypersensitivity to the active substance or any of the excipients. See SPC for full list of excipients.
- Pregnancy/breast-feeding

Special Warnings/Precautions for Use

Haemodialysis	• 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 inclisiran dosing.
Visual inspection	• Inclisiran should be inspected visually prior to administration. The 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.
Storage	• Inclisiran does not require any special storage conditions but should not be frozen.

Drug interactions

As this is a new drug, prescribers should be aware of anything they suspect to be an interaction with another drug.
Inclisiran is not expected to have clinically significant interactions with other medicinal products as inclisiran is not a substrate for common drug transporters and, although *in vitro* studies were not conducted, 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. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.
Inclisiran and PCSK9 inhibitors (alirocumab, evolocumab) should not be prescribed concurrently.

Adverse Effects

- Common adverse events (occurring in >1/100 to <1/10) - adverse reactions at injection site:

These were mild or moderate in severity, transient and resolved without sequelae. The most frequently occurring adverse reactions at the injection site were injection site reaction (3.1%), injection site pain (2.2%), injection site erythema (1.6%), and injection site rash (0.7%).

All suspected reactions should be reported to the MHRA.

- Inclisiran was generally well-tolerated in the ORION clinical trials, with a safety profile similar to placebo apart from injection-site reactions, which were more common in the inclisiran group; these were graded as mild or moderate, with none being severe or persistent. Other most common adverse events reported in patients treated with inclisiran and occurring more frequently than placebo were arthralgia, urinary tract infection, diarrhoea, bronchitis, pain in extremity and dyspnoea.

Prescribing Responsibilities/Monitoring

Stage of treatment	By Whom	Detail
Before initiation of treatment	Specialist	Clinician should review and ensure optimisation of current treatment for lipid management in line with national guidance for lipid management for secondary prevention of cardiovascular disease. This should be with reference to statin intolerance pathway to ensure statin based approaches to manage muscle symptoms are explored and LDL-C lowering options for patients with genuine statin intolerance are used in line with national guidance. <u>Monitoring</u> Baseline tests should be undertaken where necessary to exclude secondary causes and comorbidities, as per information in guidance for lipid management for primary and secondary prevention of CVD. - Review fasting LDL-C - Inclisiran can be initiated if fasting LDL-C ≥2.6 mmol/L despite maximum tolerated lipid lowering therapy as per NICE TA733 criteria above. Clinician must ensure all other eligibility criteria are fulfilled. (NB. Inclisiran and PCSK9 inhibitors (alirocumab, evolocumab) should not be prescribed concurrently – refer to SPC for information on transition).
Treatment initiation	Specialist	Clinician should discuss with the patient the possible benefits and risks (adverse effects) associated with treatment. Clinician to make arrangements to prescribe and for administration of inclisiran by the provider for the first 2 injections. Arrange follow-up with patient to confirm any adverse events to treatment and confirm arrangements for LDL-C review at 3-5 months. Note: Inclisiran will be added to the excluded drug list and Trusts will be reimbursed centrally by NHS England.
GP led Care	Specialist/GP	Ongoing GP prescribing, administration, and care of patients on inclisiran should only be considered if patient is responding to and tolerating treatment. LDL-C monitoring: - (Prior to initiation), after 3 – 5 months, then annually as per national guidance for lipid management. GP to contact Specialist if further guidance on treatment is required, prior to

		accepting prescribing responsibility.
On-going management by GPs	GP	GP to arrange ongoing prescriptions, administration (for healthcare professional administration) and monitoring. Subcutaneous injection is administered initially, again at 3 months, followed by every 6 months. Ensure appropriate scheduling and recall systems are in place to ensure patients attend for injections. *Prescribing/Ordering* Inclisiran will be available in primary care as a personally administered item via an FP34D form or on an FP10 prescription. Inclisiran will be available from the wholesaler (AAH) at £45, which is payable 30 days from the end of that month. Primary care can purchase stock from the wholesaler, and then make a claim on the monthly submitted FP34D (with the FP10 generated attached). Reimbursement will be at the Drug Tariff price of £50 per injection. *Missed doses* If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule. If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months. *Monitoring* There is no mandated laboratory monitoring by NICE or product license. Following initiation, cholesterol monitoring and adherence to medication should be in line with lipid management guidelines. LDL-C monitoring: - (Prior to initiation), after 3 – 5 months, then annually as per national guidance for lipid management. - If there are concerns regarding loss of response to inclisiran, contact specialist for advice. There are no additional monitoring requirements for inclisiran for patients with reduced renal or hepatic function.

References

- Leqvio 284mg solution for injection in pre filled syringe SPC: https://www.medicines.org.uk/emc/product/12039
- NICE Technology appraisal guidance TA 733; Inclisiran for treating primary hypercholesteraemia or mixed dyslipidaemia: 06 October 2021 https://www.nice.org.uk/guidance/ta733
- NHS Accelerated Access Collaborative; Summary of national guidance for lipid management for primary and secondary prevention of CVD, November 2021. https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/

Version	1.0 Harmonisation of Hertfordshire Medicines Management Committee (HMMC) guidance and West Essex Medicines Optimisation Programme Board (WEMOPB) guidance updates include: • Rebadging with HWE ICB and removal of ENHCCG and HVCCG headers • Review date removed and replaced with standard statement.
Developed by	ENHCCG & HVCCG PMOT
Approved by	HMMC
Date approved/updated	March 2022
Review date:	The recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.
Superseded version	1.0