AMBER GUIDANCE FOR INCLISIRAN FOR TREATING PRIMARY HYPERCHOLESTEROLAEMIA OR MIXED DYSLIPIDAEMIA

1. Background

NICE Technology appraisal guidance (TA 733) published on 6th October 2021, recommends inclisiran as an option for treating adult primary hypercholesterolaemia (heterozygous and non-familial) or mixed hyperlipidaemia as an adjuvant to diet.

It is recommended **ONLY** if:

- There is a history of the following cardiovascular events:
  - Acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
  - Coronary or other arterial revascularisation procedures
  - Coronary artery disease
  - Ischaemic stroke or
  - Peripheral arterial disease, **AND**
- Low-density lipoprotein **(LDL-c)** concentrations are **persistently 2.6mmol/L or more** despite maximal tolerated lipid lowering therapy that is:
  - Maximum tolerated statins with or without lipid-lowering therapies or,
  - Other lipid lowering therapies when statins are not tolerated or are contra-indicated
- Inclisiran is recommended only in research for treating primary hypercholesterolaemia (heterozygous familiar 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.

2. Indication

Inclisiran is indicated in adults with primary hypercholesterolaemia (heterozygous and non-familial) or mixed hyperlipidaemia as an adjuvant 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

3. Dose/Duration

The recommended dose is 284mg inclisiran administered as a single subcutaneous pre-filled injection via the following schedule:

- Inclisiran 284mg administered initially
- Inclisiran 284mg administered again at 3 months
- Inclisiran 284mg administered every 6 months thereafter

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

The brand name is Leqvio®

Method of administration

Administration is 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 sunburn, skin rashes, and inflammation or skin infections.

Each pre-filled syringe is for single use only.

Inclisiran is intended for administration by a healthcare professional

Product storage

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

Inclisiran has a 2 year shelf life

Inclisiran 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.

Missed Doses

Information on missed doses whilst on stable treatment

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 and inclisiran administer with an initial injection, again at 3 months, followed by every 6 months thereafter

Monitoring

The following baseline monitoring is recommended prior to inclisiran initiation

- Full lipid profile (LIPP)
- Renal function
- Hepatic function

The following monitoring is recommended prior to further administration of inclisiran at 3 month and 6 monthly thereafter

- Full lipid profile (LIPP)
- Renal function
- Hepatic function

There is no additional monitoring requirements for inclisiran for patients with reduced renal or hepatic function.

Patients currently prescribed specialist hospital only lipid-lowering medications (RED drugs) contact the specialist prescriber. These currently include the following:

- Bempedoic acid and Bempedoic acid + ezetimibe
- PCSK9 inhibitor subcutaneous injection therapy (evolocumab and alirocumab)

4. Contraindications and cautions

Contra-indications

Inclisiran is contra-indicated in the following situations:

- Hypersensitivity to the active substance and to any excipients

Cautions

Inclisiran should be used with caution in the following patient groups:

- **Elderly (≥65 years)**
  - No dose adjustment is necessary in elderly patients
  - In the clinical trials no difference in safety were shown between older (65 years of age or older) and younger subjects
- **Renal Impairment**
  - No dose adjustments are necessary for patients with mild to moderate renal impairment.
  - Patients with CKD stages 3b, 4 and 5 discuss with the specialist lipid clinic before initiation
  - When interpretation of renal function is difficult use the Cockcroft-Gault calculation

    - **CrCl = [(140-age) x (Wt in kg) x 1.23 (male)]/serum creatinine**
    - **CrCl = [(140-age) x (Wt in kg) x 1.04 (female)]/serum creatinine**
- **Hepatic Impairment**
    - No dose adjustment is necessary in patients with mild to moderate hepatic impairment (Child-Pugh class A and B). Inclisiran has not been studied in patients with severe hepatic impairment (Child-Pugh class C)

- **Body weight, gender and ethnicity**
    - Body weight, gender and race were not found to significantly influence the pharmacodynamics of inclisiran
    - Patient with low body weight and low BMI discuss with the specialist lipid clinic prior to initiation.

5. Adverse effects

The only adverse reactions associated with inclisiran were adverse reactions at the injection site (8.2%).

The proportion of patients who discontinued treatment due to adverse reactions at the injection site was 0.2%.

All the adverse reactions were mild or moderate in severity, transient and resolved without consequence.

The most frequently occurring injection site reactions include site pain (3.1%), site erythema (1.6%) and site rash (0.7%).

Reporting of suspected adverse reactions

Inclisiran is a black triangle drug (▼)

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. 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 Ply or Apple App Store.

6. Drug interactions

Inclisiran is not a substrate for common drug transporters and, although *in vitro* studies were not concluded, 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. Therefore, inclisiran is not expected to have significant interactions with other medicinal products. Based on limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

7. Pregnancy and Lactation

- **Pregnancy**
  - There is no or limited amount of safety data on using inclisiran during pregnancy. Therefore it is best to avoid inclisiran use during pregnancy
- **Breast-feeding**
  - It is unknown whether inclisiran is excreted in human milk. Available 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
- **Fertility**
  - There is no data on the effect of inclisiran on human fertility. Animal studies did not show any effects on fertility

8. Information for patient

Patients should be advised on common side effects of injection site reactions

All patients counselled on the administration schedule

All patients counselled if appropriate to continue statin or other lipid lowering therapies

9. How stock is ordered and supplied

Inclisiran, from Novartis, funded by NHS England, is available to all pharmacies and GPs for prescribed patients.

Available to order for same day or next delivery from your local branch, you can order inclisiran (Leqvio®) from AAH using the following codes

Product Name	EAN Code	PIP Code
Inclisiran (Leqvio®)	7613421044237	4174751

The preference is for primary care to purchase stock from the wholesaler (AAH), and then to make a claim on the monthly submitted FP34D submission document (peach) with a supporting FP10 documentation. Typically, there would be no patient prescription charge via this method. Please note, the FP34PD appendix form used when claiming for a high-volume personally administered vaccine item is not applicable for inclisiran.

For dispensing doctors:

A prescriber can issue an FP10 and the patient takes this to be dispensed via the in-practice pharmacy. The practice can then administer the treatment to the patient. The pharmacy will submit the FP10 for payment and reimbursement purposes following the same process set out above for non-dispensing doctors where the doctor administers a PA item. Please note via this route a prescription charge for the patient is not applicable.

Inclisiran can also be supplied by the FP10 route and dispensed via a community pharmacy 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.

Details of contraindications, cautions, drug interactions and adverse effects listed above are not exhaustive. For further information always check with BNF www.bnf.org.uk or SPC (www.medicines.org.uk).

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