NHS
Pan Mersey
Area Prescribing Committee

Inclisiran injection (Leqvio® ▼)
for primary hypercholesterolaemia or mixed dyslipidaemia

The Pan Mersey Area Prescribing Committee recommends the prescribing of inclisiran injection (Leqvio® ▼), for primary hypercholesterolaemia or mixed dyslipidaemia in accordance with NICE TA733.

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NICE technology appraisal (TA) 733 recommends inclisiran injection (Leqvio ® ▼) 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.[1]

NHS England is making central funding available for inclisiran so that local finances are not a barrier to local uptake. The Accelerated Access Collaborative and Academic Health Science Networks will work with system leaders to support the implementation of inclisiran within a primary care setting. Due to uncertainty around the impact on NHS services, the resource impact will need to be determined at a local level. Any interim national funding should be excluded from the resource impact at a local level.[2]

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

APC board date: 27 Oct 2021 | Last updated: 25 May 2022 Prescribing policy statement
Review date: Oct 2023 (or earlier if there is significant new evidence relating to this recommendation) Version: 2.1
APC administration provided by Midlands and Lancashire Commissioning Support Unit

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Effectiveness [1, 3, 4]

Inclisiran uses the small interfering RNA (siRNA) mechanism of action to lower LDL-C 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 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.

Clinical trial evidence is from three Phase III trials including over 3,457 patients comparing inclisiran with placebo:

- ORION-9 included people with heterozygous familial hypercholesterolaemia and elevated LDL-C levels (2.6 mmol/l or more)
- ORION-10 (n=1,561) included people with established (secondary prevention) and elevated LDL-C levels (1.8 mmol/l or more)
- ORION-11 (n= 1,617) included people with atherosclerotic cardiovascular disease (secondary prevention) and elevated LDL-C levels (≥1.8 mmol/l, mean baseline 2.8mmol/l for inclisiran, 2.7mmol/l for placebo) and people who had not had a cardiovascular event (primary prevention) but had elevated risks of atherosclerotic cardiovascular disease and LDL-C levels (2.6 mmol/l or more)
- In ORION-10 and ORION-11, subjects were taking a maximally tolerated dose of a statin, with or without other lipid modifying therapy, but still not achieving their LDL cholesterol target.

The results showed that inclisiran compared with placebo significantly reduced levels of LDL-C. From baseline to day 510, LDL-C was reduced by 47.9% (95% confidence interval [CI] 53.5 to 42.3), 52.3% (95% CI 55.7 to 48.8) and 49.9% (95% CI 53.1 to 46.6) in ORION-9, ORION-10 and ORION-11 respectively. Similar results were also seen in the co-primary end point of time-adjusted LDL-C percentage change from day 90 to day 540. None of the trials were long enough to provide data on the effectiveness of inclisiran in reducing cardiovascular events and mortality.

Safety [3]

Contraindications: hypersensitivity to the active ingredient or excipients.

Side-effects: The most common adverse reactions were injection site reactions, occurring in 8.2% and 1.8% of inclisiran and placebo patients, respectively, in the pivotal studies. All reactions were mild or moderate in severity, transient and resolved without sequelae. Elevation in liver transaminases were also reported but did not rise to clinically significant levels and resulted in no adverse effects or evidence of liver dysfunction. Refer to SPC for full details.

Pregnancy and breastfeeding: Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity but it is preferable to avoid the use of inclisiran during pregnancy as a precautionary measure due to limited information. It is unknown whether inclisiran is excreted in human milk. Available data in animals have shown excretion of inclisiran in milk. A risk to newborns/infants cannot be excluded.

Cost [1]

Annual NHS list price cost of inclisiran is £5,962 in the first year then £3,975 per annum thereafter. This does not consider the commercial arrangement (commercial access agreement).

Patient factors [3]

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. Haemodialysis should not be performed for at least 72 hours after dosing (16% is cleared through the kidneys). No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Inclisiran has not been studied in patients with severe hepatic impairment. No adjustment is needed in elderly patients ≥65 years.

Prescribing information[3]

The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, then every 6 months. There are no specific monitoring requirements for inclisiran. Following initiation, cholesterol monitoring and adherence to medication should be in line with local lipid management guidelines.

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.

Implementation notes

- Place in therapy: inclisiran is intended for patients with established atherosclerotic cardiovascular disease and lipid levels that have not been optimised with current treatment prior to referral to secondary care. The appropriate position of inclisiran in the treatment pathway is after maximum tolerated statins alone or with ezetimibe.[2]
- Inclisiran initiation and management is intended to be carried out within the most appropriate setting for the patient.[5]
- If, following inclisiran treatment, the patient's LDL-C remains persistently above 2.6 mmol/L, consider referral to a cardiologist or lipid specialist.[2]
- 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.[2]
- Inclisiran used by trusts will be reimbursed centrally by NHS England from April 2022 as inclisiran will be added to the PbR excluded drug list at this time. However, NHS England will shadow this arrangement from 1 January 2022. Trusts must ensure they are purchasing inclisiran at the Contract price agreed with Novartis and should complete the NHS England Blueteq form for inclisiran which is available on provider systems.[5]
- Treatment transition from monoclonal antibody PCSK9 inhibitors (alirocumab or evolocumab): Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor.[3]
- Inclisiran is for subcutaneous injection into the abdomen; alternative injection sites include the upper arm or thigh. Inclisiran is intended for administration by a healthcare professional.[3]

References

1. National Institute for Health and Care Excellence. Technology Appraisal 733; Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia, 6 October 2021. Accessed online 7 October 2021.
2. NHS England and NHS Improvement (2021). Information for medicines optimisation leads: Inclisiran (Leqvio). 22 September 2021.
3. Novartis Pharmaceuticals UK Ltd. Summary of Product Characteristics: Leqvio 284 mg solution for injection in pre filled syringe. 03 Sept 2021. Accessed 30 Sept 2021.
4. Issues in Emerging Health Technologies. 2019 Dec Issue 180. https://www.ncbi.nlm.nih.gov/books/NBK555477/pdf/Bookshelf_NBK555477.pdf
5. NHS England and NHS Improvement. PAR1361: Summary information on the funding and supply of inclisiran (Leqvio®); Version 1, 15 February 2022