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LEQVIO® inclisiran

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GUIDELINES FOR THE USE OF LEQVIO®▼ (INCLISIRAN) AFTER STATINS FOR ELIGIBLE PATIENTS

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.[1]

Each **1.0 mmol/L reduction in LDL-C** is associated with a **21%** relative risk reduction of major vascular events (RR=0.79; 95% CI: 0.77–0.81)[2]

Based on a meta-analysis of data from randomised statin trials over an average of 4.8 years (N=174,149 patients). The estimated absolute reduction in major vascular events in participants with a 5-year risk <10% of these events was around 11 per 1,000 over 5 years for each 1.0 mmol/L LDL-C reduction. Major vascular events were defined as non-fatal MI or coronary death, any stroke, or coronary revascularisation procedure.[2]

The effect of LEQVIO on CV morbidity and mortality has not yet been determined.[1]

Lipid-management strategies comprise **lifestyle changes** and, in some individuals, **concomitant drug intervention**, depending on CV risk and LDL-C levels, to reach treatment goals[3]

In addition to statins, a variety of lipid-management treatment options are available:[4–6]

LEQVIO: siRNA that inhibits the hepatic synthesis of PCSK9

Ezetimibe: selective cholesterol absorption inhibitor

Alirocumab and evolocumab: PCSK9i mAbs

LDL-C REDUCTION

Fibrates: (NICE recommends that fibrates should not be routinely offered to prevent CVD[7])

Bile acid sequestrants: (NICE recommends that bile acid sequestrants should not be offered to prevent CVD[7])

Please refer to the relevant SmPC before prescribing any relevant medication.

NICE recommends LEQVIO, within its licensed indication, as an option for the treatment of adult patients who:[8]

Scan the QR code or follow this link to read the full NICE TA733 guidelines

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1 **Have already had certain CV events** (acute coronary syndrome such as MI or unstable angina needing hospitalisation, coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke or PAD)

2 **Have persistently elevated LDL-C levels (≥2.6 mmol/L)** despite maximum tolerated statins with or without other lipid-lowering therapies, or other lipid-lowering therapies when statins are not tolerated or are contraindicated

Cholesterol targets for LDL-C and the role that LEQVIO may play in helping to reach these targets are defined in guidelines and guidance[3,5,7,9]

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National guidelines and guidance include:

- The 2024/2025 QOF guidance[9]
- The NHS AAC guidance[5]
- NICE guideline NG238[7]

Scan the QR code or follow this link to read the full QOF guidance

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2024/2025 QOF guidance: cholesterol management indicators[9]

CHOL003[9]

'Percentage of patients on the QOF Coronary Heart Disease, Peripheral Arterial Disease, Stroke/TIA or Chronic Kidney Disease Register who **are currently prescribed a statin**, or where a statin is declined or clinically unsuitable, **another lipid-lowering therapy**: 70–95%'

14 points

CHOL004[9]

'Percentage of patients on the QOF Coronary Heart Disease, Peripheral Arterial Disease or Stroke/TIA Register, who have a recording of **LDL cholesterol in the preceding 12 months that is 2.0 mmol/L or lower** or where LDL cholesterol is not recorded a recording of non-HDL cholesterol in the preceding 12 months that is 2.6 mmol/L or lower: 20–35%'

16 points

The aim of these indicators is to ensure that all patients with established CVD:

- **Receive treatment to reduce cholesterol** in line with NHS and NICE guidelines and guidance[5,7,9]
- **Are considered for intensification of therapy** if there is an insufficient reduction in cholesterol with first-line therapy, which is usually a statin[5,7,9]

The effect of LEQVIO on CV morbidity and mortality has not yet been determined.

NHS AAC guidance and the role of LEQVIO in the secondary prevention of ASCVD[5]

The NHS AAC has summarised the national guidance for lipid management for primary and secondary prevention of CVD[5]

Scan the QR code or follow this link for full NHS AAC guidance

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SECONDARY PREVENTION: Do not delay statin treatment in secondary prevention while managing modifiable risk factors. Prescribe a high-intensity statin (atorvastatin 80 mg daily) if possible

If maximum tolerated dose of statin does not control non-HDL-C/LDL-C well enough after 2–3 months, confirm statin adherence, then consider the following options based on shared decision-making with the patient

If recommended statin treatment is contraindicated or not tolerated, follow AAC Statin Intolerance Algorithm for advice regarding adverse effects

If statin intolerance is confirmed, consider:

- **Ezetimibe 10 mg daily**
- **Ezetimibe 10 mg/bempedoic acid 180 mg** combination when ezetimibe alone does not control non-HDL-C sufficiently

If non-HDL-C remains >2.6 mmol/L despite other lipid-lowering therapies, consider injectable therapies—arrange a fasting blood test and assess eligibility criteria

Ezetimibe 10 mg daily

Reassess after 3 months. If non-HDL-C remains >2.6 mmol/L; consider **injectable therapies**—arrange a fasting blood test and assess eligibility

Injectable therapies:*

If non-HDL-C >2.6 mmol/L, arrange fasting blood test to measure LDL-C to assess eligibility:

- **LEQVIO**—if fasting LDL-C ≥2.6 mmol/L despite maximum tolerated lipid-lowering therapy

OR

- **PCSK9i**—see NICE TAGs for LDL-C thresholds

If eligibility criteria not met, **consider ezetimibe 10 mg daily** (if not previously considered)

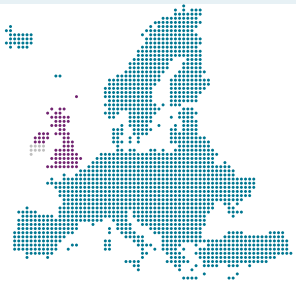
***LEQVIO** and PCSK9is should not be prescribed concurrently

Where an individual qualifies for injectable therapies such as LEQVIO, as per NICE technology appraisals, consider these in preference to ezetimibe to prevent lipid levels being lowered but remaining above the LDL-C target and below thresholds for initiating injectable therapies[10]

LEQVIO is only recommended by NICE when persistently elevated LDL-C levels are ≥2.6 mmol/L. This pathway has been adapted to show the recommendations about the use of LEQVIO, based on the full guidance. Please refer to the full national guidance for more information on lipid management for primary and secondary prevention of CVD (https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-version-7-March-2024.pdf).

Novartis Pharmaceuticals UK Ltd had no involvement in the development of this guidance.

LEQVIO may not be indicated and/or recommended for all patients in this guidance. Please consult the SmPC and the NICE TAGs before prescribing.



European guidelines:[3]

2019 ESC/EAS recommendations for the primary and secondary prevention of ASCVD

Scan the QR code or follow this link to read the full ESC/EAS guidance

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Targets for LDL-C

ESC/EAS guidelines have set different LDL-C targets for different CVD risk groups:[3]

Low risk	Moderate risk	High risk	Very high risk	Second CV event within 2 years while on a maximally tolerated statin
<3.0 mmol/L (<116 mg/dL)	<2.6 mmol/L (<100 mg/dL)	<1.8 mmol (<70 mg/dL)	<1.4 mmol (<55 mg/dL)	<1.0 mmol/L (<40 mg/dL)

…AND ≥50% reduction from baseline in high-risk patients, and in very high-risk patients who have had a second CV event within 2 years while on a maximally tolerated statin

Low risk: SCORE <1%. **Moderate risk:** SCORE ≥1% and <5%; young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factors. **High risk:** SCORE ≥5% and <10%; markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) or BP ≥180/110 mmHg; FH without other major risk factors; moderate CKD (eGFR 30–59 mL/min/1.73 m^2); DM without target organ damage, with DM duration ≥10 years or other additional risk factor. **Very high risk:** SCORE ≥10%; ASCVD (clinical/imaging); FH with ASCVD or with another major risk factor; severe CKD (eGFR <30 mL/min/1.73 m^2); DM and target organ damage: ≥3 major risk factors, or early onset of T1DM of long duration (>20 years). SCORE is calculated for 10-year risk of fatal CVD.

ESC/EAS risk-based LDL-C goals have become lower with time (e.g., in the 2016 vs 2019 guidelines)[3,11]

The ESC/EAS guidelines highlight the clinical benefit of treating to more stringent targets than ≤2 mmol/L for those patients at high risk of CVD[3]

With two maintenance doses a year, **79.4%** of patients with ASCVD on **LEQVIO achieved** the **<1.8 mmol/L LDL-C target**, in combination with a maximally tolerated statin (baseline LDL-C of 2.9 mmol/L ± 1.2)†,[12]

LEQVIO is administered in combination with a maximally tolerated statin. After an initial dose, LEQVIO is administered again at 3 months, followed by every 6 months.[1] Mean cumulative exposure to LEQVIO in ORION-8 was 3.7 years with a maximum of 6.8 years.[12]

LEQVIO had a similar safety profile to placebo in clinical trials, apart from injection-site reactions[1,13]

- Adverse reactions at the injection site occurred in 8.2% of patients in the LEQVIO group and 1.8% in the placebo group
- The proportion of patients in each group who discontinued treatment due to adverse reactions at the injection site was 0.2% and 0.0%, respectively
- All of these adverse reactions were mild or moderate in severity, transient and resolved without sequelae

*__LEQVIO__ and PCSK9is should not be prescribed concurrently.

†ORION-8 (N=3,274) assessed the long-term efficacy and safety of LEQVIO in patients who entered an open-label extension after completing either ORION-3, ORION-9, ORION-10 or ORION-11 trials.[13,14,15] Patients had a baseline LDL-C of 2.92 mmol/L (+/– 1.2), and the primary endpoints were the proportion of patients achieving prespecified LDL-C goals at end of the study, and safety.[12]

AAC=Accelerated Access Collaborative; ASCVD=atherosclerotic cardiovascular disease; BP=blood pressure; CI=confidence interval; CKD=chronic kidney disease; CV=cardiovascular; CVD=cardiovascular disease; DM=diabetes mellitus; EAS/ESC=European Atherosclerosis Society/European Society of Cardiology; eGFR=estimated glomerular filtration rate; FH=family history; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; mAb=monoclonal antibody; MI=myocardial infarction; NICE=National Institute for Health and Care Excellence; PAD=peripheral arterial disease; PCSK9i=proprotein convertase subtilisin/kexin type 9 inhibitor; QOF=Quality and Outcomes Framework; RR=rate ratio; SCORE=Systematic Coronary Risk Estimation; siRNA=small interfering ribonucleic acid; SmPC=Summary of Product Characteristics; T1=type 1; T2=type 2; TAG=Technology Appraisal Guidance; TC=total cholesterol; TIA=transient ischaemic attack.

References

1. LEQVIO Summary of Product Characteristics; **2.** CTT Collaborators. *Lancet* 2012; 380(9841):581–590; **3.** Mach F, et al. *Eur Heart J* 2020;41(1):111–188; **4.** Visseren FLJ, et al. *Eur Heart J* 2021;42(34):3227–3337; **5.** NHS AAC. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. Available from: https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/ [Last accessed: January 2025]; **6.** García-Fernández-Bravo I, et al. *Front Cardiovasc Med* 2022;9:808712; **7.** NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification [NG238]. Available from: https://www.nice.org.uk/guidance/ng238 [Last accessed: January 2025]; **8.** NICE. Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA733). 6 October 2021. Available from: https://www.nice.org.uk/guidance/ta733 [Last accessed: January 2025]; **9.** NHS England. Quality and Outcomes Framework guidance for 2024/25. 1 April 2024. Available from: https://www.england.nhs.uk/wp-content/uploads/2024/03/PRN01104-Quality-and-outcomes-framework-guidance-for-2024-25.pdf [Last accessed: January 2025]; **10.** NHS England. Lipid optimisation pathway: secondary prevention in primary care and the community. September 2024. Available from: https://www.england.nhs.uk/long-read/lipid-optimisation-pathway-secondary-prevention-in-primary-care-and-the-community [Last accessed: January 2025]; **11.** Catapano AL, et al. *Eur Heart J* 2016;37(39):2999–3058; **12.** Wright RS, et al. *Cardiovasc Res* 2024;120(12):1400-1410; **13.** Ray KK, et al. *N Engl J Med* 2020;382(16):1507-1519; **14.** Ray KK, et al. *Lancet Diabetes Endocrinol* 2023;11(2):109-119; **15.** Raal FJ, et al. *N Engl J Med* 2020;382(16):1520-1530

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