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LEQVIO® inclisiran

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USE THIS INFOGRAPHIC TO IDENTIFY WHEN TO INTRODUCE LEQVIO INTO THE TREATMENT REGIMEN OF YOUR ELIGIBLE PATIENTS

LDL-C TREATMENTS AND TREATMENT SEQUENCING WITH LEQVIO

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]

National guidance of lipid management for the secondary prevention of CVD recommend an **LDL-C target of ≤2.0 mmol/L or non-HDL-C of ≤2.6 mmol/L.**[2]

ESC/EAS guidelines set the **clinical target of <1.8 mmol/L** for **high-risk patients** and **<1.4 mmol/L** for **very high-risk patients**, as well as a ≥50% reduction from baseline for these patient groups.*[3]

At-risk patients are not meeting their LDL-C target:†[4]

- **49% more total CV events** in patients who failed to reach LDL-C target than those who did

The NHS AAC national guidance for lipid management recommends that **if the maximum tolerated dose of statin does not control LDL-C well enough** after 2–3 months, confirm statin adherence, **then consider the following options:**[2]

- Ezetimibe[5]
- LEQVIO[1]
- Alirocumab or evolocumab[6,7]

In those who are statin-intolerant or for whom statins are contraindicated:[8,9]

- Ezetimibe/bempedoic acid

Please refer to the full NHS AAC guidance for specific recommendations, and to the relevant SmPC before prescribing these medications. LEQVIO is only recommended by NICE when persistently elevated LDL-C levels are ≥2.6 mmol/L.[10]

Scan the QR code or follow this link to access NHS AAC guidance.

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NHS England's lipid optimisation pathway for secondary prevention in primary care and the community have recommended that:[11]

- where an individual qualifies for injectable therapies such as LEQVIO, as per NICE technology appraisals, **these should be considered in preference to ezetimibe** to prevent lipid levels being lowered but remaining above the LDL-C target and below thresholds for initiating injectable therapies

Extent of lipid lowering with available therapies, according to the NHS AAC national guidance[2]

Statin, dose mg/day	Approximate reduction in LDL-C (%)				
	5	10	20	40	80
Fluvastatin			21	27	33
Pravastatin		20	24	29	
Simvastatin		27	32	37	42
Atoravastatin		37	43	49	55
Rosuvastatin	38	43	48	53	
Atoravastatin + ezetimibe 10 mg		52	54	57	61

- Low-intensity statins will produce an LDL-C reduction of 20–30% from baseline
- Medium-intensity statins will produce an LDL-C reduction of 31–40% from baseline
- High-intensity statins will produce an LDL-C reduction of >40% from baseline
- Simvastatin 80 mg is not recommended due to muscle toxicity

Doubling the dose of statin will produce an average reduction in LDL-C of ≤6%[2]

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NICE recommends LEQVIO, within its licensed indication, as an option for the treatment of adult patients who:[10]

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).

AND

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.

Both criteria must be met.

This is our chance to help optimise LDL-C management

- **Using LEQVIO** in combination with a maximally tolerated statin **may help bring the ≤2.0 mmol/L LDL-C target** within reach for eligible patients[12]
- Considering which **add-on therapies** to offer and in what order to prescribe them may help to **maximise LDL-C lowering**

Please note this is a fictitious scenario.

What would you consider next for Paul?‡

- **Age:** 67 | **CV history:** ASCVD (experienced one event) | **Other health conditions:** diabetes and hypertension
- **Lipid-lowering therapy:** 3 months of maximally tolerated statin (adherence, timing of dose, diet and lifestyle have been discussed)
- **Current LDL-C levels:** 3.1 mmol/L | **National guidelines LDL-C target:** ≤2.0 mmol/L[2]

CONSIDER ADDING LEQVIO, AS RECOMMENDED BY NICE

NICE recommends LEQVIO in patients with a history of certain CV events and LDL-C levels persistently ≥2.6 mmol/L despite maximally tolerated statins.[10]

~50% Average LDL-C trial reduction with LEQVIO[12]

CONSIDER ADDING EZETIMIBE, AS RECOMMENDED BY NICE

NICE recommends ezetimibe in combination with a maximally tolerated statin in patients who are unable to reach their LDL-C (or TC) goals.[13]

~24% Average LDL-C trial reduction with ezetimibe[14]

Based on average placebo-corrected LDL-C reductions observed in pivotal trials, a patient like Paul might be able to achieve:

LDL-C LEVELS OF ~1.55 mmol/L WITH LEQVIO

✓ **MORE LIKELY TO ACHIEVE THE QOF LDL-C TARGET**

LDL-C LEVELS OF ~2.36 mmol/L WITH EZETIMIBE

✕ **LESS LIKELY TO ACHIEVE THE QOF LDL-C TARGET**

LEQVIO is only recommended by NICE when persistently elevated LDL-C levels are ≥2.6 mmol/L.[10]

Please note this is a fictitious scenario and that calculations were made based on data that are not derived from head-to-head studies. There are no head-to-head studies between LEQVIO and ezetimibe.

Please note there are differences between the clinical trials, and this is not an exhaustive list of studies conducted using either LEQVIO or ezetimibe.

A study shows that a LEQVIO-first strategy leads to greater LDL-C lowering than usual care

- VICTORION-INITIATE was a prospective, randomised, open-label clinical trial conducted in US patients with ASCVD and LDL-C levels ≥1.8 mmol/L despite receiving maximum tolerated statins (or with documented statin intolerance)[15]
- Patients were randomised to receive usual care alone, based on 2018 ACC/AHA/multi-society guidelines, which allowed for treatment intensification with any LLT (including LEQVIO) at the clinician's discretion, or LEQVIO plus usual care (mean baseline LDL-C 2.52 mmol/L).[§,15] Note. The study design permitted the use of LEQVIO in the usual care arm leading to 10 patients in the usual care arm receiving LEQVIO, which may impact comparisons between the randomised groups[15]

Coprimary endpoints were percentage change in LDL-C from baseline to Day 330 and discontinuation of statin therapy:

- At Day 330, mean LDL-C change from baseline was –60.0% (97.5% CI: –64.7% to –55.2%) with LEQVIO-first and –7.0% (97.5% CI: -12.0% to –1.9%) with usual care; between-group difference: –53.0% (97.5% CI: –60.0% to –46.0%; p<0.001)
- Statin discontinuation rates were 6.0% (97.5% CI: 1.9% to 10.2%) with LEQVIO-first and 16.7% (97.5% CI: 10.2% to 23.1%) with usual care. The difference in rates fell within the non-inferiority margin (set at 15% a priori; –10.6% [97.5% CI: –18.3% to –3.0%])

For the secondary endpoint of proportion of patients meeting prespecified LDL-C targets, significantly **more patients in the LEQVIO-first arm achieved LDL-C goals** vs usual care at Day 330 (p<0.001):[15]

Implementing LEQVIO earlier in the treatment pathway did not lead to any new safety concerns and did not lead to statin discontinuation.[15]

In clinical trials, **LEQVIO had a safety profile similar to placebo, apart from injection-site reactions** (8.2% vs 1.8% for placebo).

*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 m²); 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 m²); DM and target organ damage: ≥3 major risk factors, or early onset of T1DM of long duration (>20 years).[3]

†Based on study data (N=38,110,734) that evaluated the annual CV event rates in a subset of guideline-defined high-risk patients from the Family Heart Database, which comprised diagnostic, procedure, laboratory results and prescription data from claims in the US from 2012 to 2021.[4]

‡LEQVIO data are derived from the ORION-10 (N=1,561) and ORION-11 (N=1,617) trials.[12] Ezetimibe was studied together with simvastatin (40 mg) vs placebo with simvastatin (40 mg) in a double-blind, randomised, 6-year clinical trial (N=18,144), evaluating adult patients who had been hospitalised for an acute coronary syndrome within the preceding 10 days. Patients had LDL-C levels of 1.3–2.6 mmol/L if they were receiving lipid-lowering therapy or 1.3–3.2 mmol/L if they were not receiving lipid-lowering therapy. The primary endpoint was a composite of CV death, non-fatal MI, unstable angina requiring rehospitalisation, coronary revascularisation (≥30 days after randomisation) or non-fatal stroke.[14]

§The LEQVIO-first group received a 284 mg initial dose of LEQVIO at Month 0 and two maintenance doses at Month 3 and Month 9. LEQVIO-first patients could receive additional LLTs (except PCSK9is), if required, to reach target LDL-C levels.[16] LDL-C levels were given in mg/dL in Koren M, et al 2024 (mean baseline LDL-C 97.4 mg/dL; target LDL-C levels of 70 mg/dL and 55 mg/dL) and were converted to mmol/L for this infographic.

AAC=Accelerated Access Collaborative; ACC=American College of Cardiology; AHA=American Heart Association; 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; LLT=lipid-lowering therapy; LS=least squares; MI=myocardial infarction; NICE=National Institute for Health and Care Excellence; OR=odds ratio; 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; SmPC=Summary of Product Characteristics; T1=type 1; TAG=Technology Appraisal Guidance; TC=total cholesterol; TIA=transient ischaemic attack.

References

1. LEQVIO Summary of Product Characteristics; **2.** 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: December 2024]; **3.** Mach F, et al. *Eur Heart J* 2020;41(1):111–188; **4.** Family Heart Foundation. Prioritizing LDL-cholesterol control. 30 September 2023. Available from: https://familyheart.org/wp-content/uploads/2023/10/FamilyHeartFoundation_LDLPolicyStatement_Pages_20231026.pdf [Last accessed December 2024]; **5.** Ezetrol (ezetimibe) Summary of Product Characteristics; **6.** Praluent (alirocumab) Summary of Product Characteristics; **7.** Repatha (evolocumab) Summary of Product Characteristics; **8.** Nilemdo (bempedoic acid) Summary of Product Characteristics; **9.** Nustendi (bempedoic acid and ezetimibe) Summary of Product Characteristics; **10.** NICE. Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA733). Available from: https://www.nice.org.uk/guidance/ta733 [Last accessed: December 2024]; **11.** 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: December 2024]; **12.** Ray KK, et al. *N Engl J Med* 2020;382(16):1507–1519 and supplementary information; **13.** NICE. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (TA385). 24 February 2016. Available from: https://www.nice.org.uk/guidance/ta385 [Last accessed: December 2024]; **14.** Cannon CP, et al. *N Engl J Med* 2015;372(25):2387–2397; **15.** Koren M, et al. *J Am Coll Cardiol* 2024;83(20):1939–1952; **16.** Grundy SM, et al. *J Am Coll Cardiol.* 2019;73(24):e285–e350

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