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Drug Class Update with New Drug Evaluation: PCSK9 Modulators Focused Update

Date of Review: August 2022

Date of Last Review: August 2021
Dates of Literature Search: 08/31/2021 – 05/31/2022
Brand Name (Manufacturer): LEQVIO (Novartis)
Dossier Received: yes

Generic Name: Inclisiran

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:

- Evaluate new comparative evidence for the effectiveness and safety of proprotein convertase subtilisin kexin type 9 (PCSK9) modulators for the prevention of cardiovascular (CV) mortality and CV events in patients with established atherosclerotic cardiovascular disease (ASCVD) and patients with high CV risk.
- Analyze the data supporting the efficacy and safety of inclisiran and determine its appropriate place in therapy.

Research Questions:

1. Is there any new comparative evidence for PCSK9 modulators in reducing CV outcomes in patients treated for the primary or secondary prevention of CV disease?
2. Is there new comparative evidence for the safety of PCSK9 modulators in patients being treated for the primary or secondary prevention of CV disease?
3. What are the comparative benefits and harms of inclisiran in patients with familial hypercholesterolemia, ASCVD or at high CV risk CV patients who cannot achieve adequate low-density lipoprotein cholesterol (LDL-C) reduction with their current lipid-lowering regimen?
4. Are there specific subpopulations for which inclisiran is better tolerated or more effective than other available dyslipidemia drugs when used for CV risk reduction?

Conclusions:

- There is high quality evidence that inclisiran significantly reduces LDL-C from baseline compared to placebo with a high magnitude of benefit in patients with ASCVD and heterozygous familial hypercholesterolemia (HeFH) with an LDL-C reduction ranging from -48% to -52% and low-quality evidence of a reduction in patients with an ASCVD risk equivalent.[1,2] However, there is no data evaluating inclisiran on clinical outcomes, including CV events, CV mortality and all-cause mortality.
- Consistent LDL-reductions were seen across subgroups defined by baseline demographic characteristics and disease comorbidities. However, there is limited data in non-white populations and insufficient evidence evaluating subgroups comparable to Medicaid recipients.
- There is no new high quality comparative evidence evaluating other PCSK9 modulators, including evolocumab or alirocumab.

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Recommendations:

- No PDL changes recommended based on clinical evidence.
- Due to its unknown benefit on CV outcomes, maintain inclisiran as non-preferred on the PDL and modify prior authorization (PA) criteria for the PCSK9 modulators to limit inclisiran to its FDA indication and to those who have tried agents with evidence of CV risk reduction.
- After evaluation of comparative costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy

- There is high quality evidence that alirocumab and evolocumab decrease the risk of cardiovascular disease (CVD) and myocardial infarction (MI) compared to placebo in patients with CVD or at high CV risk with a modest absolute risk difference of 1-2%.[3] There is high quality evidence that alirocumab also decreases all-cause mortality compared to placebo (absolute risk difference of 1%). There is low quality evidence of no consistent benefit on CV outcomes or all-cause mortality with either alirocumab or evolocumab compared to ezetimibe and statins.
- There remains insufficient evidence evaluating alirocumab or evolocumab in lower CV risk patients, and long-term efficacy and safety beyond 3 years is lacking.
- There is high quality evidence that alirocumab significantly reduces LDL-C compared to placebo in adults with homozygous familial hypercholesterolemia (HoFH) on background statin therapy with a percent change reduction from baseline at week 12 of -26.9% versus 8.6%. There is insufficient evidence that alirocumab reduces risk of CVD or mortality in patients with HoFH. [4]
- Evolocumab and alirocumab currently require prior authorization for approval to limit use to patients with CVD or familial hypercholesterolemia at high risk for CV events who require additional LDL-C lowering despite use of other lipid-lowering agents, including statins.

Background:

The association between hypercholesteremia, and particularly elevated low-density lipoprotein cholesterol (LDL-C), and cardiovascular disease (CVD) is well established. In addition to optimizing a healthy lifestyle, prevention of ASCVD events involves optimization of treatments that have proven benefits on reduction in ASCVD events and/or cardiovascular (CV) mortality. Until more recently, only statins had strong and consistent evidence demonstrating ASCVD risk reduction. Therefore, statin therapy remains the cornerstone of treatment for both primary and secondary prevention of ASCVD. However, combination or non-statin therapy to reduce ASCVD risk beyond statin use may be necessary for high-risk populations.

The utilization and place in therapy of non-statin therapy has significantly evolved over the past few decades from being routine add-on therapy targeting specific LDL-C goals to having no clear indication based on a lack of data showing an improvement on CV outcomes. The recent publication of the 2018 American College of Cardiology/American Heart Association guidelines for the treatment of blood cholesterol once again re-define the role of non-statin therapy.[5] A consistent approach is to reserve non-statin add-on therapy to high-risk populations on maximally tolerated statin therapy who may require additional LDL-C lowering and to use agents which have demonstrated an improvement in CV outcomes. The updated guidelines consider an LDL-C threshold of 70 mg/dl reasonable to add a non-statin agent in those with clinical ASCVD. [5]

Currently, only ezetimibe, icosapent ethyl and the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors have shown a modest benefit on clinical outcomes of interest when added to statin therapy (**Tables 1 and 2**). Ezetimibe, an inhibitor of intestinal cholesterol absorption, is indicated as an adjunct to reduce elevated cholesterol and LDL-C.[6] It is generally well tolerated and can lower LDL-C by up to 25% when added to statin therapy. The IMPROVE-IT trial

provides modest evidence for use of ezetimibe in combination with a statin for secondary prevention of CV events.[7] In patients with recent acute coronary syndrome (ACS), ezetimibe produced an incremental reduction in the primary composite endpoint, and specifically reduced nonfatal ischemic stroke, but did not reduce all-cause mortality or CV mortality.

Evolocumab (Repatha®) and alirocumab (Praluent®) are subcutaneously injected human monoclonal antibodies that reduce LDL-C by inhibiting PCSK9.[8,9] PCSK9 promotes the degradation of the LDL receptor, resulting in an increase in plasma LDL-C. Both agents are effective at lowering LDL-C with reductions of up to 60% when combined with statin therapy. Both agents are approved as an adjunct with other lipid-lowering therapies (statins, ezetimibe) for primary hyperlipidemia (heterozygous familial hypercholesterolemia) and in patients with clinical ASCVD who require additional lowering of LDL-C. Additionally, they are both FDA approved for the risk reduction of MI, stroke, and coronary revascularization in adults with established CVD based on clinical outcome data from the FOURIER and ODYSSEY OUTCOMES trial **(Tables 1 and 2).**[8,10 11]

Table 1: Characteristics of Cardiovascular Outcome trials for Non-statins[7,10-12]

	FOURIER	**ODYSSEY**	**IMPROVE-IT**	**REDUCE-IT**
Non-Statin Study Drug	Evolocumab	Alirocumab	Ezetimibe	Icosapent ethyl 2 gm BID
Patient Population	MI, CVA or PAD	4-52 weeks post-ACS	ACS (prior 10 days)	CVD or DM and ≥ risk factor with TG ≥ 150 mg/dl
Median LDL-C	92 mg/dl	92 mg/dl	95 mg/dl	75 mg/dl (median TG 216 mg/dl)
% on High Intensity Statin	69%	89%	6%	30%
% on Ezetimibe	5%	3%	100%	6.5%
Study Duration	26 months	34 months	6 years	5 years

Abbreviations: ACS: acute coronary syndrome: BID: twice daily; CVA: cerebrovascular accident; CVD: cardiovascular disease; DM: diabetes mellitus; LDL-C: low density lipoprotein cholesterol MI: myocardial infarction; PAD: peripheral artery disease; TG: triglyceride

Table 2: Summary of Results from Cardiovascular Outcome Trials[7,10-12]

Outcome	**Evolocumab ARR/NNT**	**Alirocumab ARR/NNT**	**Ezetimibe ARR/NNT**	**Icosapent ARR/NNT**
CV Composite Outcome	1.5% / 67	1.6% / 63	2% / 50	4.8% / 21
CV Death	NS	NS	NS	0.9% / 112
Death from any cause	NS	0.6% / 167	NS	NS
Myocardial infarction	1.2% /84	1% / 100	1.7% / 59	2.3% / 44
Stroke	0.4% / 250	0.4% / 250	NS	0.8% / 125

Abbreviations: ARR: absolute risk reduction; CV: cardiovascular; NNT: number needed to treat; NS: not significant

Inclisiran (Leqvio®) was FDA approved in December 2021. It is a double-stranded small interfering ribonucleic acid (siRNA) that inhibits hepatic production of PCSK9, resulting in decreased circulating LDL-C levels.[13] Reduction in intrahepatic PCSK9 levels leads to increased recycling and expression of the LDL-C receptor

(LDLR) on the hepatocyte cell surface, which in turn increases LDL-C uptake, thus reducing circulating LDL-C.[14] It has only been used as add-on therapy to background maximally tolerated statin therapy with or without ezetimibe. Inclisiran is given as a subcutaneous (SC) injection on day 1, day 90 and every 6 months after that.[15] Initial phase II studies demonstrated reductions in LDL-C and PCSK9 levels in patients with homozygous familial hypercholesterolemia (HoFH) and showed no added benefit beyond the 300 mg dose.[16,17]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 6 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses)[13,18-20], wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[21,22].

A systematic review was done to evaluate the effects of alirocumab on cardiovascular events and all-cause mortality.[23] There were a total of 13 studies identified with an overall low risk of bias. Consistent with findings from previous high quality systematic reviews, there was high quality evidence of a reduction in CV event with alirocumab compared to placebo (10.9% versus 13.4%; relative risk [RR] 0.89; 95% confidence interval [CI] 0.83 to 0.95) with no significant difference in CV mortality (2.3% vs. 2.7%; RR 0.87; 95% CI 0.74 to 1.04). [23] This review did find a reduction in all-cause mortality with alirocumab compared to placebo (1.6% vs. 2.1%; RR 0.80; 95% CI 0.66 to 0.96). Although this is likely from non-CV mortality, it is uncertain whether alirocumab will lower all-cause mortality.

New Guidelines:
No High-Quality Guidelines identified.

After review, 1 guideline was excluded due to poor quality which was based on weak recommendations and largely on expert opinion and shared decision making.[24]

New Formulations or Indications:
None

New FDA Safety Alerts:
None

Randomized Controlled Trials:
A total of 15 citations were manually reviewed from the initial literature search and 7 RCTs were identified after initial evaluation. After further review, 5 citations were excluded because of wrong study design (e.g., observational)[25-28], comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[29]. The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Furtado, et al[30]	Evolocumab vs. placebo	Adults with stable ASCVD, LDL ≥ 70 mg/dl (n=17,073)	MACE (Composite of cardiovascular death, MI, stroke, unstable angina, or coronary revascularization) with or without prior PCI	<u>MACE: Prior PCI</u> Evolocumab: 951 (11.2%) Placebo: 1128 (13.2%) HR 0.84; 95 % CI 0.77-0.91 <u>MACE: No Prior PCI</u> Evolocumab: 391 (7.4%) Placebo: 434 (8.3%) HR 0.88; 95 % CI 0.77-1.01 P for interaction: 0.51*	Pre-specified subgroup analysis from FOURIER trial Differences in populations at baseline *There was no difference in the reduction in MACE with evolocumab in those with or without prior PCI
Deedwania, et al[31]	Evolocumab vs. placebo	Adults with stable ASCVD, LDL ≥ 70 mg/dl stratified by MetS (n=17,073)	MACE (Composite of cardiovascular death, MI, stroke, unstable angina, or coronary revascularization) with or without MetS	<u>MACE: MetS</u> Evolocumab: 13.5% Placebo: 15.8% HR 0.83; 95 % CI 0.76-0.91 <u>MACE: No Prior PCI</u> Evolocumab: 11.2% Placebo: 12.9% HR 0.89; 95 % CI 0.79-1.01 P for interaction: 0.39*	Pre-specified subgroup analysis from FOURIER trial *There was no difference in the reduction in MACE with evolocumab in those with or without MetS
Abbreviation: ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; HR = hazard ratio; LDL = low density lipoprotein cholesterol; MACE = major adverse cardiovascular event; MetS = metabolic syndrome; MI = myocardial infarction; PCI = percutaneous coronary intervention					

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Inclisiran is an siRNA directed at PCSK9 mRNA indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical ASCVD, who require additional lowering of LDL-C.[15]

Approval was based on 3 similarly designed RCTs (ORION-9, ORION-10, and ORION-11) evaluating the efficacy of four subcutaneous (SC) injections of inclisiran 300 mg over 18 months in patients with HeFH, established ASCVD, and high risk for ASCVD who all required additional LDL-C lowering.[1,2] Each was a double-blind, placebo-controlled RCT including patients with LDL-C ≥ 70 mg/dl or 100 mg/dl, depending on risk category, despite maximally tolerated LDL-C lowering therapy. The primary endpoint in each trial was change in LDL-C from baseline to day 510. More details on study design and risk of bias are included in **Table 6**.

ORION-9 included patients with HeFH based on genetic confirmation or the phenotypic Simon Broome criteria (LDL-C > 190 mg/dl plus physical finding of tendon xanthomas or DNA based evidence of LDL-receptor mutation) who had an LDL-C of ≥ 100 mg/dl on maximally tolerated statin therapy with or without ezetimibe.[1] The study population was primarily white (94%) and 90% were on statin therapy, including 75% who were receiving high-intensity statin therapy. Overall, there was a significant difference in percent reduction in LDL-C from baseline (difference -47.9%; 95% CI -52.5% to -42.3%) with inclisiran compared to placebo and more patients in the inclisran group who achieved goal LDL-C levels of < 100 mg/dl and < 70 mg/dl.[1] Subgroup analysis showed similar LDL reductions in all subgroups evaluated.

There was unclear selection bias due to minor differences in baseline characteristics. More patients in the placebo group had ASCVD (30.4% vs. 24.4%) and diabetes (11.7% vs. 8.3%) compared to the inclisiran group. More patients in the inclisiran group were on high-intensity statin (76.4% vs. 71.2%) and ezetimibe (55.8% vs. 50%) compared to the placebo group. The primary outcome was measured at month 17 compared to the more traditional month 3 to allow for steady state concentrations to be achieved of inclisran. The FDA reviewer notes missing data as a result from measuring the primary outcome this late.[13] This may also increase the risk of unblinding if a patient had an LDL-C drawn in the meantime. Lastly, 94% of the study population was white and there is limited applicability to non-white patients.

ORION-10 and ORION-11 were similarly designed but ORION-10 included patients with clinical ASCVD and LDL-C ≥ 70 mg/dl and ORION-11 included patients with ASCVD and LDL ≥ 70 mg/dl or an ASCVD risk equivalent (type 2 diabetes, familial hypercholesterolemia, or 10-year ASCVD risk ≥ 20%), and LDL ≥ 100 mg/dl.[2] In both populations, inclisiran significantly lowered LDL-C from baseline compared to placebo with a difference of -52.3% (95% CI -55.7% to -48.8%) and -49.9% (95% CI -53.1% to -46.6%), respectively.[2] There were also significant reductions in non-HDL and apolipoprotein B (Apo-B). Results were similar across subgroups, and there was a trend toward increased magnitude of effect with lower baseline LDL-C in both trials and a trend towards greater treatment effect in patients on statin compared to not on a statin in ORION-11.[13]

Most patients in ORION-11 had ASCVD (87.5%) making the two study populations relatively similar and limiting generalizability to patients with an ASCVD risk equivalent. Thirty-three percent of the screened patients in ORION-10 did not meet randomization criteria, limiting applicability to the general population. The most common criteria not met were LDL ≥ 70 mg/dl and having "any condition that interferes with the study". It is unclear what specific conditions this included. Similarly, 32% of screened patients in ORION-11 did not meet randomization criteria.

In all studies, use of PCSK9 inhibitors were excluded and the safety and efficacy of use of inclisiran in addition to a PCSK9 inhibitor remains unknown. The majority of patients in all studies were on background high-intensity statins, but there were few patients on ezetimibe (<10%). There are no data evaluating the effects of inclisiran on CV events or CV mortality.

Clinical Safety:

From the primary 3 RCTs submitted for FDA approval (n=3655), there were very few discontinuations due to adverse events in the inclisiran (5.6%) and placebo (7.2%) groups, and inclisiran was generally well tolerated in the short term.[13] The most common adverse event that occurred more frequently than placebo was injection site reactions (8.2% vs. 1.8%, respectively). This was also the most common reason for withdrawal of treatment. Other adverse effects occurring more commonly than placebo are included in **Table 4.** There were slightly more serious adverse events in the placebo arm (23%) compared to inclisiran (20%) and most were well balanced between groups. The most commonly reported serious adverse events were cardiac disorders which is likely a reflection of the high-risk cardiovascular population. There was no significant difference in changes in creatine kinase between inclisiran and placebo, with a 1% increase in incidence of arthralgia with inclisran and 0.7% increase in pain in extremity. Long term safety beyond 18 months remains uknown.

Table 4: Adverse Reactions Occurring in >3% of Patients and Greater than Placebo[15]

Reactions	Placebo (N = 1822) %	Inclisiran (N = 1833) %
Injection site reaction	1.8%	8.2%
Arthralgia	4%	5%
Urinary Tract Infection	3.6%	4.4%
Diarrhea	3.5%	3.9%
Bronchitis	2.7%	4.3%
Pain in extremity	2.6%	3.3%
Dyspnea	2.6%	3.2%

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Cardiovascular mortality
2) Non-fatal cardiovascular events
3) All-cause mortality
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Percent change in LDL-C from baseline to day 510

Table 5. Pharmacology and Pharmacokinetic Properties.[15]

Parameter	
Mechanism of Action	Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA). In hepatocytes, inclisiran utilizes the RNA interference mechanism and directs catalytic breakdown of mRNA for PCSK9. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.
Oral Bioavailability	N/A (subcutaneous injection)
Distribution and Protein Binding	87% protein bound; volume of distribution 500 L with high uptake in the liver
Elimination	16% cleared through the kidney
Half-Life	9 hours
Metabolism	Primarily metabolized by nuclease; no CYP450 metabolism

Abbreviations: L = liters, LDL-C = low density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilsin-kexin type 9; N/A = not applicable; RNA = ribonucleaic acid.

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. ORION-9[1,13] Phase III, PC, DB, RCT	1. inclisiran 300 mg SC 2. placebo On days 1, 90, 270 and 450	Demographics: mean age 56 y/o 47% men 94% white Mean LDL-C 153 mg/dl 90% on statins; 75% on high-intensity 25% ASCVD Key Inclusion Criteria: • Adults with HeFH • LDL-C ≥ 100 mg/dl • TG < 400 mg/dl • eGFR > 30 ml/min • maximally tolerated statin Key Exclusion Criteria: • NYHA class IV HF • EF < 25% • SBP > 180 mmHg • active liver disease • uncontrolled or serious disease • alcohol and/or drug abuse in last 5 years	ITT: 242 240 PP: 230 234 Attrition: 9 (3.8%) 7 (2.9%)	Primary Endpoint: Percent change in LDL-C from baseline: 1. -39.7% 2. + 8.2% Difference -47.9%; 95% CI -52.5% to -42.3%; P<0.001 Exploratory Endpoints: Reduction from baseline in mean LDL-C of ≥ 50%: 1. 92 (38%) 2. 2 (0.8%) P<0.001*	NA ARR 38% / NNT 3	Discontinue due to adverse events: 1. 0 2. 0 p-values not reported	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear; randomization via automated interactive response technology; some minor differences in baseline characteristics. Performance Bias: low, double-blinded using appropriate blinding techniques and blinded syringes. Unblinding due to lower LDL-C possible prior to day 510. Detection Bias: unclear; no details about blinding of outcome assessors Attrition Bias: low; low overall attrition in both groups. ITT analysis performed. Reporting Bias: low; results for all pre-specified outcomes were reported Other Bias: unclear; funded by the Medicines Company which was acquired by the manufacturer of inclisran **Applicability**: Patient: limited representation of non-white patients, limited generalizability to Medicaid population Intervention: Dose regimen selected based on phase I and II dose ranging studies Comparator: placebo comparator Outcomes: surrogate outcome Setting: 46 sites in 8 countries (37% South Africa, 17% Spain, 13% US, 10% Denmark)

2. ORION-10 [2,13] Phase 3, PC, DB, PG, RCT	1. inclisiran 300 mg SC 2. placebo On days 1, 90, 270 and 450	Demographics: Male 69.4% Mean age 66 y/o 85.6% white 12.6% black Mean LDL-C 105 Key Inclusion Criteria: • Adults with ASCVD • LCD-C ≥ 70 mg/dl, • background lipid lowering therapy • TG < 400 mg/dl • eGFR > 30ml/min Key Exclusion Criteria: See above	ITT: 781 780 PP: 729 715 Attrition: 60 (7.7%) 86 (11%)	Primary Endpoint: Percent change in LDL-C from baseline: 1. -51.3% 2. + 1% Difference -52.3%; 95% CI -55.7% to -48.8%; P<0.001 Exploratory Endpoints: Reduction from baseline in mean LDL-C of ≥ 50%: 1. 503 (72.8%) 2. 17 (2.6%) OR 67.1; 95% CI 41.8 to 107.6 P<0.001	NA ARR 70.2%/ NNT 2	Discontinue due to adverse events: 1. 8 (1.0%) 2. 5 (0.6%) p-values not reported	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: low; randomization via automated interactive response technology; groups balanced at baseline Performance Bias: low, double-blinded using appropriate blinding techniques and blinded syringes. Unblinding possible due to lower LDL-C prior to day 510. Detection Bias: unclear; no details about blinding of outcome assessors Attrition Bias: low; low overall attrition in both groups. ITT analysis performed. Reporting Bias: low; results for all pre-specified outcomes were reported Other Bias: unclear; funded by the Medicines Company which was acquired by the manufacturer of inclisran **Applicability**: Patient: 33% of screened patients did not meet randomization criteria. Patients with relevant comorbidities included (HTN, DM). Limited representation from Asian or American Indian groups. Intervention: Dose regimen selected based on phase I and II dose ranging studies Comparator: placebo comparator Outcomes: surrogate outcome Setting: 146 sites in the US
3. ORION-11 [2] Phase 3, PC, DB, PG, RCT	1. inclisiran 300 mg SC 2. placebo On days 1, 90, 270 and 450	Demographics: 71.7% male Mean age 64.8 y/o 98.1% white 87.5 ASCVD Key Inclusion Criteria: • Adults with ASCVD or • ASCVD risk equivalent (T2DM, FH, or 10-year ASCVD risk ≥ 20%) • LDL ≥ 70 mg/dl • background lipid lowering therapy • TG < 400 mg/dl • eGFR > 30ml/min Key Exclusion Criteria: See above	ITT: 810 807 PP: 782 779 Attrition: 38 (4.7%) 37 (4.6%)	Primary Endpoint: Percent change in LDL-C from baseline: 1. -45.8% 2. + 4% Difference -49.9%; 95% CI -53.1% to -46.6% P<0.001 Exploratory Endpoints: Reduction from baseline in mean LDL-C of ≥ 50%: 1. 418 (57.7%) 2. 17 (2.3%) OR 49.3; 95% CI 30.3 to 80.3 P<0.001	NA ARR 55.4%/ NNT 2	Discontinue due to adverse events: 1. 4 (0.5%) 2. 0 p-values not reported	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: low; randomization via automated interactive response technology; groups balanced at baseline Performance Bias: low, double-blinded using appropriate blinding techniques and blinded syringes. Unblinding due to lower LDL-C possible prior to day 510. Detection Bias: unclear; no details about blinding of outcome assessors Attrition Bias: low; low overall attrition in both groups. ITT analysis performed. Reporting Bias: low; results for all pre-specified outcomes were reported Other Bias: unclear; funded by the Medicines Company which was acquired by the manufacturer of inclisran **Applicability**: Patient: 32% of screened patients did not meet randomization criteria; limited representation of non-white patients, limited generalizability to Medicaid population Intervention: Dose regimen selected based on phase I and II dose ranging studies Comparator: placebo comparator Outcomes: surrogate outcome Setting: 72 centers in 8 countries (Europe and South Africa)

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; DM = diabetes mellitus; EF = ejection fraction; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HF = heart failure; HTN = hypertension; ITT = intention to treat; LDL-C = low density lipoprotein cholesterol; N = number of subjects; MC = multicenter; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NYHA = new York heart association; OR = odds ratio; PC = placebo controlled; PCSK9 = proprotein convertase subtilsin-kexin type 9; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SBP = systolic blood pressure; SC = subcutaneous; T2DM = type 2 diabetes; TG = triglyceride; y/o = years old.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
cholestyramine (with sugar)	CHOLESTYRAMINE	ORAL	POWD PACK	Y
cholestyramine (with sugar)	QUESTRAN	ORAL	POWD PACK	Y
cholestyramine (with sugar)	CHOLESTYRAMINE	ORAL	POWDER	Y
cholestyramine (with sugar)	QUESTRAN	ORAL	POWDER	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	ORAL	POWD PACK	Y
cholestyramine/aspartame	PREVALITE	ORAL	POWD PACK	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	ORAL	POWDER	Y
cholestyramine/aspartame	PREVALITE	ORAL	POWDER	Y
cholestyramine/aspartame	QUESTRAN LIGHT	ORAL	POWDER	Y
evolocumab	REPATHA SURECLICK	SUBCUT	PEN INJCTR	Y
evolocumab	REPATHA SYRINGE	SUBCUT	SYRINGE	Y
evolocumab	REPATHA PUSHTRONEX	SUBCUT	WEAR INJCT	Y
ezetimibe	EZETIMIBE	ORAL	TABLET	Y
ezetimibe	ZETIA	ORAL	TABLET	Y
fenofibrate	FENOFIBRATE	ORAL	TABLET	Y
fenofibrate nanocrystallized	FENOFIBRATE	ORAL	TABLET	Y
fenofibrate nanocrystallized	TRICOR	ORAL	TABLET	Y
fenofibrate,micronized	ANTARA	ORAL	CAPSULE	Y
fenofibrate,micronized	FENOFIBRATE	ORAL	CAPSULE	Y
fenofibric acid (choline)	FENOFIBRIC ACID	ORAL	CAPSULE DR	Y
fenofibric acid (choline)	TRILIPIX	ORAL	CAPSULE DR	Y
omega-3 acid ethyl esters	LOVAZA	ORAL	CAPSULE	Y
omega-3 acid ethyl esters	OMEGA-3 ACID ETHYL ESTERS	ORAL	CAPSULE	Y
alirocumab	PRALUENT PEN	SUBCUT	PEN INJCTR	N
bempedoic acid	NEXLETOL	ORAL	TABLET	N
bempedoic acid/ezetimibe	NEXLIZET	ORAL	TABLET	N
colesevelam HCl	COLESEVELAM HCL	ORAL	POWD PACK	N
colesevelam HCl	WELCHOL	ORAL	POWD PACK	N
colesevelam HCl	COLESEVELAM HCL	ORAL	TABLET	N
colesevelam HCl	WELCHOL	ORAL	TABLET	N
colestipol HCl	COLESTID	ORAL	GRANULES	N
colestipol HCl	COLESTIPOL HCL	ORAL	GRANULES	N
colestipol HCl	COLESTID	ORAL	PACKET	N
colestipol HCl	COLESTIPOL HCL	ORAL	PACKET	N
colestipol HCl	COLESTID	ORAL	TABLET	N
colestipol HCl	COLESTIPOL HCL	ORAL	TABLET	N
evinacumab-dgnb	EVKEEZA	INTRAVEN	VIAL	N
fenofibrate	FENOFIBRATE	ORAL	CAPSULE	N
fenofibrate	LIPOFEN	ORAL	CAPSULE	N

fenofibrate	FENOFIBRATE	ORAL	TABLET	N
fenofibrate	FENOGLIDE	ORAL	TABLET	N
fenofibric acid	FENOFIBRIC ACID	ORAL	TABLET	N
gemfibrozil	GEMFIBROZIL	ORAL	TABLET	N
gemfibrozil	LOPID	ORAL	TABLET	N
icosapent ethyl	ICOSAPENT ETHYL	ORAL	CAPSULE	N
icosapent ethyl	VASCEPA	ORAL	CAPSULE	N
inclisiran sodium	LEQVIO	SUBCUT	SYRINGE	N
inositol	INOSITOL	ORAL	TABLET	N
lomitapide mesylate	JUXTAPID	ORAL	CAPSULE	N
niacin	NIACIN	ORAL	CAPSULE ER	N
niacin	NIACIN ER	ORAL	TAB ER 24H	N
niacin	NIASPAN	ORAL	TAB ER 24H	N
niacin	NIACIN	ORAL	TABLET	N
choline	CHOLINE	ORAL	TABLET	N
niacin	NIACIN	ORAL	TABLET ER	N
niacin	NIADELAY	ORAL	TABLET ER	N
niacinamide	NIACINAMIDE	ORAL	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

1. Furtado R., Aurelio Fagundes A., Oyama K. et al. Effect of Evolocumab in Patients With Prior Percutaneous Coronary Intervention. *Circ Cardiovasc Interv*. 2022 Mar;15(3):e011382. doi: 10.1161/CIRCINTERVENTIONS.121.011382. Epub 2022 Feb 25.

Background: Patients with prior percutaneous coronary intervention (PCI) are at high residual risk for multiple types of coronary events within and beyond the stented lesion. This risk might be mitigated by more intensive LDL-C (low-density lipoprotein cholesterol)-lowering beyond just with statin therapy.

Methods: FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) randomized 27 564 patients with stable atherosclerotic disease on statin to the PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitor evolocumab or placebo with a median follow-up of 2.2 years. The end points of interest were major adverse cardiovascular events (MACE; a composite of cardiovascular death, myocardial infarction, stroke, unstable angina or coronary revascularization), and major coronary events (a composite of coronary heart death, myocardial infarction, or coronary revascularization). We compared the risk of MACE and the magnitude of relative and absolute risk reductions with evolocumab in patients with and without prior PCI.

Results: Seventeen thousand seventy-three patients had prior PCI. In the placebo arm, those with prior PCI had higher rates of MACE (13.2% versus 8.3%; hazard ratio [HR]adj 1.61 [95% CI, 1.42-1.84]; P<0.0001) and major coronary events (11.5% versus 6.0%; HRadj, 1.72 [95% CI, 1.49-1.99]; P<0.0001). Relative risk reductions with evolocumab were similar in patients with and without prior PCI (MACE: HR, 0.84 [0.77-0.91] versus HR, 0.88 [0.77-1.01]; Pinteraction 0.51; major coronary events: HR, 0.82 [0.75-0.90] versus HR, 0.88 [0.75-1.04]; Pinteraction 0.42). Absolute risk reductions for MACE were 2.0% versus 0.9% (Pinteraction 0.14) and for major coronary events 2.0% versus 0.7% (Pinteraction 0.045). In those with prior PCI, the effect of evolocumab on coronary revascularization (HR, 0.76 [0.69-0.85]) was directionally consistent across types of revascularization procedures: coronary artery bypass grafting (HR, 0.71 [0.54-0.94]); any PCI (HR, 0.77 [0.69-0.86]); PCI for de novo lesions (HR, 0.76 [0.66-0.88]); and PCI for stent failure or graft lesions (HR, 0.76 [0.63-0.91]).

Conclusions: Evolocumab reduces the risk of MACE in patients with prior PCI including the risk of coronary revascularization, with directionally consistent effects across several types of revascularization procedures, including coronary artery bypass grafting and PCI for stent or graft failure.

2. Deedwania P, Murphy SA, Scheen A, Badariene J, Pineda AL, Honarpour N, Keech AC, Sever PS, Pedersen TR, Sabatine MS, Giugliano RP. Efficacy and Safety of PCSK9 Inhibition With Evolocumab in Reducing Cardiovascular Events in Patients With Metabolic Syndrome Receiving Statin Therapy: Secondary Analysis From the FOURIER Randomized Clinical Trial. *JAMA Cardiol.* 2021 Feb 1;6(2):139-147. doi: 10.1001/jamacardio.2020.3151.

Objective: To investigate outcomes with evolocumab in patients with and without MetS.

Design, setting, and participants: The FOURIER trial randomized patients worldwide with stable atherosclerotic cardiovascular disease receiving statin to evolocumab vs placebo with follow-up for a median of 2.2 years. Data were collected February 2013 to November 2016. For this prespecified analysis, patients with the requisite data were stratified based on the National Cholesterol Education Program Adult Treatment Panel III MetS criteria; in secondary analyses, patients were further substratified by diabetes at baseline. Analysis was intention to treat. Analysis began March 2018 and ended April 2020.

Interventions: Patients were randomized to evolocumab or placebo.

Main outcomes and measures: The primary end point was cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary end point was cardiovascular death, myocardial infarction, or stroke.

Results: Of 27 342 patients (mean [SD] age, 63 [9] years; 20 623 men [75.4%]) included in this analysis, 16 361 (59.8%) with baseline MetS were, when compared with patients without MetS, at higher risk of cardiovascular events (adjusted hazard ratio [95% CI], 1.31 [1.18-1.46]; P < .001 for the primary and 1.38 [1.20-1.57]; P < .001 for the key secondary end point). Evolocumab reduced low-density lipoprotein cholesterol similarly in patients with MetS (median [interquartile range], 92 [79-109] mg/dL vs 30 [19-48] mg/dL; P < .001) and without MetS (median [interquartile range], 92 [81-108] mg/dL vs 29 [18-44] mg/dl; P < .001). For the primary end point, the hazard ratios (95% CI) with evolocumab vs placebo were 0.83 (0.76-0.91) and 0.89 (0.79-1.01) in patients with and without MetS (P for interaction = .39). For the key secondary end point, the corresponding hazard ratios (95% CIs) were 0.76 (0.68-0.86) and 0.86 (0.74-1.01) (P for interaction = .23), respectively. Evolocumab did not increase the risk of new-onset diabetes or other major safety outcomes including worsening glycemic control, compared with placebo in patients with MetS.

Conclusions and relevance: Patients with atherosclerotic cardiovascular disease and MetS have substantial residual risk of cardiovascular events despite statin therapy. Evolocumab significantly reduced low-density lipoprotein cholesterol and cardiovascular risk in patients with MetS without increasing new-onset diabetes, worsening glycemic control, or other major safety events. These data suggest the addition of evolocumab to statin therapy in patients with atherosclerotic cardiovascular disease and MetS is safe and efficacious to reduce residual cardiovascular risk.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to May 18, 2022>

1	evolocumab.mp.	909
2	alirocumab.mp.	817
3	PCSK9 inhibitors.mp. or PCSK9 Inhibitors/	1709
4	inclisiran.mp.	164
5	cardiovascular events.mp.	41853
6	cardiovascular mortality.mp.	15671
7	Mortality/ or mortality.mp.	1318953
8	Myocardial Infarction/ or Cardiovascular Diseases/ or major adverse cardiovascular events.mp.	340307
9	1 or 2 or 3 or 4	2459
10	5 or 6 or 7 or 8	1596548
11	9 and 10	979
12	limit 11 to (english language and humans and yr="2021 -Current" and (clinical trial, phase iii or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or "systematic review"))	22
13	from 12 keep 1-3,6-11,13,15-18,22	15

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LEQVIO safely and effectively. See full prescribing information for LEQVIO.

LEQVIO® (inclisiran) injection, for subcutaneous use
Initial U.S. Approval: 2021

----------INDICATIONS AND USAGE----------
LEQVIO is a small interfering RNA (siRNA) directed to PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C). (1)

Limitations of Use:
The effect of LEQVIO on cardiovascular morbidity and mortality has not been determined. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of LEQVIO, in combination with maximally tolerated statin therapy, is 284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months. (2.1)
- LEQVIO should be administered by a healthcare professional. (2.2)
- Inject LEQVIO subcutaneously into the abdomen, upper arm, or thigh. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 284 mg/1.5 mL (189 mg/mL) in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------ADVERSE REACTIONS----------
Common adverse reactions in clinical trials (≥ 3%): injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremity, and dyspnea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2021

Appendix 5: Key Inclusion Criteria

Population	Individuals with cardiovascular disease or high-risk cardiovascular disease
Intervention	PCSK9 modulator
Comparator	Placebo or active control
Outcomes	Cardiovascular events, all-cause mortality, cardiovascular mortality
Timing	At least 12 weeks
Setting	Outpatient or inpatient after acute coronary syndrome

PCSK9 Modulators

Goal(s):

- Promote use of PCSK9 modulators that is consistent with medical evidence
- Promote use of high value products

Length of Authorization:

- Up to 12 months

Requires PA:

- All PCSK9 modulators (pharmacy and provider administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for the renewal of a previously approved prior authorization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code; go to #3	

Approval Criteria		
3. Does the patient have very high-risk clinical atherosclerotic cardiovascular disease (ASCVD), defined as documented history of multiple major ASCVD events **OR** one major ASCVD event and multiple high-risk conditions (See below) <u>Major ASCVD events</u> • Recent ACS (within past 12 months) • History of MI (other than recent ACS from above) • History of ischemic stroke • Symptomatic peripheral artery disease <u>High-Risk Conditions:</u> • Age ≥ 65 • Heterozygous familial hypercholesterolemia • History of prior CABG or PCI • Diabetes Mellitus • Hypertension • Chronic Kidney Disease • Current smoking • Persistently elevated LDL-C ≥ 100 despite maximally tolerated statin therapy and ezetimibe • History of congestive heart failure	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
4. Has the patient taken a daily high-intensity statin (see table below) and ezetimibe 10 mg daily for at least 3 months with a LDL-C still ≥ 70 mg/dl? Prescriber to submit chart documentation of: 1) Doses and dates initiated of statin and ezetimibe; 2) Baseline LDL-C (untreated); 3) Recent LDL-C	**Yes:** Confirm documentation; go to #5 1. Statin: Dose: Date Initiated: 2. Ezetimibe 10 mg daily Date Initiated: Recent LDL-C _____ mg/dL Date:_____	**No:** Go to #6
5. Is the patient adherent with a high-intensity statin and ezetimibe?	**Yes:** Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (both lipid-lowering prescriptions refilled 5 months' supply in last 6 months)	**No:** Pass to RPh; deny for medical appropriateness

Approval Criteria		
6. Does the patient have: • A history of rhabdomyolysis caused by a statin; or alternatively, • a history of creatinine kinase (CK) levels >10-times upper limit of normal with muscle symptoms determined to be caused by a statin; or • Intolerable statin-associated side effects that have been re-challenged with ≥ 2 statins Note: Prescriber must provide chart documentation of diagnosis or CK levels. A recent LDL-C level (within last 12 weeks) must also be submitted.	**Yes:** Confirm chart documentation of diagnosis or labs and approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness
7. Does the patient have a diagnosis of homozygous or heterozygous familial hypercholesterolemia? Note: Prescriber must provide chart documentation of diagnosis and recent LDL-C (within last 12 weeks).	**Yes:** Go to #8	**No:** Pass to RPh; deny for medical appropriateness.
8. Does the patient still have a LDL-C of ≥ 100 mg/dl while taking a maximally tolerated statin and ezetimibe?	**Yes:** Go to #9 Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness.
9. Is the request for inclisiran?	**Yes:** Go to #10	**No:** Approve for up to 12 months

Approval Criteria		
10. Has the patient tried and failed a PCSK9 inhibitor with evidence of a reduction in cardiovascular events (i.e., evolocumab or alirocumab) or have a contraindication to one of these agents? *Failure of a PCSK9 inhibitor includes adherence to PCSK9 inhibitor for at least 12 weeks with an LDL-C that remains > 70 mg/dl with evidence of clinical atherosclerotic cardiovascular disease (ASCVD)	**Yes:** Go to #11	**No:** Pass to RPh; deny for medical appropriateness.
11. Is the patient currently still receiving a PCSK9 inhibitor (alirocumab or evolocumab)?	**Yes:** Pass to RPh; deny for medical appropriateness.	**No:** Approve for up to 12 months. Note: Any current PA approvals for PCSK9 inhibitors will be end-dated.

Renewal Criteria		
1. What is the most recent LDL-C (within last 12 weeks)?	Recent LDL-C _____ mg/dL Date:_____ ; go to #2	
2. Has the patient experienced and maintained a reduction in LDL-C compared to baseline labs (prior to initiating PCSK9 modulator)?	**Yes:** Go to #3	**No:** Pass to RPh; deny for medical appropriateness
3. Is the patient adherent with PCSK9 modulator therapy?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh; deny for medical appropriateness

High- and Moderate-intensity Statins.

High-intensity Statins (≥50% LDL-C Reduction)	**Moderate-intensity Statins** (30 to <50% LDL-C Reduction)	
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Fluvastatin 80 mg Lovastatin 40-80 mg	Rosuvastatin 5-10 mg Pravastatin 40-80 mg Simvastatin 20-40 mg

P&T / DUR Review: *8/22 (MH) 8/21; 8/20; 5/19; 1/18; 11/16; 11/15*
Implementation: *10/1/22; 7/1/2019; 3/1/18; 1/1/1*