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Drug Class Update with new Drug Evaluation: Other Dyslipidemia Drugs

Date of Review: August 2026

Date of Last Review: Bempedoic Acid Dec 2023
PCSK9 Modulators Aug 2022
Dates of Literature Search: 08/01/2022 - 07/31/2026
Brand Name (Manufacturer): Lerochol (LIB Therapeutics)
Lipfendra (Merck)

Generic Name: lerodalcibep-liga
enlicitide

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

Plain Language Summary:

- High cholesterol can increase the risk of heart attack and stroke. Low density lipoprotein, or LDL, is often called “bad” cholesterol because high LDL can cause cholesterol to build up in the blood vessels.
- Many people with high cholesterol take a statin. Some people may need another medicine if their LDL is still too high or if they cannot take a statin.
- Medicines such as ezetimibe and PCSK9 inhibitors can lower LDL and reduce the risk of heart attack and stroke. People with higher LDL levels may get more benefit from these medicines.
- Alirocumab and evolocumab are PCSK9 inhibitors. Both medicines lower the risk of heart problems. There is not enough information to know if one works better or is safer than the other.
- Lerodalcibep is a new PCSK9 inhibitor that is given by an injection into the skin once a month. It lowers LDL as well as other PCSK9 inhibitors. We do not yet know if it lowers the risk of heart attack or stroke. Lerodalcibep can also be stored at room temperature for longer than some other PCSK9 inhibitors.
- Enlicitide is a new PCSK9 inhibitor that is taken by mouth. It lowers LDL as well as other PCSK9 inhibitors. We do not yet know if it lowers the risk of heart attack or stroke.
- New cholesterol guidelines give LDL goals for people at high risk for heart disease. Some people should have an LDL below 70 mg/dL. People at very high risk should have an LDL below 55 mg/dL. More people may need two or more medicines to reach these LDL goals.
- The Drug Use Research and Management group recommends that enlicitide and lerodalcibep be nonpreferred medicines on the Preferred Drug List. Patients would need prior authorization for these medicines because we do not yet know if they lower the risk of heart attack or stroke.

Purpose for Class Update:

- Evaluate new comparative evidence for the effectiveness and safety of non-statin medications for the prevention of cardiovascular (CV) mortality and CV events in patients with established atherosclerotic cardiovascular disease (ASCVD) and high-risk CV patients.

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- Analyze the data supporting the efficacy and safety of lerodalcibep and enlicitide, 2 new non-statin therapies, and determine their appropriate place in therapy.

Research Questions:

1. Is there any new comparative evidence for non-statin lipid lowering agents 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 non-statin lipid-lowering agents in patients being treated for the primary or secondary prevention of CV disease?
3. What are the comparative benefits and harms of lerodalcibep and enlicitide in patients with familial hypercholesterolemia, ASCVD or high-risk CV patients who cannot achieve adequate low-density lipoprotein cholesterol (LDL-C) reduction with their current lipid-lowering regimen?

Conclusions:

- There is low-quality evidence of no significant differences between alirocumab and evolocumab for myocardial infarction, stroke, coronary revascularization, hospitalization for heart failure, cardiovascular death, or all-cause mortality. [1]
- There is moderate-quality evidence that non-statin lipid-lowering therapies, including ezetimibe and PCSK9 inhibitors, reduce major adverse cardiovascular events (MACE), with greater absolute cardiovascular benefit observed among patients with higher baseline low density lipoprotein cholesterol (LDL-C) levels. [2]
- There is moderate-quality evidence that evolocumab, a PCSK9 inhibitor, reduces MACE in adults without a history of myocardial infarction (MI) or stroke who are at high risk for a first cardiovascular event (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.65 to 0.86). [3]
- There is moderate-quality evidence that lerodalcibep, a monthly subcutaneous PCSK9 inhibitor, produces clinically meaningful reductions in LDL-C compared with placebo in patients with heterozygous familial hypercholesterolemia (HeFH) and in patients with established ASCVD or high cardiovascular risk receiving background lipid-lowering therapy. [4], [5] The magnitude of LDL-C reduction is generally consistent with that observed with other monoclonal antibody PCSK9 inhibitors. A cardiovascular outcomes trial is ongoing, and there is currently insufficient evidence to determine whether lerodalcibep reduces ASCVD events. Lerodalcibep is self-administered and has greater room-temperature stability than alirocumab and evolocumab, which may provide an advantage for patients with medication storage or refrigeration limitations.
- There is moderate-quality evidence that enlicitide, an oral PCSK9 inhibitor, produces clinically meaningful reductions in LDL-C compared with placebo in patients with established ASCVD or high cardiovascular risk and in patients with HeFH receiving background lipid-lowering therapy. [6,7] The magnitude of LDL-C reduction is generally consistent with that observed with other PCSK9 inhibitors. A cardiovascular outcomes trial is ongoing, and there is currently insufficient evidence to determine whether enlicitide reduces ASCVD events.
- The 2026 ACC/AHA dyslipidemia guideline reintroduces specific LDL-C treatment targets, including <70 mg/dL for patients at high primary prevention risk and <55 mg/dL for those with ASCVD at very high risk. [8] The guideline also expands the role of non-statin therapies, including ezetimibe, bempedoic acid, and PCSK9-targeting therapies, when LDL-C goals are not achieved with maximally tolerated statin therapy. These recommendations are likely to increase the use of combination lipid-lowering therapy and the need for individualized selection of non-statin agents based on cardiovascular risk, magnitude of LDL-C reduction needed, clinical evidence, administration, tolerability, and cost

Recommendations:

- Make enlicitide and lerodalcibep nonpreferred on the Preferred Drug List (PDL) in the non-statin dyslipidemia drug class due to a lack of CV outcome data and include these 2 new agents in the *Non-Statin Medications for Dyslipidemia* prior authorization (PA) criteria (Appendix 7).
- Update PA criteria for non-statin medications based on new FDA approved indications, expanded labels, and updated guideline recommended LDL-C goals (Appendix 7).
- Replace Bempedoic Acid, and PCSK9 inhibitor PA criteria with the Non-Statin Medications for Dyslipidemia PA criteria and remove icosapent ethyl from the Omega-3 Fatty Acids PA criteria.
- After review of costs at executive session, colesevelam, icosapent ethyl, and gemfibrozil tablets were made preferred.

Summary of Prior Reviews and Current Policy:

- Current PA polices for PCKS9 inhibitors, bempedoic acid and omega-3 fatty acids are included in **Appendix 4.**
- There is moderate quality evidence that ezetimibe combined with a statin result in a modest (2%) improvement in CV outcomes with a long duration of follow-up (approximately 7 years).[9]
- Moderate quality evidence comparing statin monotherapy to a statin in combination with niacin, fibrates, or omega 3 fatty acids show no significant effect on reducing all-cause mortality, death from coronary heart disease (CHD) and inconsistent effects on other CV outcomes.
- There is low-quality evidence that high dose icosapent ethyl (2 gm twice daily) may prevent a CV event (17.2% vs. 22.2%; HR 0.75; 95% CI 0.68 to 0.83; absolute risk reduction (ARR) 4.8%; number needed to treat [NNT] 21 over 4.9 years) in patients with hypertriglyceridemia and CV disease or with diabetes plus other CV risks on statin therapy.[10]
- 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%.[11] 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 based on one study that shows evinacumab significantly reduces LDL-C compared to placebo at 24 weeks (-47% vs. 2%, respectively; difference -49%; 95% CI -65% to -33.1%) in adults with homozygous familial hypercholesterolemia (HoFH) on maximally tolerated lipid lowering therapy.[12] However, there is no data evaluating evinacumab on clinical outcomes, including CV events, CV mortality and all-cause mortality
- There is moderate-quality evidence that bempedoic acid lowers risk of a composite of death from CV causes, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization compared to placebo [11.7% versus 13.3%; absolute risk reduction (ARR) 1.6% / number needed to treat (NNT) 63; p = 0.004] in patients with a history of CV event or at high-risk for a CV event who cannot tolerate more than a low dose of a statin.[13]

Background:

The association between hypercholesteremia, and particularly elevated LDL cholesterol, 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 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 with a focus on medications that have proven to reduce CV risk when added on to statin therapy. The 2026 dyslipidemia guideline reintroduces explicit LDL-C and non-HDL-C targets, with goals of < 55mg/ml in the highest risk individuals with ASCVD.[8] 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. Evidence suggests improved outcomes with lower LDL-C targets in ASCVD and no difference in harms.[14] A recent meta-analysis found that in primary prevention trials, each 1 mmol/L reduction in LDL-C was associated with a 30% relative risk reduction in MACE.[15]

Currently, ezetimibe, icosapent ethyl, the PCSK9 inhibitors, and bempedoic acid have shown a modest benefit on clinical outcomes of interest when added to statin therapy and in statin intolerant individuals (**Tables 1 and 2**). Ezetimibe, an inhibitor of intestinal cholesterol absorption, is indicated as an adjunct to reduce elevated cholesterol and LDL-C.[16] 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.[9] 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. The manufacturer of ezetimibe applied for an additional indication for the expanded use of ezetimibe in combination with statin therapy for reduction of CV events in patients with coronary heart disease, but an FDA advisory committee voted against the expanded indication as they felt the ezetimibe/simvastatin combination provides a weak and not particularly robust effect on CV outcomes.[16] Additionally, a moderate-intensity statin was used as the study comparator, which is not consistent with current practice recommendations.[9]

Evolocumab (Repatha®) and alirocumab (Praluent®) are subcutaneously injected human monoclonal antibodies that reduce LDL-C by inhibiting PCSK9.[17,18] 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).**[17,19 20] Inclisiran is a double-stranded small interfering RNA (siRNA) that inhibits hepatic production of PCSK9, resulting in decreased LDL-C levels. Inclisiran is given as a subcutaneous (SC) injection on day 1, day 90 and every 6 months after that. The phase 3 trial evaluating CV outcomes with inclisiran is still ongoing.

There are two newly approved PCSK9 inhibitors, lerodalcibep and enlicitide. Lerodalcibep is a slightly smaller molecule allowing for a smaller volume given less frequently (monthly) and offers extended room-temperature stability for up to 3 months.[21] It is administered subcutaneously monthly and is FDA approved to reduce LDL-C in adults with hypercholesterolemia, including heterozygous familial hypercholesterolemia (HeFH).[21] Enlicitide is the first oral PCSK9 inhibitor indicated to reduce LDL-C in adults with hypercholesterolemia, including HeFH.[22]

Icosapent ethyl is an ethyl ester of EPA (eicosapentaenoic acid) without any DHA (docosahexaenoic acid). The REDUCE-IT trial suggests it may prevent a CV event in high-risk CV patients (NNT 21) over 5 years in patients with elevated triglycerides despite statin therapy.[10] Icosapent ethyl gained FDA approval as an add-on therapy to reduce CV events for adults with elevated triglycerides [3] (150 mg/dl) in December 2019. This is conflicting with data with lower doses or other omega-3 fatty acids. Furthermore, icosapent ethyl can cause atrial fibrillation (number needed to harm [NNH] 71) and may increase the risk of bleeding. [10]

Currently there is no evidence on CV outcomes and a limited place in therapy for other LDL-C lowering agents (fibrates, bile acid sequestrants, omega-3 fatty acids). Fibric acid derivatives should be reserved for patients with severe hypertriglyceridemia (triglycerides ≥ 500 to 1000 mg/dl). The long-term follow up of the

ACCORD trial showed no benefit in fatal or non-fatal CV events with fenofibrate plus simvastatin versus simvastatin alone in patients with diabetes mellitus.[23] Gemfibrozil should not be used in combination with statin therapy due to an increased risk of muscle symptoms and rhabdomyolysis. Omega-3 fatty acids (i.e., Lovaza®) other than icosapent ethyl have not shown a consistent benefit in the primary or secondary prevention of CV outcomes.[24]

Table 1: Characteristics of Cardiovascular Outcome trials for Non-statins

	FOURIER	ODYSSEY	IMPROVE-IT	REDUCE-IT	CLEAR-OUTCOMES
Non-Statin Study Drug	Evolocumab	Alirocumab	Ezetimibe	Icosapent ethyl 2 gm BID	Bempedoic acid
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	CVD or high CV risk with statin intolerance
Median LDL-C	92 mg/dl	92 mg/dl	95 mg/dl	75 mg/dl (median TG 216 mg/dl)	139 mg/dl
% on High Intensity Statin	69%	89%	6%	30%	0% (23% on low intensity)
% on Ezetimibe	5%	3%	100%	6.5%	17%
Study Duration	26 months	34 months	6 years	5 years	24 months

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

Outcome	Evolocumab ARR/NNT	Alirocumab ARR/NNT	Ezetimibe ARR/NNT	Icosapent ARR/NNT	Bempedoic Acid ARR/NNT
CV Composite Outcome	1.5% / 67	1.6% / 63	2% / 50	4.8% / 21	1.6%/63
CV Death	NS	NS	NS	0.9% / 112	NS
Death from any cause	NS	0.6% / 167	NS	NS	NS
Myocardial infarction	1.2% /84	1% / 100	1.7% / 59	2.3% / 44	1.1%/91
Stroke	0.4% / 250	0.4% / 250	NS	0.8% / 125	NA

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

Evinacumab is a fully human monoclonal antibody approved for homozygous familial hypercholesteremia (HoFH). HoFH is a rare genetic condition affecting an estimated 200-300 patients in the United States.[25] The genetic mutation causes changes in LDL-C processing and ineffective plasma clearance of LDL-C, resulting in persistent, severe hyperlipidemia (> 400 mg/dl) beginning in childhood and premature CV disease and death. The most common mutations (90%) involve both alleles of the LDL receptor. Current treatment consists of standard LDL-C lowering therapy with statins, PCSK9 inhibitors and ezetimibe. Apheresis is reserved for individuals who do not respond to first-line treatments. Evinacumab was granted Breakthrough Therapy designation for the treatment of HoFH based on preliminary evidence from a phase 2 trial.[26] It is the first treatment to reduce LDL-C independent of the LDL receptor. This is theoretically advantageous in HoFH since many patients do not have functional LDL receptors and are more difficult to treat with conventional therapies.

Apolipoprotein CIII (APOC3) inhibitors are the newest class of medications that reduce the APOC3 protein through mRNA interference, leading to increased clearance of plasma triglycerides (TGs).[27] There are currently two FDA approved agents, olezarsen and plozasiran, approved for TG lowering in patients with familial chylomicronemia syndrome (FCS). More recently, olezarsen was FDA approved for severe hypertriglyceridemia (TG ≥ 500 mg/dl) based on two phase 3 trials demonstrating a significantly great reduction in TG level at 6 months and in the incidence of acute pancreatitis compared to placebo.[28]

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, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) 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.

New Systematic Reviews:
After review, 13 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria)[29-32], wrong study design of included trials[33,34] (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[35-43]

There were no systematic reviews identified from high-quality sources, including 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, the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA). There were also no systematic reviews from Cochrane Collaboration since our last review of this class.

The following systematic reviews were included for review:

1. A systematic review included RCTs) evaluating alirocumab or evolocumab compared with placebo or standard therapy in patients with high cardiovascular risk or hypercholesterolemia.[1] Risk of bias (RoB) was assessed using the Cochrane RoB 2 tool, and relative risks were pooled using meta-analysis. Six RCTs including 62,119 patients were included; all were considered to have a low risk of bias. Alirocumab significantly reduced myocardial infarction (RR 0.85; 95% CI 0.77 to 0.93), stroke (RR 0.75; 95% CI 0.60 to 0.94), and hospitalization for unstable angina (RR 0.58; 95% CI 0.39 to 0.86), while evolocumab significantly reduced myocardial infarction (RR 0.75; 95% CI 0.68 to 0.83) and coronary revascularization (RR 0.81; 95% CI 0.75 to 0.88).[1] There were no significant differences between alirocumab and evolocumab for myocardial infarction, stroke, coronary revascularization, hospitalization for heart failure, cardiovascular death, or all-cause mortality. Alirocumab was associated with a significantly greater reduction in hospitalization for unstable angina compared with evolocumab (RR 0.58 vs. 0.98; P=0.02).[1] Overall, both PCSK9 inhibitors reduced CV events, with limited evidence of differences between the agents.

2. A systematic review and meta-analysis evaluated RCTs of oral eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementation compared with placebo, usual care, or no supplementation in patients with established cardiovascular disease, including secondary prevention and perioperative populations.[44] The authors searched Embase, PubMed/MEDLINE, Scopus, and Web of Science and identified 25 RCTs including 25,578 patients. Risk of bias was assessed using the Cochrane RoB 2 tool, and random-effects meta-analysis was used to pool outcomes. Overall, moderate-dose combined EPA and DHA supplementation did not significantly reduce MACE (odds ratio [OR] 1.04; 95% CI 0.95 to 1.15; P=0.40) or atrial fibrillation, including postoperative atrial fibrillation (AF) (OR 0.82; 95% CI 0.61 to 1.10; P=0.19). [44] Subgroup analyses by cardiovascular disease population and duration of therapy also found no significant benefit for MACE or AF. The authors concluded that combined EPA+DHA supplementation does not provide a broad cardiovascular or AF-prevention benefit in patients with established CVD receiving standard medical therapy.

3. A systematic review and meta-analysis evaluated randomized controlled trials of statins, ezetimibe, and PCSK9 inhibitors to assess cardiovascular benefits and adverse effects according to baseline LDL-C.[2] PubMed, EMBASE, Cochrane, and Web of Science were searched through August 2023. Baseline LDL-C was categorized as <100, 100–129, 130–159, and ≥160 mg/dL, and relative risks and numbers needed to treat were calculated. A total of 46 RCTs including 237,870 participants were included. Meta-regression analysis demonstrated a greater absolute reduction in MACE with lipid-lowering therapy as baseline LDL-C increased. Statins significantly reduced MACE overall (NNT to benefit [NNTB] 31; 95% CI 25–37), although a significant benefit was observed only among patients with baseline LDL-C ≥100 mg/dL. [2] Ezetimibe and PCSK9 inhibitors also significantly reduced MACE, with NNTBs of 18 (95% CI 11–41) and 18 (95% CI 16–24), respectively. Statins and ezetimibe were not associated with a statistically significant increase in adverse outcomes, while PCSK9 inhibitors were associated with injection-site reactions (NNTH 41; 95% CI 26–80).[1] Overall, the findings suggest that the absolute cardiovascular benefit of lipid-lowering therapy increases as baseline LDL-C increases.

4. A systematic review and meta-analysis evaluated randomized controlled trials comparing bempedoic acid with placebo or other lipid-lowering therapy in adults with hypercholesterolemia or cardiovascular disease. [45] A literature search identified 12 RCTs including 18,439 patients. Bempedoic acid significantly reduced LDL-C compared with control (mean difference -20.69%; 95% CI -23.20% to -18.19%). Bempedoic acid was also associated with a significant reduction in major adverse cardiovascular events (MACE; RR 0.86; 95% CI 0.80 to 0.94). Overall, there was no significant difference in the incidence of adverse events between bempedoic acid and control. The findings support bempedoic acid as an effective LDL-C-lowering therapy and suggest a reduction in cardiovascular events, particularly among patients who are unable to tolerate or achieve adequate LDL-C reduction with statin therapy

New Guidelines:

High-Quality Guidelines:

1. The 2026 ACC/AHA Guideline on the Management of Dyslipidemia were published in 2026 and address the evaluation, management, and monitoring of patients with dyslipidemias, including high blood cholesterol, hypertriglyceridemia, and elevated Lp(a) through an extensive literature search and grading of the evidence and strength of recommendations (**Table 3**).[8] Patient groups included in the guidelines include: 1) primary prevention, 2) severe hypercholesterolemia, 3) diabetes, 4) clinical ASCVD, 5) subclinical atherosclerosis, and 6) hypertriglyceridemia.

Table 3: ACC/AHA Strength of Recommendation and Quality of Evidence

Class (Strength) of Recommendation	Level (Quality of Evidence)
Class 1 (Strong)	Level A

Benefit >>> Risk	• High-quality evidence from more than 1 RCT • Meta-analysis of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
Class 2a (Moderate) Benefit >> Risk	Level B-R (Randomized) • Moderate quality evidence from 1 or more RCTs • Meta-analysis of moderate quality RCTs
Class 2b (Weak) Benefit ≥ Risk	Level B-NR (Nonrandomized) • Moderate quality evidence from 1 or more well designed nonrandomized, observational, or registry studies • Meta-analysis of such studies
Class 3: No Benefit (Moderate) Benefit = Risk	Level C-LD (Limited Data) • Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analysis of such studies • Physiological or mechanistic studies in human subjects
Class 3: Harm (Strong) Risk > Benefit	Level C-EO (Expert Opinion) • Consensus of expert opinion based on clinical experience

The updated guidelines return to specific LDL-C and non-HDL goals based on overall CV risk with an LDL-C goal of < 55 mg/ml for the highest risk population (**Table 4**). The guidelines recommend using the PREVENT-ASCVD equation to estimate 10-year ASCVD risk (Class of Recommendation [COR] 1; Level of Evidence [LOE] B-NR) which replaces the pooled cohort equation. This categorizes individuals into low (< 3%), borderline (3% to <5%), intermediate (5% to < 10%), or high (≥ 10%) ASCVD risk.

Table 4: Lipoprotein Goals for ASCVD Risk reduction[8]

Patient population	**LDL-C < 100 mg/dl** **Non-HDL C < 130 mg/dl**	**LDL-C < 70 mg/dl** **Non-HDL C < 100 mg/dl**	**LDL-C < 55 mg/dl** **Non-HDl C < 85 mg/dl**
Primary prevention	Prevent-ASCVD < 10%	PREVENT-ASCVD ≥ 10%	n/a
Severe hypercholesterolemia (LDL-C ≥ 190 mg/dl)	Without FH, ASCVD risk factors, and subclinical atherosclerosis	With FH, ASCVD risk factors, or subclinical atherosclerosis	With chronic ASCVD
Diabetes	Without ASCVD risk factors or diabetes specific risk modifies	With ASCVD risk factors for diabetes-specific risk factors	n/a
Subclinical atherosclerosis	CAC = 1-99 AU and < 75 percentile for age, sex, and race	CAC ≥ 100 to 299 AU or ≥ 75 percentile for age, sex, race	CAD ≥ 1000 AU
Hypertriglyceridemia	≤ 50 yr old with no additional risk enhancers	With clinical ASCVD not at very high risk	With clinical ASCVD
Clinical ASCVD	N/A	Not at very high risk	At very high risk or with CKD

Recommendations related to drug therapy include the following[8]:

Primary Prevention in Adults 30 to 70 years of age with LDL-C 70 to 189 mg/dl: [8]

- In adults at low (< 3%) ASCVD 10-yr risk, a moderate intensity statin is reasonable to reduce cumulative exposure to atherogenic lipoproteins (COR 2a; LOE C-LD)
- In adults at borderline (3% to < 5%) 10-year ASCVD risk, a moderate intensity statin is reasonable (COR 2a; LOE A)
- In adults at intermediate (5% to < 10%) 10-year ASCVD risk, at least a moderate-intensity statin is recommended; for those in the higher end of risk range, a high-intensity statin is beneficial to further reduce LDL-C and reduce ASCVD risk
- In adults at high (> 10%) ASCVD risk, high intensity statin is recommended to achieve an LDL-C reduction of ≥ 50% to reduce the risk of ASCVD
- In adults at high ASCVD risk on maximally tolerated statin, it is reasonable to add ezetimibe if a goal of LDL < 70 mg/dl and non-HDL < 100 mg/dl is not achieved (COR 2a; LOE B-R)
- In adults at high ASCVD risk on maximally tolerated statin with or without ezetimibe, it may be reasonable to add a PCSK9 inhibitor or bempedoic acid if LDL-C and non-HDL goals are not met (COR 2b; LOE B-NR)

Severe Hypercholesterolemia:

- In adults with severe hypercholesteremia, treatment with maximally tolerated statin therapy is recommended (COR 1; LOE B-R)
- The addition of ezetimibe, a PCSK9 inhibitor, and/or bempedoic acid is recommended to achieve a LDL-C and non-HDL goals based on risk factors and presence of ASCVD (Table 4)

Diabetes without established ASCVD:

- Moderate-intensity statin is indicated to achieve LDL-C and non- DL goals (COR 1; LOE A)
- In adults with diabetes who have statin-attributed side effects, initiation of ezetimibe and/or bempedoic acid or a PCSK9 inhibitor is recommended (COR 1; LOE B-R)
- If there are multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy (COR 2A; lOE-BR)
- With elevated fasting TG (150-499 mg/dl), additional ASCVD risk factors, and diabetes on a statin, the addition of icosapent ethyl may be considered (LOE 2b; LOE B-R)
- It may be reasonable to add ezetimibe or a PCSK9 inhibitor to achieve LDL-C and non-HDL goals (COR 2b; LOE C-LD)

Secondary ASCVD Prevention:

Not at very high risk

- High intensity statin should be initiated (COR 1; LOE A)
- It is reasonable to add ezetimibe, a PCSK9 inhibitor, or bempedoic acid to achieve LDL-C and non-HDL goals (COR 2a; LOE B-R)

At very high risk (≥ 2 major ASCVD events or 1 major ASCVD event and ≥ 2 high-risk conditions)

- High intensity statin should be initiated
- Ezetimibe and/or a PCSK9 inhibitor should be added to achieve LDL-C < 55 mg/dl and non-HDL-C of < 85 mg/dl (COR 1; LOE A)
- Bempedoic acid may be added to achieve LDL-C and non-HDL goals (COR 2a; LOE B-R)

Additional Populations:

- In people living with HIV, statin therapy is recommended to reduce the risk of a first ASCVD event (COR 1; LOE B-R)
- In adults with CKD stage 3 or higher, moderate-intensity statin or a moderate-intensity statin combined with ezetimibe is recommended to reduce ASCVD risk (COR 1; LOE B-R)
- In adults with CKD and clinical ASCVD, a high intensity statin, with or without ezetimibe and/or a PCSK9 inhibitor is recommended to achieve a goal of LDL-C of < 55 mg/dl and non-HDL < 85 mg/dl to reduce ASCVD risk (COR 1; LOE B-R)

2. The Department of Veterans Affairs (VA) and the Department of Defense (DOD) clinical practice guideline on lipid management for cardiovascular disease risk reduction was published in 2025.[46] It was based on a systematic review of clinical and epidemiological evidence and developed by a panel of multidisciplinary experts. The GRADE approach was used to determine the strength of recommendation and quality of evidence.

   Recommendations related to drug therapy include the following:

<u>Primary Prevention in Adults 30 to 70 years of age with LDL-C 70 to 189 mg/dl:</u>

- For primary prevention among patients who have diabetes or 10-year cardiovascular risk ≥10% or low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dL, we recommend using at least a moderate-intensity statin (Strong Recommendation).
- For primary prevention among patients without diabetes who have low-density lipoprotein cholesterol (LDL-C) <190 mg/dL and a 10-year cardiovascular risk between approximately 5% to less than 10%, we suggest using a moderate-intensity statin (Weak Recommendation).
- For primary prevention in patients with human immunodeficiency virus (HIV), we suggest a moderate intensity statin that has a low risk of interactions with antiretroviral therapy, even when 10-year risk estimates are low (i.e., <5%) (Weak Recommendation).

<u>Secondary Prevention</u>

- For secondary prevention, we suggest treating with one of the following (Weak Recommendation):
  - High intensity statin
  - Moderate intensity statin with ezetimibe
  - Moderate intensity statin with PCSK9 inhibitor
- For secondary prevention in very high-risk patients, we suggest a combination therapy of one of the following (Weak Recommendation):
  - High-intensity or maximally tolerated statin with ezetimibe
  - High-intensity or maximally tolerated statin with PCSK9 inhibitor
  - High intensity of maximally tolerated statin with ezetimibe and PCSK9 inhibitor
- For secondary prevention, we suggest icosapent ethyl in patients on statin therapy with persistently elevated fasting triglycerides ≥ 150 mg/dl (Weak Recommendation)
- For secondary prevention, there is insufficient evidence to recommend a treat-to-target strategy over a fixed dose high intensity statin strategy

<u>Statin Intolerance:</u>

- For primary and secondary prevention in patients unable to take a statin, we suggest one of the following nonstatins: bempedoic acid, ezetimibe, fibrates, or PCSK9 inhibitors (Weak Recommendation).

New Formulations or Indications:

- In July 2025, the FDA removed the requirement to be on maximally tolerated statin therapy for inclisiran use. The updated indication for inclisiran is as adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia, including HeFH.[47] This broader indication no longer requires HeFH or clinical ASCVD. This was not based on new published data.

- In February 2026, the label of inclisiran was expanded to include pediatric patients aged 12 years and older with HeFH and HoFH.[47] This was based on the ORION-16 trial, a two-part (1-year double-blind, 1-year open-label) randomized, phase 3 trial in adolescents (ages 12 to 18 years) with HeFH and elevated LDL-C on maximally tolerated statin treatment.[48] Patients were randomly assigned to inclisiran (n=141) or placebo (n-93). Overall, in the double-blind period, inclisiran statistically significantly reduced LDL-C compared with placebo (-27.1% vs. 1.4%; difference of -28.5%; 95% CI -36.9 to -21.3). [48] These reductions were maintained in the open-label extension period. Rates of serious adverse events and discontinuations due to adverse events were low and similar between the two groups.

- In March 2024, the FDA approved labels for bempedoic acid and bempedoic acid/ezetimibe were updated to remove previous statin-use restrictions. They are now FDA approved for primary or secondary prevention in patients at increased risk for CV events as an adjunct to statin therapy or in patients who cannot take statin therapy.[49] This was based on the CLEAR-Outcomes trial, which was reviewed in a previous update.

- The FDA labeled indications for the monoclonal PCSK9 inhibitors, alirocumab and evolocumab, were updated to include a broader population and removing language requiring adjunct to statin therapy. The FDA labeled indications are as follows:
  - Alirocumab:
    - To reduce the risk of major adverse CV events in adults at increased risk for these events
    - As adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia, adults and pediatric patients aged 8 years and older with HeFH, and adults with HoFH.
  - Evolocumab:
    - To reduce the risk of major adverse CV events in adults at increased risk for these events
    - As adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia, adults and pediatric patients aged 10 years and older with HeFH, and adults and pediatric patients aged 10 years and older with HoFH.

- Expanded approval of alirocumab in pediatric patients with HeFH was based on a phase 3, RCT evaluating the efficacy of alirocumab in pediatric patients aged 8 to 17 years with HeFH, LDL-C of 130 mg/dl or greater, on background statin therapy with or without other lipid lowering medications (n=153). Alirocumab resulted in a statistically significant reduction in LDL-C compared to placebo at week 24 with dosing every 2 weeks and dosing every 4 weeks (-43.3%; 95% CI -56 to -30 and -33.8%; 95% CI -46.4% to -21.2%).[50]

Randomized Controlled Trials:
A total of 10 citations were manually reviewed from the initial literature search. After further review, 5 citations were excluded because of wrong study design[51,52] (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[3,53-55].

The other clinical trials identified supported FDA approval of newer therapies, including olezarsen, plozasiran, enlicitide, and lerodalcibep are included in the appropriate new drug evaluation summaries.

The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
VESALIUS-CV[3] Phase 3, RCT	Evolocumab 140 mg SC every 2 weeks vs. placebo (n=12,257)	Adults with LDL-C ≥ 90 mg/dl on stable LLT without a history of MI or stroke but with at least one of the following: CAD, atherosclerotic cerebrovascular disease, PAD, or high-risk diabetes and 1 additional CV risk factor	Composite of CV death, MI, or ischemic stroke (3-point MACE) Composite of CV death, MI, ischemic stroke, or revascularization (4-point MACE)	3-point MACE: Evolocumab: 336 (6.2%) Placebo: 443 (8%) HR 0.75; 95% CI 0.65 to 0.86 4-point MACE: Evolocumab: 747 (13.4%) Placebo: 901 (16.2%) HR 0.81; 95% CI 0.73 to 0.89	Although this is primary prevention, it is still a population at very high risk for a first event. Results cannot be generalized to lower risk primary prevention cohorts.

Abbreviations: CAD = coronary artery disease; CV = cardiovascular; HR =. Hazard ratio; LDL-C = low density lipoprotein cholesterol; LLT = lipid lowering therapy; MI = myocardial infarction; PAD = peripheral artery disease; RCT = randomized clinical trial; etc.

NEW DRUG EVALUATION: Lerodalcibep (Lerochol)

See **Appendix 5** 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. Pharmacology and pharmacokinetic properties are listed in **Appendix 6**.

Clinical Efficacy:
Lerodalcibep-liga is a PCSK9 inhibitor indicated as an adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia, including HeFH.[21] It was FDA approved based on three phase 3, double blind, placebo controlled RCTs in adults with hypercholesterolemia, including HeFH. Two of these studies have

been published and are included in the table below. Lerodalcibep is a once monthly self-injectable PCSK9 inhibitor that can be stored at room temperature for up to 3 months.

In one double-blind, multicenter, RCT with unclear risk of bias, lerodalcibep 300 mg SC monthly (n=615) was compared to placebo (n=307) in patients with CVD or at high to very high CV risk on maximally tolerated statin therapy with or without additional lipid lowering therapy.[4] Overall, 48% had CVD, 43.2% had diabetes, 9.6% had familial hypercholesterolemia, 92% were taking a lipid lowering agent, 83% were taking a statin, and 16.6% were taking ezetimibe.[4] More participants in the placebo group were taking it for secondary prevention compared to the treatment group. In patients with CVD or high-risk CVD, there was a significantly greater reduction in LDL-C at week 52 compared to placebo (-56% vs. -0.1%; least square (LS) mean difference -56.2%; 95% CI -60.5% to -51.9%).[4] There were also significantly greater reductions in non-HDL, apolipoprotein B, and LP(a) compared to placebo.[4] More participants on lerodalcibep achieved a 50% reduction in LDL-C compared to placebo (94% vs. 19%; OR 76.7; 95% CI 48.2 to 121) and achieved target LDL-C goals of less than 55 mg/dl and less than 70 mg/dl.[4]

In one randomized, double-blind, multicenter, placebo-controlled phase 3 trial, lerodalcibep 300 mg SC every 4 weeks (n=319) was compared with placebo (n=159) for 24 weeks in adults with heterozygous familial hypercholesterolemia (HeFH) receiving stable, maximally tolerated oral lipid-lowering therapy who required additional LDL-C reduction.[5] The mean baseline LDL-C was approximately 150 mg/dL, and approximately half of participants were female. The co-primary endpoints were percent change from baseline in LDL-C at week 24 and the mean LDL-C at weeks 22 and 24. At week 24, lerodalcibep produced a significantly greater reduction in LDL-C compared with placebo (-58.6%; LS mean difference -58.6%; 95% CI -65.0% to -52.2%; P<0.0001). [5] Lerodalcibep also significantly reduced apolipoprotein B by approximately 46% and lipoprotein(a) by approximately 24%. Approximately 68% of patients receiving lerodalcibep achieved both a ≥50% reduction in LDL-C and the recommended LDL-C target compared with a substantially smaller proportion receiving placebo.

In another randomized, double-blind, multicenter, placebo-controlled phase 3 trial, lerodalcibep 300 mg SC every 4 weeks (n=614) was compared with placebo (n=308) for 52 weeks in patients with established CVD or at very high cardiovascular risk who required additional LDL-C lowering despite maximally tolerated statin and other oral lipid-lowering therapy.[56] The mean baseline LDL-C was approximately 102 mg/dL, with approximately 85% of patients receiving a statin and 15% receiving ezetimibe. The co-primary endpoints were percent change from baseline in LDL-C at week 52 and the mean LDL-C at weeks 50 and 52. At week 52, lerodalcibep produced a significantly greater placebo-adjusted reduction in LDL-C compared with placebo (-62.0%; P<0.0001). Lerodalcibep also significantly reduced other atherogenic lipid parameters, including apolipoprotein B by approximately 45% and lipoprotein(a) by approximately 33%. More than 90% of patients receiving lerodalcibep achieved both a ≥50% reduction in LDL-C and an LDL-C target of <55 mg/dL.[56] This trial remains unpublished and cannot be assessed for quality.

There is a lack of data demonstrating a reduction in CV events with lerodalcibep and no comparative evidence evaluating it to other PCSK9 inhibitors or statin add on LDL-lowering agents. It results in similar LDL-lowering as other FDA approved PCSK9 inhibitors and may offer an option for those patients who have drug storage limitations.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Major adverse cardiovascular events
2) Cardiovascular deaths

Primary Study Endpoint:
1) Percent change from baseline in LDL-C at week 52

3) All-cause mortality
4) Serious adverse events
5) Study withdrawal due to an adverse event

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. Klug et al.[4] Phase 3, DB, RCT	1. Lerodalcibep 300 mg SC Q4W (LIB300) (n=615) 2. Placebo (n=307) 52 weeks	Demographics: Mean age 64.5 45% female 78% white 48% with CVD Mean LDL 116.2 mg/dl Key Inclusion Criteria: • Adults with CVD or high CV risk • on maximally tolerated statins +/- other LLT • LDL-C ≥ 70 mg/dl or ≥ 100 mg/dl if at high CV risk • TG ≤ 400 mg/dl Key Exclusion Criteria: • PCSK9i use • NYHA Class III-IV • Uncontrolled HTN • eGFR < 30 ml/min • Active liver disease • HgA1c ≥ 9%	mITT: 546 (88.8%) 274 (89.3%) PP: 433 (70.4%) 228 (74.3%) Attrition: 74 (12%) 37 (12%)	Primary Endpoint: Change from baseline in LDL-C LIB300: -56% Placebo: -0.14% LS mean difference -56.2%; 95% CI -60.5 to -51.9 P< 0.001 Secondary Endpoints: Reduction in LDL-C of ≥50% LIB300: 580 (94%) Placebo: 59 (19.2%) OR 76.7; 95% CI 48.2 to 121.9 p<0.0001	NA ARR 74%/ NNT 2	Discontinuations due to adverse events: LIB300: 26 (4.2%) Placebo: 12 (3.9%) Serious AE LIB300: 76 (12.4% Placebo: 14 (4.6%)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear; randomized but randomization details not provided, slight differences in baseline characteristics Performance Bias: low; double-blinded, double dummy design. Potential unblinding due to injection site reactions. Detection Bias: unclear; unclear if outcome assessors blinded. Attrition Bias: unclear; modified ITT excluded patients without an LDL-measurement at week 52; attrition low and equal between groups Reporting Bias: low; outcomes reported as prespecified. **Applicability**: Patient: Extensive exclusion criteria limits generalizability; no information on why participants did not meet screening criteria Intervention: dose selected base on phase 2 dose finding trial Comparator: placebo-controlled; lack of active comparator (other PCSK9 inhibitor or add-on LLT) Outcomes: LDL-C is a surrogate outcome. Study was not designed to evaluate clinically meaningful CV outcomes. Setting: 70 sites in US, Canada, Europe, South Africa, Asia, Australia, and Middle East

2. Raal et al.[5] Phase 3, PC, DB, RCT	1. Lerodalcibep 300 mg SC Q4W (LIB300) (n=319) 2. Placebo (n=159) 24 weeks	Demographics: Mean age 53 5.7% female 87% white 47.6% CVD 88.3% on statins Key Inclusion Criteria: • Adults with HeFH • on maximally tolerated statins +/- other LLT • LDL-C ≥ 70 mg/dl or ≥ 100 mg/dl if no CVD • TG ≤ 400 mg/dl Key Exclusion Criteria: • HoFH • PCSK9i use • NYHA Class III-IV • Uncontrolled HTN • eGFR < 30 ml/min • Active liver disease • HgA1c ≥ 9%	ITT: 319 159 PP: 306 159 Attrition: 13 (4%) 4 (2.5%)	Primary Endpoint: Percent change from baseline in LDL-C at week 24 1. -56.2% 2. 7.45% LS mean difference -63.6%; 95% CI -70% to -57% P<0.0001 Secondary Endpoints: Reduction in LDL-C of ≥50% LIB300: 86.2% Placebo: 3.8% OR 186* p<0.0001 *95% CI not provided		Discontinuations due to adverse events: LIB300: 5 (1.6%) Placebo: 3 (1.9%) Serious AE LIB300: 9 (2.8%) Placebo: 9 (5.7%)	 NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear; no randomization details provided. Performance Bias: low – double blinded and dummy design Detection Bias: low; outcome assessors blinded Attrition Bias: low; low overall attrition and similar between groups, ITT analysis done Reporting Bias: Other Bias: low; outcomes reported as prespecified. **Applicability**: Patient: Screening period, extensive exclusion criteria limits generalizability; short duration of 24 weeks and variable screening period dependent on whether they required a diet/lipid stabilization and/or washout Intervention: dose selected base on phase 2 dose finding trial Comparator: placebo-controlled; lack of active comparator (other PCSK9 inhibitor or add-on LLT) Outcomes: LDL-C is a surrogate outcome. Study was not designed to evaluate clinically meaningful CV outcomes Setting: 60 sites in the US, Canada, Central and South America, Europe, South Africa, Asia, Australia, and the Middle East

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesteremia; HoFH = homozygous familial hypercholesterolemia; ITT = intention to treat; LLT = lipid lowering therapy; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol

Clinical Safety:
In two pooled 52-week trials, adverse reactions that occurred in at least 2% of lerodalcibep treated participants and more frequently than placebo are included in **Table 7**. [21]

Across the three pivotal phase 3 trials, lerodalcibep was generally well tolerated, with a safety profile like placebo. The most common adverse reaction were injection-site reactions, which occurred more frequently with lerodalcibep than placebo (12% vs. 5% in the two pooled 52-week trials and 18% vs. 3% in the 24-week HeFH trial). [21] Injection-site reactions were generally mild to moderate and infrequently led to treatment discontinuation. Other adverse reactions occurring more frequently with lerodalcibep included nasopharyngitis (15% vs. 14%), peripheral edema (2% vs. <1%), diarrhea (3% vs. 1% in the HeFH trial), and nausea (2% vs. 0% in the HeFH trial). [21] Overall rates of serious adverse events, adverse events leading to discontinuation, and other clinically important adverse events were similar between lerodalcibep and placebo. No clinically meaningful differences in hepatic, muscle, or glucose-related adverse events were identified.

Table 7: Adverse events that occurred more frequently than placebo[21]

Adverse Reaction	Lerodalcibep (n=1,229)	Placebo (n
Nasopharyngitis	15%	14%
Injection site reactions	12%	5%
Peripheral edema	2%	< 1%

NEW DRUG EVALUATION: Enlicitide (Lipfendra)

See **Appendix 5** 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. Pharmacology and pharmacokinetic properties are listed in **Appendix 6**.

Clinical Efficacy:
Enlicitide 20 mg daily is an oral PCSK9 inhibitor FDA approved as an adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia, including HeFH. FDA approval was based on two phase 3 RCTs.[6,7] Both were randomized, double-blind, placebo-controlled phase 3 trials using enlicitide 20 mg orally once daily for 52 weeks, with the primary efficacy endpoint being LDL-C change at week 24. One trial was in patients with ASCVD or high risk for ASCVD and the second was in HeFH. Participants were advised to take enlicitide with small amounts of water first thing in the morning after an overnight fast and to withhold food and beverages for at least 30 minutes.

In one multinational, double-blind, randomized, placebo-controlled phase 3 trial, enlicitide 20 mg orally once daily (n=1,935) was compared with placebo (n=969) for 52 weeks in adults with established ASCVD requiring additional LDL-C lowering (LDL-C ≥55 mg/dL) or at high risk for a first ASCVD event (LDL-C ≥70 mg/dL).[7] Approximately 58% had a history of a major ASCVD event and 42% were at risk for a first event; mean age was 63 years, 39% were women, and mean baseline LDL-C was 96.1 mg/dL. At week 24, LDL-C decreased by 57.1% with enlicitide compared with a 3.0% increase with placebo, corresponding to an adjusted

between-group difference of -55.8 percentage points (95% CI -60.9 to -50.7; P<0.001). LDL-C reduction was sustained through week 52. Enlicitide also significantly reduced non-HDL-C, apolipoprotein B, and lipoprotein(a) compared with placebo. Adverse events occurred at similar frequencies between groups, and no major safety signal was identified during the 52-week treatment period. The trial was not designed or powered to evaluate cardiovascular outcomes.

In another double-blind, randomized, placebo-controlled phase 3 trial, enlicitide 20 mg orally once daily (n=202) was compared with placebo (n=101) for 52 weeks in adults with heterozygous familial hypercholesterolemia (HeFH) receiving stable lipid-lowering therapy including a moderate- or high-intensity statin.[6] Patients were required to have an LDL-C ≥55 mg/dL with a history of major ASCVD or an LDL-C ≥70 mg/dL without a history of major ASCVD. Mean age was 52 years, 51% were women, mean baseline LDL-C was 119 mg/dL, 81.5% were receiving a high-intensity statin, and 64.4% were receiving ezetimibe. At week 24, LDL-C decreased by 58.2% with enlicitide compared with a 2.6% increase with placebo, corresponding to a between-group difference of -59.4 percentage points (95% CI -65.6 to -53.2; P<0.001). The reduction was sustained through week 52 (-55.3% vs. 8.7%; between-group difference -61.5%; 95% CI -69.4 to -53.7). At week 24, enlicitide also significantly reduced non-HDL-C by 53.0%, apolipoprotein B by 49.1%, and lipoprotein(a) by 27.5% compared with placebo. Approximately 71% of patients receiving enlicitide achieved both a ≥50% LDL-C reduction and an LDL-C <70 mg/dL compared with 1% receiving placebo, while 67% achieved both a ≥50% reduction and LDL-C <55 mg/dL compared with 1% with placebo. Adverse events, serious adverse events, and treatment discontinuations due to adverse events were similar between groups.

In addition to the pivotal RCTs, a phase 3, double-blind, active comparator RCT randomized participants with ASCVD or high CV risk on background statin therapy (N=301) to enlicitide 20 mg, bempedoic acid 180 mg, ezetimibe 10 mg, or co-administered 180 mg bempedoic acid and 10 mg ezetimibe for 56 days.[57] The primary outcome was percentage change from baseline in LDL-C to day 56. Of the 435 participants screened, 134 did not meet eligibility criteria. The baseline mean LDL-C was 91.6 mg/dl and 44.2% of participants had a history of a major ASCVD event. The mean percentage change in LDL-C from baseline to day 56 were -64.6% in the enlicitide group, -6.3% in the bempedoic acid group, -27.8% in the ezetimibe group and -36.5% in the bempedoic acid plus ezetimibe group. This resulted in mean differences of -56.7% (95% CI: 64.3% to 49.0%) vs bempedoic acid, -36.0% (95% CI: 41.8% to 30.2%) vs ezetimibe, and -28.1% (95% CI: 33.6% to 22.6%) vs bempedoic acid plus ezetimibe (P < 0.001 for all pairwise comparisons).[57] This is a small trial of short duration that lacks a placebo arm. However, it demonstrates a greater reduction in LDL-lowering with enlicitide compared to other non-statin medications.

There is insufficient evidence currently that enlicitide results in a reduction in CV events. However, it produces a similar LDL-C lowering ability that other available PCSK9 inhibitors that have proven to reduce ASCVD risk. Despite the complex administration instructions, adherence to drug therapy was high in clinical trials. Real world adherence will likely be lower in more complex patient populations.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Major adverse cardiovascular events
2) Cardiovascular deaths
3) All-cause mortality
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
2) Percent change from baseline in LDL-C at week 24

Table 8: 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. Navar et al.[7] Phase 3, DB, PC RCT	1. Enlicitide (n=1935) 2. Placebo (n=969) 52 weeks	Demographics: Mean age 62.8 39% female 53.9% white 58% ASCVD Key Inclusion Criteria: • Adults with ASCVD and LDL ≥ 55 mg/dl or immediate-to-high CV risk and LDL ≥ 70 mg/dl • On stable dose of LLT Key Exclusion Criteria: • PCSK9i use • Uncontrolled diabetes • Active liver disease • TG ≥ 400 mg/dl	mITT: 1935 969 PP: 1711 861 Attrition: 224 (11.6%) 108 (11.1%)	Primary Endpoint: Change from baseline in LDL-C at week 24 1. -57.1% 2. 3.0% LS mean difference -55.8%; 95% CI -60.5 to -50.7 P< 0.001 Secondary Endpoints: Reduction in LDL-C to < 70 mg/dl with a reduction of 50% or more from baseline 1. 1361 (70.3%) 2. 15 (1.5%) **OR not provided*	NA ARR 68%/ NNT 2	Discontinuations due to adverse events: 1. 62 (3.2%) 2. 39 (4.0%) Serious AE 4. 191 (9.9%) 5. 116 (12%)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: low; randomized but randomization details not provided, groups similar at baseline Performance Bias: low; double-blinded, double dummy design. Detection Bias: unclear; unclear if outcome assessors blinded. Attrition Bias: low; attrition low and similar between groups. ITT analysis completed. Reporting Bias: low; outcomes reported as prespecified. Other bias: unclear; study was designed and funded by drug sponsor **Applicability**: Patient: Extensive exclusion criteria limits generalizability; 30% of participants failed screening. Intervention: dose selected based on phase 2 dose finding trial Comparator: placebo-controlled; lack of active comparator; the enlicitide formulation contained the excipient sodium caprate; the matching placebo did not contain sodium caprate Outcomes: LDL-C is a surrogate outcome. Study was not designed to evaluate clinically meaningful CV outcomes. Setting: multicenter; at 168 sites in 14 countries
2. Ballantyne, et al. [6] Phase 3, PC, DB, RCT	1. Enlicitide (n=202) 2. Placebo (n=101) 52 weeks	Demographics: Mean age 52 51% female Mean LDL 119 mg/dl 100% on statins Key Inclusion Criteria:	ITT: 202 101 PP: 189 92 Attrition:	Primary Endpoint: Percent change from baseline in LDL-C at week 24 1. -58.2% 2. 2.6% LS mean difference -59.4%; 95% CI -65.6% to -53.2% P<0.0001	NA	Discontinuations due to adverse events: 1. 3 (2%) 2. 2 (3%) Serious AE	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: low; randomization performed centrally using an interactive response technology and computer-generated algorithm; groups balanced at baseline Performance Bias: low – double blinded and dummy design Detection Bias: low; outcome assessors blinded

		• Adults with HeFH • on maximally tolerated statins +/- other LLT <u>Key Exclusion Criteria</u>: • HoFH • PCSK9i use • NYHA IV • Uncontrolled HTN • Poorly controlled DM • Active liver disease	7 (3.5%) 5 (5%)			6. 9 (4.5%) 7. 4 (4%)		<u>Attrition Bias</u>: low; low overall attrition and similar between groups, ITT analysis done <u>Reporting Bias</u>: low; outcomes reported as prespecified. <u>Other bias</u>: unclear; study was designed and funded by drug sponsor **Applicability**: <u>Patient</u>: generalizability limited to those with confirmed HeFH without significant comorbidities <u>Intervention</u>: dose selected based on phase 2 dose finding trial <u>Comparator</u>: placebo-controlled; lack of active comparator; the enlicitide formulation contained the excipient sodium caprate; the matching placebo did not contain sodium caprate <u>Outcomes</u>: LDL-C is a surrogate outcome. Study was not designed to evaluate clinically meaningful CV outcomes <u>Setting</u>: 59 sites across 17 countries
<u>Abbreviations</u> [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesteremia; HoFH = homozygous familial hypercholesterolemia; ITT = intention to treat; LLT = lipid lowering therapy; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol								

Clinical Safety:

Across the two pivotal phase 3 trials, enlicitide was generally well tolerated, with an overall safety profile similar to placebo. In the RCT in participants with hypercholesterolemia and ASCVD or increased CV risk, the incidence of serious adverse events was similar with enlicitide and placebo events (9.9% vs. 12.0%), as were adverse events leading to treatment discontinuation (3.1% vs. 4.1%), and deaths (0.7% vs. 0.7%). No apparent differences were observed in clinically important adverse events, and no cases of drug-induced liver injury were identified. New-onset or worsening diabetes occurred at similar rates with enlicitide and placebo (6.1% vs. 5.8%).[22]

In the RCT of participants with HeFH, adverse events were also similar between treatment, as were serious adverse events (4.5% vs. 4.0%), and adverse events leading to treatment discontinuation (2.0% vs. 3.0%). The most common adverse events were nasopharyngitis, influenza, headache, and nausea, but most occurred at similar frequencies with placebo. The adverse reactions occurring more frequently with enlicitide than placebo were dizziness (7% vs. 4%) and diarrhea (7% vs. 2%). [22]

Because enlicitide is administered orally, injection-site reactions were not observed, which are common with the injectable PCSK9 inhibitors.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
cholestyramine (with sugar)	CHOLESTYRAMINE	ORAL	POWD PACK	Y
cholestyramine	CHOLESTYRAMINE LIGHT	ORAL	POWD PACK	Y
cholestyramine	PREVALITE	ORAL	POWD PACK	Y
cholestyramine (with sugar)	QUESTRAN	ORAL	POWD PACK	Y
cholestyramine (with sugar)	CHOLESTYRAMINE	ORAL	POWDER	Y
cholestyramine	CHOLESTYRAMINE LIGHT	ORAL	POWDER	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	ORAL	POWDER	Y
cholestyramine	PREVALITE	ORAL	POWDER	Y
cholestyramine (with sugar)	QUESTRAN	ORAL	POWDER	Y
cholestyramine	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
fenofibrate,micronized	FENOFIBRATE	ORAL	CAPSULE	Y
omega-3 acid ethyl esters	OMEGA-3 ACID ETHYL ESTERS	ORAL	CAPSULE	Y
fenofibric acid (choline)	FENOFIBRIC ACID	ORAL	CAPSULE DR	Y
ezetimibe	EZETIMIBE	ORAL	TABLET	Y
fenofibrate	FENOFIBRATE	ORAL	TABLET	Y
fenofibrate nanocrystallized	FENOFIBRATE	ORAL	TABLET	Y
fenofibrate nanocrystallized	TRICOR	ORAL	TABLET	Y
ezetimibe	ZETIA	ORAL	TABLET	Y
lomitapide mesylate	JUXTAPID	ORAL	CAPSULE	N
colestipol HCl	COLESTID	ORAL	GRANULES	N
colestipol HCl	COLESTIPOL HCL	ORAL	GRANULES	N
colestipol HCl	COLESTIPOL HCL	ORAL	PACKET	N
colesevelam HCl	COLESEVELAM HCL	ORAL	POWD PACK	N
colesevelam HCl	WELCHOL	ORAL	POWD PACK	N
colesevelam HCl	COLESEVELAM HCL	ORAL	TABLET	N
colestipol HCl	COLESTID	ORAL	TABLET	N
colestipol HCl	COLESTIPOL HCL	ORAL	TABLET	N
colesevelam HCl	WELCHOL	ORAL	TABLET	N
olezarsen sodium	TRYNGOLZA	SUBCUT	AUTO INJCT	N
alirocumab	PRALUENT PEN	SUBCUT	PEN INJCTR	N
inclisiran sodium	LEQVIO	SUBCUT	SYRINGE	N
evinacumab-dgnb	EVKEEZA	INTRAVEN	VIAL	N
fenofibrate	FENOFIBRATE	ORAL	CAPSULE	N

icosapent ethyl	ICOSAPENT ETHYL	ORAL	CAPSULE	N
fenofibrate	LIPOFEN	ORAL	CAPSULE	N
niacin	NIACIN	ORAL	CAPSULE ER	N
niacin	NIACIN ER	ORAL	TAB ER 24H	N
choline	CHOLINE	ORAL	TABLET	N
fenofibrate	FENOFIBRATE	ORAL	TABLET	N
gemfibrozil	GEMFIBROZIL	ORAL	TABLET	N
gemfibrozil	LOPID	ORAL	TABLET	N
bempedoic acid	NEXLETOL	ORAL	TABLET	N
bempedoic acid/ezetimibe	NEXLIZET	ORAL	TABLET	N
niacin	NIACIN	ORAL	TABLET	N
niacinamide	NIACINAMIDE	ORAL	TABLET	N
niacinamide	VITAMIN B3	ORAL	TABLET	N
niacin	NIACIN	ORAL	TABLET ER	N
niacin	NIADELAY	ORAL	TABLET ER	N
niacin	SLO-NIACIN	ORAL	TABLET ER	N
plozasiran sodium	REDEMPLO	SUBCUT	SYRINGE	
niacinamide	VITAMIN B3	ORAL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

- Bohula, et al. Evolocumab in Patients without a Previous Myocardial Infarction or Stroke. N Engl J Med. 2026 Jan 8;394(2

  Background: The proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor evolocumab reduces the risk of major adverse cardiovascular events (MACE) among patients with a previous myocardial infarction, stroke, or symptomatic peripheral artery disease. The effect of evolocumab on the risk of MACE among patients without a previous myocardial infarction or stroke is unknown.

  Methods: We conducted an international, double-blind, randomized, placebo-controlled trial of evolocumab in patients with atherosclerosis or diabetes and without a previous myocardial infarction or stroke who had a low-density lipoprotein cholesterol level of at least 90 mg per deciliter. Patients were randomly assigned in a 1:1 ratio to receive evolocumab at a dose of 140 mg every 2 weeks or placebo. The two primary end points were a composite of death from coronary heart disease, myocardial infarction, or ischemic stroke (3-point MACE) and a composite of 3-point MACE or ischemia-driven arterial revascularization (4-point MACE).

  Results: A total of 12,257 patients were randomly assigned to receive evolocumab (6129 patients) or placebo (6128) and were included in the efficacy analyses. The median age of the patients was 66 years, 43% were women, and 93% were White. The median follow-up was 4.6 years. A 3-point MACE event occurred in 336 patients (5-year Kaplan-Meier estimate, 6.2%) in the evolocumab group, as compared with 443 (8.0%) in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001). A 4-point MACE event occurred in 747 patients (5-year Kaplan-Meier estimate, 13.4%) in the evolocumab group, as compared with 907 (16.2%) in the placebo group (hazard ratio, 0.81; 95% CI, 0.73 to 0.89; P<0.001). No evidence of a between-group difference was seen in the incidence of safety events.

  Conclusions: PCSK9 inhibition with evolocumab led to a lower risk of first cardiovascular events than placebo among patients with atherosclerosis or diabetes and without a previous myocardial infarction or stroke. (Funded by Amgen; VESALIUS-CV ClinicalTrials.gov number, NCT03872401.).

Appendix 3: Medline Search Strategy

[Example]

Ovid MEDLINE(R) ALL <1946 to August 1, 2026>

1 ezetimibe.mp. or Ezetimibe/ 5449
2 bile acid sequestrants.mp. 587
3 colestipol.mp. or Colestipol/ 568
4 cholestyramine.mp. or Cholestyramine Resin/ 3772
5 colesevelam.mp. or Colesevelam Hydrochloride/ 380
6 alirocumab.mp. 1252
7 evolocumab.mp. 1520
8 PCSK9 inhibitors.mp. 3134
9 fenofibrate.mp. or Fenofibrate/ 4849
10 gemfibrozil.mp. or Gemfibrozil/ 2415
11 icosapent ethyl.mp. 446
12 omega-3 fatty acids.mp. or Fatty Acids, Omega-3/ 23560
13 niacin.mp. or Niacin/ 15016
14 bempedoic acid.mp. 702
15 evinacumab.mp. 233
16 nonstatin.mp. 453
17 cardiovascular disease.mp. or Cardiovascular Diseases/ 339465
18 atherosclerotic cardiovascular disease.mp. 10947
19 olezarsen.mp. 110
20 plozasiran.mp. 72
21 Dyslipidemias/ or dyslipidemia.mp. 54667
22 Hypertriglyceridemia/ 7462
23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 19 or 20 58145
24 17 or 18 or 21 or 22 384791
25 23 and 24 9361
26 limit 25 to (english language and humans and yr="2022 -Current" and (clinical trial, phase iii or controlled clinical trial or meta analysis or network meta-analysis or randomized controlled trial or "systematic review")) 376
27 from 26 keep 4-5,10,13,17-18,20,23,27-29,33,36,45,61-62,64-65,74-75,80,95-96,101,103,105,112,118-120,126,130,132-134,142,146,148,150,152,154,160,162-163,169-170,199-200,204,211,219,227,238-239,259-260,271,338,352-353 60
28 from 27 keep 2,6,10-12,18,20,23,26,28-30,34-36,38,43,46,48,52-56,60 25

Appendix 5: Prescribing Information Highlights

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

LEROCHOL™ (lerodalcibep-liga) injection, for subcutaneous use
Initial U.S. Approval: 2025

INDICATIONS AND USAGE

LEROCHOL is a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor indicated as an adjunct to diet and exercise: to reduce low-density lipoprotein cholesterol (LDL-C) in adults with hypercholesterolemia, including heterozygous familial hypercholesterolemia (HeFH). (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage of LEROCHOL is 300 mg administered subcutaneously once monthly. (2.1)
- Inject LEROCHOL subcutaneously into the abdomen or thigh. A caregiver or healthcare professional can administer into the upper arm. (2.2)
- Refer to the Instructions for Use for administration of prefilled syringe. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/1.2 mL (250 mg/mL) solution in a single-dose prefilled syringe. (3)

CONTRAINDICATIONS

None. (4)

ADVERSE REACTIONS

Common adverse reactions occurring in ≥1% of patients treated with LEROCHOL were injection site reactions, nasopharyngitis, diarrhea, nausea and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LIB Therapeutics, Inc. at 1-877-2-LEROCHOL or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2025

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

LIPFENDRA® (enlicitide) tablets, for oral use
Initial U.S. Approval: 2026

----------INDICATIONS AND USAGE----------
LIPFENDRA is a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor indicated as an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in adults with hypercholesterolemia, including heterozygous familial hypercholesterolemia (HeFH).

Cardiovascular outcomes trials have demonstrated that reducing LDL-C lowers the risk for major adverse cardiovascular events (MACE) in adults at increased risk when treated with statins or monoclonal antibody PCSK9 inhibitors as an add-on to statin therapy. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of LIPFENDRA is one 20 mg tablet taken orally once daily. (2.1)
- Take LIPFENDRA on an empty stomach in the morning with water, black coffee, or plain tea. (2.2)
- Swallow the tablet whole. Do not split, crush, or chew the tablet. (2.2)
- After taking LIPFENDRA, wait at least 30 minutes before eating food or drinking beverages other than water, black coffee, or plain tea. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Film-Coated Tablets: 20 mg enlicitide (3)

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

----------ADVERSE REACTIONS----------
The frequencies of adverse reactions in adults with hypercholesterolemia were similar between those treated with LIPFENDRA and those receiving placebo. The most common adverse reactions in a study of adults with HeFH treated with LIPFENDRA were diarrhea and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2026

Appendix 6. Pharmacology and Pharmacokinetic Properties.

Lerodalcibep[21]

Parameter	
Mechanism of Action	A recombinant fusion protein that binds PCSK9, a negative regulator of the low-density lipoprotein receptor. By inhibiting binding of PCSK9, it increases the number of LDL receptors available to clear LDL from the blood, lowering LDL levels.
Oral Bioavailability	n/a; administered subcutaneously
Distribution and Protein Binding	Volume of distribution is 5.3L.
Elimination	n/a
Half-Life	10 days
Metabolism	Metabolized into small peptides by catabolic pathways

Abbreviations:

Enlicitide[22]

Parameter	
Mechanism of Action	Enlicitide is a macrocyclic peptide that binds to PCSK9. PCSK9 binds to the LDLR on the surface of hepatocytes to promote LDLR degradation within the liver. By inhibiting the binding of PCSK9 to LDLR, enlicitide increases the number of LDLRs available to clear low-density lipoprotein cholesterol (LDL-C) from the blood, thereby lowering LDL-C levels.
Oral Bioavailability	1%
Distribution and Protein Binding	Vd 2,384 L; Protein binding 94%
Elimination	Urine (73%); Feces (8%)
Half-Life	14 hours
Metabolism	Minimal

Non-Statin Dyslipidemia Medications

Goal(s):
- Promote use of non-statin medications 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)
- Bempedoic Acid (Nexletol™)
- Bempedoic acid and ezetimibe (Nexlizet™)

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. Has the patient taken a daily high-intensity statin (see table below) or maximally tolerated statin therapy for at least 3 months and still requires additional LDL-C lowering according to current guideline recommendations, OR have a history of statin intolerance*? Prescriber to submit chart documentation of: 1) Doses and dates initiated of statin 2) Recent LDL-C *Statin intolerance includes: • rhabdomyolysis caused by a statin, OR • a history of creatinine kinase (CK) levels >10-times upper limit of normal with muscle symptoms determined to be caused by a statin, OR • statin intolerance, defined as one or more adverse effects associated with statin therapy that improves with dose reduction or discontinuation and a trial of at least 2 statin medications at the lowest approved daily dose?	**Yes:** Confirm documentation; go to #4 1. Statin: Dose: Date Initiated: Recent LDL-C _____ Date:_____	**No:** Pass to RPh; deny for medical appropriateness.
4. Does the patient have clinical atherosclerotic cardiovascular disease (ASCVD), defined as documented history of one or more ASCVD events (see below) **OR** a diagnosis of heterozygous familial hypercholesterolemia (HeFH)? <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 • Coronary artery disease	**Yes:** Go to #7	**No:** Go to #5

Approval Criteria		
5. Does the patient have diabetes mellitus or is at high risk for cardiovascular disease, including any of the following, and still requires additional LDL-C lowering based on guideline recommended LDL-C goals? • 10-year ASCVD risk of 10% or greater? • Subclinical atherosclerosis • Severe hypercholesterolemia (baseline LDL-C ≥ 190 mg/dl)	**Yes:** Go to #6	**No:** Pass to RPh; deny for medical appropriateness.
6. Has the patient taken ezetimibe 10 mg daily for at least 3 months and still requires additional LDL-C lowering **OR** have a contraindication to ezetimibe?	**Yes:** Confirm documentation; go to #7 Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness.
7. Is the request for inclisiran, enlicitide, or lerodalcibep?	**Yes:** Go to #8	**No:** Approve for up to 12 months.
8. 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:** Approve for up to 12 months	**No:** Pass to RPh; deny for medical appropriateness.

Renewal Criteria	
1. What is the most recent LDL-C (within last 12 weeks)?	Recent LDL-C _____ mg/dL Date:_____ ; go to #2

Renewal Criteria		
2. Has the patient experienced and maintained a reduction in LDL-C compared to baseline labs?	**Yes:** Go to #3	**No:** Pass to RPh; deny for medical appropriateness
3. Is the patient adherent with therapy?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh; deny for medical appropriateness

P&T/DUR Review: 10/26 (retirement/consolidation of multiple other PAs)
Implementation: 1/1/27

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

Lipoprotein Goals for ASCVD Risk reduction

Patient population	**LDL-C < 100 mg/dl** **Non-HDL C < 130 mg/dl**	**LDL-C < 70 mg/dl** **Non-HDL C < 100 mg/dl**	**LDL-C < 55 mg/dl** **Non-HDl C < 85 mg/dl**
Primary prevention	Prevent-ASCVD < 10%	PREVENT-ASCVD ≥ 10%	n/a
Severe hypercholesterolemia (LDL-C ≥ 190 mg/dl)	Without FH, ASCVD risk factors, and subclinical atherosclerosis	With FH, ASCVD risk factors, or subclinical atherosclerosis	With chronic ASCVD
Diabetes	Without ASCVD risk factors or diabetes specific risk modifies	With ASCVD risk factors for diabetes-specific risk factors	n/a
Subclinical atherosclerosis	CAC = 1-99 AU and < 75 percentile for age, sex, and race	CAC ≥ 100 to 299 AU or ≥ 75 percentile for age, sex, race	CAD ≥ 1000 AU
Hypertriglyceridemia	≤ 50 yr old with no additional risk enhancers	With clinical ASCVD not at very high risk	With clinical ASCVD
Clinical ASCVD	N/A	Not at very high risk	At very high risk or with CKD

APOLIPOPROTEIN C-III (APOC3) Inhibitors

Goal(s):

- Promote use of APOC3 Inhibitors that is consistent with medical literature.
- Promote use of high value products.

Length of Authorization:

- Up to 12 months

Requires PA:

- Olezarsen (Tryngolza)
- Plozasiran (Redemplo)

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 renewal of a previously approved FFS prior authorization?	**Yes**: Go to **Renewal Criteria**	**No**: Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Does the patient have a diagnosis of familial chylomicronemia syndrome (FCS), confirmed by genetic testing? Please submit a copy of the genetic testing results	**Yes**: Go to #4	**No:** Go to #7
4. Is the medication prescribed by or in consultation with a specialist in familial chylomicronemia syndrome (FCS)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have a current triglyceride level of 1000 mg/dL or greater within the previous 6 months?	**Yes:** Go to #6 **Recent TG Level**_____ **Date** _____	**No:** Pass to RPh. Deny; medical appropriateness

6. Does the patient agree to adhere to a low-fat diet (≤ 20 g of fat per day)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for an FDA-approved indication?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have clinically diagnosed severe hypertriglyceridemia with triglyceride levels ≥ 500 mg/dL on at least 2 occasions within the previous 6 months?	**Yes:** Go to #9 Recent TG Level_____ Date _____	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient on maximally tolerated statin therapy?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Has the patient failed to have adequate benefit with (triglycerides remain > 500 mg/dl), or have a contraindication to, an adequate trial (at least 8 weeks) of a fibric acid derivative (fenofibrate or gemfibrozil) and high-dose omega 3 fatty acid (4 gm daily)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation of a positive clinical response (i.e. clinically meaningful reduction in triglyceride level or reduction in episodes of acute pancreatitis) within the previous 6 months?	Yes: Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 10/26; 8/26, 2/26 (MH)
Implementation: 10/1/26; 3/1/26