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Drug Class Update with New Drug Evaluation: Other Dyslipidemia Drugs (non-statin)

Date of Review: August 2020

Generic Name: Bempedoic acid; Bempedoic acid and Ezetimibe

Date of Last Review: May 2019
Dates of Literature Search: 03/01/2019 – 05/31/2020
Brand Name (Manufacturer): Nexletol™; Nexlizet™ (Esperion Therapeutics, Inc.)
Dossier Received: Yes

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

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.
- Analyze the data supporting the efficacy and safety of bempedoic acid and determine its 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 bempedoic acid and bempedoic acid/ezetimibe in patients with 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 no new comparative evidence for the effectiveness or safety of non-statin medications for the prevention of CV mortality and CV events in high risk CV patients.
- There is moderate quality evidence that bempedoic acid modestly lowers LDL-C compared to placebo (17% to 18% placebo-adjusted treatment difference from baseline at week 12) in patients with established CVD on maximally tolerated statin therapy who require additional LDL-C lowering (i.e. LDL ≥ 70 mg/dl).[1,2]
- There is low quality evidence that the combination of bempedoic acid and ezetimibe lowers LDL-C compared to placebo, bempedoic acid monotherapy and ezetimibe monotherapy (treatment difference of -38.2%, -18.9% and -13.5%, respectively).[3]

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- There is insufficient evidence to determine the long-term effectiveness of bempedoic acid or combination bempedoic acid and ezetimibe on clinically meaningful outcomes, including cardiovascular mortality and major adverse cardiovascular events.
- There are several concerning safety signals seen in 52-week trials of bempedoic acid including tendon rupture, gout, nephrolithiasis, and new-onset benign prostatic hypertrophy (BPH). More data are needed to better quantify the risks associated with therapy. Additionally, bempedoic acid resulted in multiple changes to lab parameters during treatment, including increases in serum creatinine, liver transaminases, creatinine kinase and decreases in white blood cell (WBC) count, neutrophils and hemoglobin.

Recommendations:

- Due to its unknown benefit on CV outcomes and multiple safety concerns, maintain bempedoic acid and bempedoic acid/ezetimibe as non-preferred.
- Include prior authorization to limit utilization to high-risk CV patients requiring additional LDL-lowering on maximally tolerated statin therapy and ezetimibe. (**Appendix 4**).
- Update prior authorization to include new FDA approved indication for icosapent ethyl (**Appendix 4)**.
- After evaluation of comparative costs in executive session, recommend making generic omega-3 fatty acids preferred without prior authorization. Recommend making Triglide®/Tricor® (fenofibrate nanocrystalized tab), Antara® (fenofibrate micronized cap), Trilipix® (fenofibric acid [choline]) cap) and their generics preferred.

Summary of Prior Reviews and Current Policy

- Current PA polices for PCKS9 inhibitors and omega-3 fatty acids are included in **Appendix 4.**
- There is moderate quality evidence that ezetimibe combined with a statin results in a modest (2%) improvement in CV outcomes with a long duration of follow-up (approximately 7 years).[4]
- Moderate quality evidence comparing statin monotherapy to a statin in combination with niacin, fibrates or omega 3 fatty acids shows 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; ARR 4.8%; NNT 21 over 4.9 years) in patients with hypertriglyceridemia and CV disease or with diabetes plus other CV risks on statin therapy.[5] However, this is inconsistent with prior studies and meta-analysis that have not shown a CV benefit with omega-3 fatty acids. Additionally, there are serious limitations to the study including the use of mineral oil as placebo, the disconnect between the modest triglyceride lowering seen and greater than predicted CV benefit, as well as significant funding and involvement in the study oversight and data interpretation by the manufacturer. More data are needed to confirm these findings and icosapent ethyl remains non-preferred.
- There is high quality evidence of a decrease in CV events with alirocumab versus placebo in patients with nonfamilial hypercholesterolemia (9.5% vs. 11.1%; hazard ratio [HR] 0.85; 95% CI 0.78 to 0.93; absolute risk reduction [ARR] 1.6%; number-needed-to-treat [NNT] 63) and moderate quality evidence of lower risk of overall mortality (3.5% vs. 4.1%; HR 0.85; 95% CI 0.73 to 0.99), but no significant difference in death due to CV causes (2.5% vs. 2.9%).[6]
- There is high quality evidence of a similar decrease in CV events with evolocumab versus placebo in patients with nonfamilial hypercholesterolemia (9.8% vs. 11.3%; HR 0.85; 95% CI 0.79 to 0.92; ARR 1.5%; NNT 67). The incidence of death from any cause was similar between groups after 26 months (3.2% vs. 3.1%; HR 1.04; 95% CI 0.91 to 1.19).[7]
- 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 (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 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.[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. The updated guidelines consider an LDL-C threshold of 70 mg/dl reasonable to add a non-statin agent in those with clinical ASCVD. [8]

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.[9] 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.[4] 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.[9] Additionally, a moderate-intensity statin was used as the study comparator, which is not consistent with current practice recommendations.

Evolocumab (Repatha®) and alirocumab (Praluent®) are subcutaneously injected human monoclonal antibodies that reduce LDL-C by inhibiting PCSK9.[10,11] 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 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).**[7,10] [6] 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.[5] This is in patients with elevated triglycerides despite statin therapy. Icosapent ethyl gained FDA approval as an add-on therapy to reduce CV events for adults with elevated triglycerides ($\geq$ 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 (NNH 71) and may increase the risk of bleeding. [5]

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.[12] 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 in a recent large-scale clinical trial.

Table 1: Characteristics of Cardiovascular Outcome trials for Non-statins[4-7]

	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 2116 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[4-7]

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

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 2**, 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:
A systematic review included RCTs comparing PCSK9 inhibitors with placebo or lipid-lowering therapy evaluating all-cause mortality and major adverse cardiovascular events (MACE).[13] A total of 23 trials (n=88,041) with low risk of bias were included in the analysis evaluating alirocumab (n=16), evolocumab (n=5) and bococizumab (n=2). The majority of trials (14) involved secondary prevention of CVD, but studies in primary prevention (n=9) were also included. PCSK9 inhibitors were not associated with a reduction in either all-cause mortality (OR 0.91; 95% CI 0.78 to 1.06) or CV deaths (OR 0.95; 95% CI 0.84 to 1.07). [13] Treatment with a PCSK9 inhibitor was associated with a reduction in MACE (OR 0.82; 95% CI 0.77 to 0.87) and myocardial infarction (MI) (0.80; 95% CI 0.71 to 0.91). [13] Mega-regression showed that the benefit was not impacted by LDL-C, age and duration of follow up. There was heterogeneity in the included population, since both subjects with CVD and high-risk primary prevention patients were included. Longer term follow up may be necessary for a mortality reduction to be seen.

A systematic review and meta-analysis evaluated RCTs (n=11) comparing omega 3 fatty acids in adults experiencing a MI within 6 weeks.[14] Six of the trials were found to have moderate or high risk of bias due to incomplete blinding, allocation concealment and attrition bias. There was no statistically significant reduction in all-cause mortality (RR 0.86; 95% CI 0.72 to 1.02), but there was a reduction in CV mortality (RR 0.77; 95% CI 0.65 to 0.91) and recurrent MI (RR 0.77; 95% CI 0.6 to 0.99) in patients with a recent MI.[14] There was no significant reduction in any clinical outcomes when including only trials with low risk of bias which makes the overall pooled estimates difficult to interpret.

New Guidelines:
None identified

New Formulations or Indications:
In April 2019, alirocumab was FDA approved to reduce the risk of MI, stroke and unstable angina in adults with established CVD. This approval was based on the ODYSSEY OUTCOMES trial which was evaluated in a previous review.[14] This study demonstrated a 1.6% absolute risk reduction over 3 years in a composite of coronary heart disease (CHD) death, MI, ischemic stroke and unstable angina in adults with ACS 1-12 months prior.

In December 2019, FDA expanded the label for icosapent ethyl as adjunct to statin therapy to reduce the risk of MI, stroke, coronary revascularization and unstable angina in adults with TG levels ≥ 150 mg/dL based on the REDUCE-IT trial.[5] This data were reviewed in a previous update.

New FDA Safety Alerts:
None identified

Randomized Controlled Trials:
A total of 7 citations were manually reviewed from the initial literature search.[15-21] After further review, all were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

See **Appendix 3** 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:
Bempedoic acid is an adenosine triphosphate-citrate lyase (ACL) inhibitor indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C.[22]

Bempedoic acid was approved based on two pivotal secondary prevention trials in high risk patients including those with clinical ASCVD or heterozygous familial hypercholesterolemia (HeFH) on maximally tolerated statin therapy (**Table 5**) (CLEAR Harmony and CLEAR Wisdom).[1,2] Both were 52-week randomized, double-blind trials comparing bempedoic acid to placebo in patients on baseline lipid-modifying therapy with LDL ≥ 70 mg/dl. Study design and inclusion/exclusion criteria were similar (**Table 5**). However, in CLEAR Wisdom, a 4-week run in period for statin optimization and compliance was included.[1] The majority of patients in both trials had established ASCVD (~95%) and data in those with HeFH is limited (<5% of subjects). While the majority of patients were on statin therapy, only half of patients were on the recommended high intensity dosing.

Both trials resulted in a significant reduction in LDL-C from baseline at week 12 compared to placebo (treatment difference -18.1%; 95% CI -20 to -16.1% in CLEAR Harmony and -17.4%; 95% CI -21 to -13.9% in CLEAR Wisdom). [1,2] LDL lowering was consistent across subgroups, including baseline CV risk, baseline LDL, baseline lipid-lowering therapy, and baseline statin intensity. However, the effect was smaller in subjects on background statins Significant reductions in non-HDL cholesterol, total cholesterol, apolipoprotein B and high-sensitivity C-reactive protein were also observed. There were minimal effects on triglycerides (TG). The magnitude of LDL-lowering is similar to observations of ezetimibe when added to statin therapy (-13 to -20%) and lower than what is seen from the PCSK9 inhibitors (-47% to -63% additional lowering). Additionally, the efficacy was reduced after week 12, but still remained statistically superior to placebo at week 52.

Both trials had significant exclusion criteria **(Table 5)** and a high percentage of screen failures (34.3% in CLEAR Harmony and 66.1% in CLEAR Wisdom) during the run-in and/or screening periods. [1,2] Therefore, there are substantial concerns with external validity and generalizability of these results.

Two additional supportive phase 3 trials included primary and secondary prevention patients with hyperlipidemia who were considered statin-intolerant.[23,24] Patients were on either no statin, very-low-dose statin or low-dose statin and ezetimibe. Both trials included a 4-week placebo run-in period for compliance with a high percentage of screening failures (42.7% and 56.3%), limiting generalizability of these results. In one of the supportive trials, more bempedoic acid treated patients discontinued due to adverse events compared to placebo (2.6% vs. 0.9%, respectively). [23,24] Most patients were enrolled for primary prevention and mean baseline LDL-C values were 157.6 mg/dl and 127.6 mg/dl. More than half of patients were not on any lipid lowering therapy (50% and 58%). Bempedoic acid resulted in a significant reduction in LDL-C from baseline compared to placebo in both trials (treatment difference -21%; 95% CI -25.0% to -17.0% and -28.6%; 95% CI -34.9% to -22.4%).[23,24] Overall, there was a larger reduction in LDL-C in those who were not on statin therapy at baseline.

The combination of bempedoic acid 180 mg and ezetimibe 10 mg was also FDA approved as adjunct to maximally tolerated statin therapy for the treatment of adults with HeFH or established ASCVD who require additional lowering of LDL-C.[3] Approval was based on one 12-week RCT (**Table 5**) with unclear risk of bias comparing the combination of bempedoic acid/ezetimibe to each individual drug and active placebo in patients with ASCVD, HeFH or high risk CV patients

(primary prevention) on maximally tolerated statin therapy. Three of the study sites were found to have data irregularities indicating possible fraud and data from these sites were excluded from the post hoc efficacy and safety analysis and from the FDA analysis.[25] The FDA review notes that the trial was adequately powered despite exclusion of this data and exclusion did not introduce any additional bias.[25]

Approximately 60% of patients had ASCVD or HeFH and 40% were primary prevention patients with CV risk factors.[3] However, only 65% were on maximally tolerated statin therapy and approximately 21% were on high intensity statins. The FDA review suggests that the enrolled patient population did not adequately reflect the intended clinical population due to the low rates of adequate treatment at baseline. [25] Additionally, over half of patients screened did not meet the randomization criteria.

Overall, there was a statistically significant reduction in LDL-C with the combination of bempedoic acid and ezetimibe compared to the individual drug components and placebo, demonstrating that both agents contribute to the drug's treatment effect. The placebo-adjusted treatment difference in LDL-C at week 12 for the combination, bempedoic acid, and ezetimibe was -38.2%, -19.3% and -24.7%, respectively (**Table 5**).[3] Ezetimibe appears to contribute to the treatment effect more than bempedoic acid and the treatment effect was larger than expected based on the previous studies of bempedoic acid monotherapy. This may be due to different patient populations (mix of primary and secondary prevention) and higher baseline LDL-C values than the pivotal bempedoic acid subjects.

None of the clinical trials were designed or powered to evaluate the effects of bempedoic acid on CV outcomes. Until further data is available on clinically important outcomes, statin therapy should be optimized in patients with CV disease and HeFH. In high risk patients requiring additional LDL-lowering therapy, non-statin agents (i.e. ezetimibe) with some potential CV benefit and more safety data should be prioritized.

Clinical Safety:

In the pivotal trials, there were significantly more discontinuations due to adverse events in the bempedoic group compared to placebo (10.9% vs. 7.5%).[26] The incidence of muscle-related adverse events was similar in the two groups. The most common reasons for discontinuation were diarrhea, musculoskeletal pain, elevated liver enzymes, other gastrointestinal symptoms and headache. More patients on bempedoic experienced gout (1.5%) compared to placebo (0.4%), increases in serum uric acid (3.5% vs. 1.1%), tendon rupture (0.5% vs. 0%) and new-onset BPH in men (1.3% vs. 0.1%).[26] Bempedoic acid competes for the same renal transporters as uric acid and therefore can increase uric acid levels. Adverse effects occurring at higher rates than placebo are included in **Table 3**.

Table 3: Adverse Events Occurring at 0.5% Higher Frequency in Treatment Arm compared to Placebo[26]

	Bempedoic Acid (n=2009) N(%)	Placebo (n=999) N(%)
Upper respiratory tract infection	91 (4.5)	40 (4.0)
Muscle spasms	73 (3.6)	23 (2.3)
Increased uric acid	70 (3.5)	11 (1.1)
Back pain	66 (2.2)	22 (2.2)
Pain in extremity	61 (3.0)	17 (1.7)
Anemia	57 (2.8)	19 (1.9)

Elevated liver enzymes	44 (2.2)	10 (1.0)
Abdominal pain	39 (1.9)	14 (1.4)
Atrial fibrillation	34 (1.7)	11 (1.1)
Gout	31 (1.5)	4 (0.4)
Vomiting	27 (1.3)	2 (0.2)
Increases in Scr/Decreases in eGFR	27 (1.3)	4 (0.4)
Renal insufficiency	18 (0.9)	1 (0.1)
Benign prostatic hyperplasia	18 (0.9)	3 (0.3)

In the pivotal RCTs, there was an imbalance in total deaths, with 25 deaths in the bempedoic acid group (1.2%) compared to 8 in the placebo group (0.8%).[26] The death imbalance appears to be driven by malignancy-associated deaths.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) All-cause and CV mortality
2) Fatal and non-fatal CV events
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Percent change from baseline to Week 12 in LDL-C

Table 4. Pharmacology and Pharmacokinetic Properties

Parameter	
Mechanism of Action	Bempedoic acid is a prodrug metabolized in the liver to an active adenosine triphosphate-citrate lyase inhibitor that lowers LDL-C by inhibition of cholesterol synthesis upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.
Oral Bioavailability	~70%
Distribution and Protein Binding	18 L. 99% protein bound.
Elimination	70% recovered in urine (primarily as acyl glucuronide metabolite), 30% recovered in feces. <5% excreted as unchanged bempedoic acid.
Half-Life	21 hours
Metabolism	<2% renal clearance. Primary route is through metabolism of the acyl glucuronide.

Abbreviations:

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARI/NNH	Risk of Bias/ Applicability
1. Ray, et al. CLEAR Harmony[2] DB, PC, MC, RCT	1. Bempedoic Acid 180 mg daily 2. Placebo 52 weeks duration	Demographics: •Mean age 66 •27% Female •96% white •71% DM •97% ASCVD •3.5% HeFH •50% High intensity statin at baseline •9% ezetimibe •Mean LDL 103 mg/dl Key Inclusion Criteria: •≥ 18 years, nonpregnant •LDL-C ≥ 70 mg/dl •HeFH OR ASCVD •On maximally tolerated statin +/- other lipid lowering therapies Key Exclusion Criteria: •TG ≥ 500 mg/dl •eGFR < 30 ml/min •BMI ≥ 50 kg/m2 •Use of PCSK9 inhibitors •Recent ACS (within 3 months) •SBP ≥ 160 mm Hg •HgA1C ≥ 10% •Liver dysfunction, HCV, HBV •Hgb < 10 g/dl •Active malignancy •CK > 3 x ULN •Drug, alcohol abuse	ITT: 1. 1488 2. 742 PP: 1. 1404 2. 706 Attrition: 1. 84 (5.7%) 2. 36 (4.9%)	Change in LDL-C from baseline to week 12 1. -19.2 mg/dl (-16.5%) 2. 0.2 mg/dl (1.6%) Difference -18.1%; 95% CI -20 to -16.1); p<0.001	N/A	Discontinuation due to AE: 1. 162 (10.9%) 2. 53 (7.1%) P=0.005 Serious AE 1. 216 (15.4%) 2. 104 (14%) NS Major adverse cardiac event 1. 68 (4.6%) 2. 42 (5.7%) NS	ARI 3.8% / NNH 27 NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: low; groups similar at baseline. Randomization and allocation concealment through Interactive Web-based Response System. Performance Bias: low; double-blind, matching placebo Detection Bias: low; blinded clinical events committee adjudicated clinical outcomes Attrition Bias: unclear; majority of patients completed the study in each group (~95%) but high rates of treatment discontinuation in treatment (23.2%) and placebo group (19.1%). Missing lipid values were imputed based on observed values in their randomized treatment group Reporting Bias: low; outcomes reported as specified Other Bias: high; funded by Esperion Therapeutics which was involved in trial design, data collection and analysis and manuscript development. **Applicability**: Patient: Significant exclusion criteria and screening period limits generalizability to real world patients. 34.4% (n=1165) of screened patients were not randomized due to failure to meet criteria or withdrawal Intervention: 180 mg demonstrates maximal LDL-lowering in dose-ranging studies with no significant increase in dose-related laboratory changes (Scr, uric acid, Hg, BUN) Comparator: Placebo. Active comparator (i.e ezetimibe) lacking Outcomes: LDL-C is a surrogate outcome. Not powered or designed to evaluate CV outcomes. Setting: Multicenter in 5 countries (U.S., Canada, Germany, Netherlands, Poland, U.K). 65% Europe and 34% North America (25% U.S.)

2. Goldberg et al CLEAR Wisdom[1] DB, PC, MC, RCT	1. Bempedoic Acid 180 mg daily 2. Placebo 52 weeks duration	Demographics: • Mean age 64 •35% Female •95% white •70% DM •94% ASCVD •5% HeFH •53% High intensity statin at baseline •8% ezetimibe •Mean LDL 120 mg/dl Key Inclusion Criteria: See Ray et al Key Exclusion Criteria: See Ray et al PLUS Noncompliance with 4-week placebo run-in	ITT: 1. 522 2. 257 PP: 1. 490 2. 250 Attrition: 1. 32 (6.1%) 2. 7 (2.7%)	Change in LDL-C from baseline to week 12 1. -15.1% 2. 2.4% Difference -17.4%; 95% CI -21 to -13.9%); p<0.001	N/A	Discontinuation due to AE: 1. 57 (10.9%) 2. 22 (8.6%) *p-value not provided Serious AE 1. 106 (20.3%) 2. 48 (18.7%) NS Major adverse cardiac event 1. 43 (8.2%) 2. 26 (10.1%) RR 0.81; 95% CI 0.51 to 1.29	N/A* NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: low; groups similar at baseline. Randomization and allocation concealment through Interactive Web-based Response System. Performance Bias: low; double-blind, matching placebo Detection Bias: low; blinded clinical events committee adjudicated clinical outcomes Attrition Bias: unclear; More patients in the treatment group withdrew from the study and discontinued drug. Reporting Bias: low; outcomes reported as specified Other Bias: high; funded by Esperion Therapeutics which was involved in trial design, data collection and analysis and manuscript development **Applicability**: Patient: Significant exclusion criteria and a 4-week placebo run-in period for statin optimization and compliance prior to randomization limits generalizability. 66.1% of patients screened failed to enter the randomization process for not meeting criteria or withdrawal. Intervention: See Ray et al Comparator: See Ray et al Outcomes: See Ray et al Setting: Multicenter (86 sites in 6 countries) 71% Europe, 29% North America (27% U.S)

3. Ballantyne et al.[3] DB, PC, MC, RCT	1. Bempedoic Acid 180 mg/ ezetimibe 10 mg daily 2. Bempedoic Acid 180 mg 3. Ezetimibe 10 mg 4. placebo 12 weeks duration	Demographics: •60% ASCVD or HeFH •40% with CV Risk factors •Mean LDL 146-152 mg/dl •65% on maximally tolerated statin •28% on no therapy Key Inclusion Criteria: •≥ 18 years •LDL-C ≥ 100 mg/dl (ASCVD) or 130 mg/dl (CV risk factors) •HeFH OR ASCVD or multiple CVD risk factors •On maximally tolerated statin • Key Exclusion Criteria: •TG ≥ 500 mg/dl •eGFR < 30 ml/min •BMI ≥ 40 kg/m2 •Use of PCSK9 inhibitors, fibrates, niacin, bile acid sequestrants •Recent ACS (within 3 months) •SBP ≥ 160 mm Hg •HgA1C ≥ 10% •Liver dysfunction, HCV, HBV •Hgb < 10 g/dl •Active malignancy •CK > 3 x ULN •Drug, alcohol abuse	ITT: 1. 108 2. 110 3. 109 4. 55 FAS* 1. 86 2. 88 3. 86 4. 41 PP*: 1. 81 2. 82 3. 81 4. 40 Attrition: 1. 5 (5.8%) 2. 6 (6.8%) 3. 5 (5.8%) 4. 1 (2.4%) *Excluding 3 clinical sites with unreliable data	Change in LDL-C from baseline to week 12 1. -36.2% 4. 2.0% Treatment difference -38.2% 95% CI -46.9 to -29.4) P<0.001 1. -36.2% 2. -17.3% Treatment difference -18.9% 95% CI -26.3 to -11.5) P<0.001 1. -36.2% 3. -22.7% Treatment difference -13.5% 95% CI -20.6 to -6.3) P<0.001	N/A	Discontinuation due to AE: 1. 7 (8.2%) 2. 9 (10.2%) 3. 10 (11.6) 4. 2(4.9) P values not provided Serious AE 1. 8 (9.4%) 2. 7 (8%) 3. 9 (10.5%) 4. 1 (2.4%) P values not provided	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear; unclear randomization and allocation concealment methods. Patients in the combination group were younger, more obese and had higher baseline TGs. Performance Bias: low; double-blind, matching placebo Detection Bias: unclear; unclear blinding of outcome assessors Attrition Bias: unclear; majority of patients completed the study in each group (~95%) but slight differences in each group and higher rates of study discontinuation (11-15%). Additional attrition from exclusion of 3 clinical sites. Reporting Bias: unclear; Fraudulent data identified at 3 clinical sites in which subjects in active study drug groups who reported ingestion of study drug had no detectable study drug in samples. Data from these 3 sites were excluded from the analysis (n=81) Other Bias: high; funded by Esperion pharmaceuticals. **Applicability**: Patient: 54% of screened patients were not randomized due to reasons unknown. Lower number of subject on baseline statin therapy than expected in clinical practice could inflate LDL-C lowering effects. Intervention: 180 mg demonstrates maximal LDL-lowering in dose-ranging studies with no significant increase in dose-related laboratory changes (Scr, uric acid, Hgb, BUN) Comparator: No concerns Outcomes: LDL-C is a surrogate outcome. Not powered or designed to evaluate CV outcomes. Setting: Multicenter (78 sites) in the U.S.

Abbreviations [alphabetical order]: ACS = acute coronary syndrome; AE = adverse events; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BUN = blood urea nitrogen; CI = confidence interval; CK = creatinine kinase; CV = cardiovascular; DM = diabetes mellitus; HBV = hepatitis B virus; HCV = hepatitis C virus; HeFH = heterozygous familial hypercholesterolemia; HgA1C = hemoglobin A1C; Hgb = hemoglobin; ITT = intention to treat; mITT = modified intention to treat; LDL = low density lipoprotein; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; SBP = systolic blood pressure; SCr = serum creatinine; TG = triglycerides; ULN = upper limit of normal

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
cholestyramine (with sugar)	CHOLESTYRAMINE	POWD PACK	Y
cholestyramine (with sugar)	QUESTRAN	POWD PACK	Y
cholestyramine (with sugar)	CHOLESTYRAMINE	POWDER	Y
cholestyramine (with sugar)	QUESTRAN	POWDER	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	POWD PACK	Y
cholestyramine/aspartame	PREVALITE	POWD PACK	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	POWDER	Y
cholestyramine/aspartame	PREVALITE	POWDER	Y
cholestyramine/aspartame	QUESTRAN LIGHT	POWDER	Y
evolocumab	REPATHA SURECLICK	PEN INJCTR	Y
evolocumab	REPATHA SYRINGE	SYRINGE	Y
evolocumab	REPATHA PUSHTRONEX	WEAR INJCT	Y
ezetimibe	EZETIMIBE	TABLET	Y
ezetimibe	ZETIA	TABLET	Y
fenofibrate	FENOFIBRATE	TABLET	Y
alirocumab	PRALUENT PEN	PEN INJCTR	N
colesevelam HCl	COLESEVELAM HCL	POWD PACK	N
colesevelam HCl	WELCHOL	POWD PACK	N
colesevelam HCl	COLESEVELAM HCL	TABLET	N
colesevelam HCl	WELCHOL	TABLET	N

colestipol HCl	COLESTID	GRANULES	N
colestipol HCl	COLESTIPOL HCL	GRANULES	N
colestipol HCl	COLESTID	PACKET	N
colestipol HCl	COLESTIPOL HCL	PACKET	N
colestipol HCl	COLESTID	TABLET	N
colestipol HCl	COLESTIPOL HCL	TABLET	N
fenofibrate	FENOFIBRATE	CAPSULE	N
fenofibrate	LIPOFEN	CAPSULE	N
fenofibrate	FENOFIBRATE	TABLET	N
fenofibrate	FENOGLIDE	TABLET	N
fenofibrate nanocrystallized	FENOFIBRATE	TABLET	N
fenofibrate nanocrystallized	TRICOR	TABLET	N
fenofibrate nanocrystallized	TRIGLIDE	TABLET	N
fenofibrate,micronized	ANTARA	CAPSULE	N
fenofibrate,micronized	FENOFIBRATE	CAPSULE	N
fenofibric acid	FENOFIBRIC ACID	TABLET	N
fenofibric acid	FIBRICOR	TABLET	N
fenofibric acid (choline)	FENOFIBRIC ACID	CAPSULE DR	N
fenofibric acid (choline)	TRILIPIX	CAPSULE DR	N
gemfibrozil	GEMFIBROZIL	TABLET	N
gemfibrozil	LOPID	TABLET	N
icosapent ethyl	VASCEPA	CAPSULE	N
inositol	INOSITOL	TABLET	N
inositol	INOSITOL	TABLET	N
lomitapide mesylate	JUXTAPID	CAPSULE	N
niacin	NIACIN	CAPSULE ER	N
niacin	NIACIN	CAPSULE ER	N
niacin	NIACIN ER	TAB ER 24H	N
niacin	NIASPAN	TAB ER 24H	N
niacin	NIACIN	TABLET	N
niacin	NIACIN	TABLET	N
niacin	NIACOR	TABLET	N
niacin	NIACIN	TABLET ER	N
niacin	SLO-NIACIN	TABLET ER	N
omega-3 acid ethyl esters	LOVAZA	CAPSULE	N
omega-3 acid ethyl esters	OMEGA-3 ACID ETHYL ESTERS	CAPSULE	N
choline	CHOLINE	TABLET	
niacin	NIACIN	TABLET ER	
niacin	NIACIN	TABLET ER	

niacin	NIADELAY	TABLET ER
niacin	SLO-NIACIN	TABLET ER
niacin (inositol niacinate)	NIACIN INOSITOL	CAPSULE
niacinamide	NIACINAMIDE	TABLET
niacinamide	NIACINAMIDE	TABLET

Appendix 2: Medline Search Strategy

Database: Ovid MEDLINE(R) <2019 to May Week 4 2020>

Search Strategy:

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1 (Cholestyramine Resin or Colesevelam Hydrochloride or Colestipol or Docosahexaenoic Acids or Eicosapentaenoic acid or ezetimibe or ezetimibe, simvastatin drug combination or Fatty acids, Omega-3 or Fenofibrate or Fenofibrate micronized or Gemfibrozil or Icosapent ethyl or Fenofibric acid or Niacin or Nicotinamide or Nicotinic acid or Lovaza or Bile acid sequestrants or Statin, high-intensity or alirocumab or evolocumab or psck9 inhibitors).af. (38939)

2 (Coronary Artery Disease or Coronary Disease or Dyslipidemia or Dyslipidemias or Hypertriglyceridemias or Myocardial Infarction or Stroke or Cardiovascular Disease or Cardiovascular Diseases).af. (457555)

3 ((Cholestyramine Resin or Colesevelam Hydrochloride or Colestipol or Docosahexaenoic Acids or Eicosapentaenoic acid or ezetimibe or ezetimibe, simvastatin drug combination or Fatty acids, Omega-3 or Fenofibrate or Fenofibrate micronized or Gemfibrozil or Inositol or Icosapent ethyl or Fenofibric acid or Niacin or Nicotinamide or Nicotinic acid or Lovaza or Bile acid sequestrants or Statin, high-intensity or Lomitapide or Mipomersen or alirocumab or evolocumab or psck9 inhibitors) and (Coronary Artery Disease or Coronary Disease or Dyslipidemia or Dyslipidemias or Hypertriglyceridemias or Myocardial Infarction or Stroke or Cardiovascular Disease or Cardiovascular Diseases)).af. (4436)

4. to (english language and humans and yr="2019 -Current" and (clinical trial, all or clinical trial, phase iii or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or "systematic review")) (23)

Appendix 3: Prescribing Information Highlights

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

NEXLETOL (bempedoic acid) tablets, for oral use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
NEXLETOL is an adenosine triphosphate-citrate lyase (ACL) inhibitor indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C. (1)

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

----------DOSAGE AND ADMINISTRATION----------
Administer 180 mg orally once daily with or without food. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 180 mg (3)

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

----------WARNINGS AND PRECAUTIONS----------
- *Hyperuricemia*: Elevations in serum uric acid have occurred. Assess uric acid levels periodically as clinically indicated. Monitor for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate. (5.1)
- *Tendon Rupture:* Tendon rupture has occurred. Discontinue NEXLETOL at the first sign of tendon rupture. Avoid NEXLETOL in patients who have a history of tendon disorders or tendon rupture. (5.2)

----------ADVERSE REACTIONS----------
Most common (incidence ≥ 2% and greater than placebo) adverse reactions are upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Esperion at 833-377-7633 (833 ESPRMED) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- *Simvastatin:* Avoid concomitant use of NEXLETOL with simvastatin greater than 20 mg. (7)
- *Pravastatin:* Avoid concomitant use of NEXLETOL with pravastatin greater than 40 mg. (7)

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy*: Based on mechanism of action, may cause fetal harm. (8.1)
- *Lactation*: Breastfeeding is not recommended with NEXLETOL. (8.2)

SEE 17 FOR PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

REVISED: 02/2020

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEXLIZET™ safely and effectively. See full prescribing information for NEXLIZET.

NEXLIZET (bempedoic acid and ezetimibe) tablets, for oral use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------

NEXLIZET, which contains an adenosine triphosphate-citrate lyase (ACL) inhibitor and a cholesterol absorption inhibitor, is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C. (1)

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

----------DOSAGE AND ADMINISTRATION----------

- Administer one tablet (180 mg bempedoic acid and 10 mg ezetimibe) orally once daily with or without food. (2.1)
- Swallow the tablet whole. (2.1)
- Coadministration with Bile Acid Sequestrants: Administer at least 2 hours before or at least 4 hours after bile acid sequestrants. (2.2, 7)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 180 mg bempedoic acid/10 mg ezetimibe (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to ezetimibe tablets. (4, 6.2)

----------WARNINGS AND PRECAUTIONS----------

- *Hyperuricemia*: Elevations in serum uric acid have occurred. Assess uric acid levels periodically as clinically indicated. Monitor for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate. (5.1)
- *Tendon Rupture:* Tendon rupture has occurred. Discontinue NEXLIZET at the first sign of tendon rupture. Avoid NEXLIZET in patients who have a history of tendon disorders or tendon rupture. (5.2)

----------ADVERSE REACTIONS----------

Most common (incidence ≥2% and greater than placebo) adverse reactions are upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes, diarrhea, arthralgia, sinusitis, fatigue, and influenza. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Esperion at 833-377-7633 (833 ESPRMED) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Simvastatin: Avoid concomitant use of NEXLIZET with simvastatin great than 20 mg. (7)
- *Pravastatin:* Avoid concomitant use of NEXLIZET with pravastatin greater than 40 mg. (7)
- *Cyclosporine:* Monitor cyclosporine concentrations. (7)
- *Fibrates:* If cholelithiasis is suspected in a patient receiving NEXLIZET and fenofibrate, consider alternative lipid-lowering therapy. (6.2, 7)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy*: Based on mechanism of action, may cause fetal harm. (8.1)
- *Lactation*: Breastfeeding is not recommended with NEXLIZET. (8.2)

SEE 17 FOR PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

REVISED: 02/2020

PCSK9 Inhibitors

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

- All PCSK9 inhibitors

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: Baseline LDL-C _____ mg/dL Date:_____ 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:** Approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	**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. Is the patient adherent with PCSK9 inhibitor therapy?	**Yes:** Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (PCSK9 inhibitor prescription refilled 10 months' supply in last 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	Pitavastatin 1-4 mg Pravastatin 40-80 mg Simvastatin 20-40 mg Rosuvastatin 5-10 mg

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

Omega-3 Fatty Acids

Goal(s):

- Restrict use of non-preferred omega-3 fatty acids to patients at increased risk for pancreatitis.
- Promote use of agents that have demonstrated a substantial benefit on cardiovascular outcomes that is consistent with medical evidence

Length of Authorization:

- Up to 12 months

Requires PA:

- Icosapent Ethyl (Vascepa®)

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. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4
4. Does the patient have clinically diagnosed hypertriglyceridemia with triglyceride levels ≥ 500 mg/dL?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Has the patient failed or have a contraindication to an adequate trial (at least 8 weeks) of a fibric acid derivative (fenofibrate or gemfibrozil) at a maximum tolerable dose (as seen in dosing table below); **OR** Is the patient taking a statin and unable to take a fibric acid derivative due to an increased risk of myopathy?	**Yes:** Approve up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of other agent(s).
6. Is the prescription for icosapent ethyl?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Does the patient have established clinical atherosclerotic cardiovascular disease (ASCVD), (defined as documented history of acute coronary syndrome, ischemic stroke, peripheral artery disease, coronary artery disease) or type 2 diabetes mellitus and ≥ 2 CV risk factors?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Does the patient have triglycerides greater than or equal to 150 mg/dl while on maximally tolerated statin treatment?	**Yes:** Approve up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness.

Table 1: Dosing of Fenofibrate and Derivatives for Hypertriglyceridemia.

Trade Name (generic)	Recommended dose	Maximum dose
Antara (fenofibrate capsules)	43-130 mg once daily	130 mg once daily
Fenoglide (fenofibrate tablet)	40-120 once daily	120 mg once daily
Fibricor (fenofibrate tablet)	25-105 mg once daily	105 mg once daily
Lipofen (fenofibrate capsule)	50-150 mg once daily	150 mg once daily
Lofibra (fenofibrate capsule)	67-200 mg once daily	200 mg once daily
Lofibra (fenofibrate tablet)	54-160 mg once daily	160 mg once daily
Lopid (gemfibrozil tablet)	600 mg twice daily	600 mg twice daily
Tricor (fenofibrate tablet)	48-145 mg once daily	145 mg once daily
Triglide (fenofibrate tablet)	50-160 mg once daily	160 mg once daily
Trilipix (fenofibrate DR capsule)	45-135 mg once daily	135 mg once daily

Bempedoic Acid

Goal(s):

- Promote use of bempedoic acid that is consistent with medical evidence
- Promote use of high value products

Length of Authorization:

- Up to 12 months

Requires PA:

- 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. What diagnosis is being treated?	Record ICD10 code; go to #2

Approval Criteria		
2. 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 #3	**No:** Go to #6

Approval Criteria		
3. 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 #4 1. Statin: Dose: Date Initiated: 2. Ezetimibe 10 mg daily Date Initiated: Baseline LDL-C _____ Date:_____ Recent LDL-C _____ Date:_____	**No:** Go to #5
4. Is the patient adherent with a high-intensity statin and ezetimibe?	**Yes:** Go to #8 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
5. 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? 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 Go to #8 Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness

Approval Criteria		
6. 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 #7	**No:** Pass to RPh; deny for medical appropriateness.
7. Does the patient still have a LDL-C of ≥ 100 mg/dl while taking a maximally tolerated statin and ezetimibe?	**Yes:** Go to #8 Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness.
8. Does the patient have a history of gout or hyperuricemia?	**Yes:** Pass to RPh; deny for medical appropriateness.	**No:** Approve for up to 12 months

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	Pitavastatin 1-4 mg Pravastatin 40-80 mg Simvastatin 20-40 mg Rosuvastatin 5-10 mg

P&T / DUR Review: *08/20 (MH)*
Implementation: *9/1/20*