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Drug Class Update with New Drug Evaluation: Other Dyslipidemia Drugs

Date of Review: August 2021

Generic Name: Evinacumab-dgnb

Date of Last Review: August 2020
Dates of Literature Search: 05/31/2020 – 06/01/2021
Brand Name (Manufacturer): Evkeeza™ (Regeneron)
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 evinacumab 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 evinacumab 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 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%.[1] 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.

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- There is high quality evidence that alirocumab significantly reduces LDL-C compared to placebo in adults with homozygous familial hypercholesterolemia (HoFH) on background statin therapy with a percent change reduction from baseline at week 12 of -26.9% versus 8.6%. There is insufficient evidence that alirocumab reduces risk of CVD or mortality in patients with HoFH. [2]
- There is moderate quality evidence that omega-3 fatty acids 4 grams per day over 3 years does not reduce CV outcomes compared to corn oil in high CV risk patients on stable statin therapy. [3]
- There is high quality evidence based on one study with a high magnitude of benefit that evinacumab significantly reduces LDL-C compared to placebo at 24 weeks (-47% vs. 2%, respectively; difference -49%; 95% Confidence Interval [CI] -65% to -33.1%) in adults with homozygous familial hypercholesterolemia (HoFH) on maximally tolerated lipid lowering therapy. [4] However, there is no data evaluating evinacumab on clinical outcomes, including CV events, CV mortality and all-cause mortality. Data in pediatric and elderly patients are insufficient.
- There is insufficient evidence evaluating the efficacy and safety in patient with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).
- Evinacumab is associated with hypersensitivity reactions and is considered teratogenic. It should not be used in pregnancy. The overall study sample is small and currently lacks adequate safety data to detect additional adverse events.

Recommendations:

- Due to its unknown benefit on CV outcomes and limited use to HoFH, make evinacumab non-preferred and include prior authorization to limit utilization to patients with HoFH requiring additional LDL-lowering on maximally tolerated lipid lowering therapies.
- After evaluation of comparative costs in executive session, no PDL changes were recommended.

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 results in a modest (2%) improvement in CV outcomes with a long duration of follow-up (approximately 7 years).[5]
- 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.[6] 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%).[7]
- 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).[8]

- 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.
- 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.

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.[9] 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. [9]

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.[10] 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.[5] 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.[10] Additionally, a moderate-intensity statin was used as the study comparator, which is not consistent with current practice recommendations.[5]

Evolocumab (Repatha®) and alirocumab (Praluent®) are subcutaneously injected human monoclonal antibodies that reduce LDL-C by inhibiting PCSK9.[11, 12] PCSK9 promotes the degradation of the LDL receptor, resulting in an increase in plasma LDL-C. Both agents are effective at lowering LDL-C with reductions of up to 60% when combined with statin therapy. Both agents are approved as an adjunct with other lipid-lowering therapies (statins, ezetimibe) for primary hyperlipidemia (heterozygous familial hypercholesterolemia) and in patients with clinical ASCVD who require additional lowering of LDL-C. Additionally, they are both FDA approved for the risk reduction of MI, stroke, and coronary revascularization in adults with established CVD based on clinical outcome data from the FOURIER and ODYSSEY OUTCOMES trial **(Tables 1 and 2).**[8, 11 7] 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.[6] Icosapent ethyl gained FDA approval as an add-on therapy to reduce CV events for adults with elevated triglycerides (≥ 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. [6]

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.[13] 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.[14]

Table 1: Characteristics of Cardiovascular Outcome trials for Non-statins[5-8]

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

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

Table 2: Summary of Results from Cardiovascular Outcome Trials[5-8]

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

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. [15] 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.[16] 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.

Methods:

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

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

Systematic Reviews:

After review, 13 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses),[17-20] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), drug (not FDA approved)[21] or outcome studied (e.g., LDL-C).[22, 23 24-29]

- A Cochrane Collaboration systematic review aimed to evaluate the effectiveness and safety of PCSK9 inhibitors for prevention of CVD.[1] RCTs with at least 24 weeks of follow-up comparing alirocumab or evolocumab to placebo or active treatments were included. The primary efficacy outcomes were composite endpoint of CVD, all-cause mortality, MI, and stroke. Twenty-four studies were included (n=60,997). Eighteen trials included alirocumab and six trials included evolocumab. [1] All but one study, were industry-sponsored, multicenter trials and the majority included patients with either established CVD or high CV risk. Most of the trials had low or unclear risk of bias. Four studies were open-label and had high risk of performance bias and detection bias, and 7 studies had high risk of attrition bias.

  There was high certainty evidence (10 studies) that, compared to placebo, alirocumab decreased the risk of CVD (absolute risk difference [RD] -2%; OR 0.87; 95% CI 0.80-0.94), mortality (RD -1%; OR 0.83; 95% CI 0.72 to 0.96), and MI (RD -2%; OR 0.86; 95% CI 0.79 to 0.94). [1] There was low-certainty evidence, few supporting studies, and a small absolute difference between alirocumab and active treatment (ezetimibe and/or statins for CVD (RD 1%; OR 1.37; 95% CI 0.65 to 3.87) and mortality (RD -1%; OR 0.51; 95% CI 0.18 to 1.40) demonstrating no significant benefit. [1] Results were consistent for evolocumab compared to placebo with high-certainty evidence for a reduction in CVD (RD -2%; OR 0.84; 95% CI 0.78 to 0.91) and MI (RD -1%; OR 0.72; 95% CI 0.64 to 0.82) with slightly smaller absolute difference and fewer supporting studies. [1] There was no significant difference in all-cause mortality (OR 1.04; 95% CI 0.91 to 1.19) with evolocumab compared to placebo. Compared to active treatment (ezetimibe and/or statins), there was low-certainty evidence with a small absolute difference with evolocumab on CVD (RD <1%; OR 0.66; 95% CI 0.14 to 3.04), MI (RD <1%; OR 0.66; 95% CI 0.23 to 1.85) and mortality (RD < 1%; OR 0.43; 95% CI 0.14 to 1.30) with no clear decreased risk. [1] Evidence was rated as low certainty based on low number of events and open-label treatment allocation.

The authors concluded that there is strong evidence supporting PCSK9 inhibitors for those not eligible for other lipid-lowering therapies or who cannot meet their lipid goals despite standard treatments, but the evidence base comparing PCSK9 inhibitors with ezetimibe and statins is much weaker and it remains unknown if these agents can be used as replacement therapies. Furthermore, the absolute risk reduction remains small (often less than 1%) for all clinical outcomes. Evidence regarding PCSK9 inhibitors for treatment of people at low risk remains uncertain and long-term efficacy and safety beyond 3 years is lacking. There is very limited evidence overall on any potential safety issues of evolocumab and alirocumab.

- The Institute for Clinical and Economic Review (ICER) evaluated bempedoic acid with or without ezetimibe and inclisiran in the treatment of HeFH.[30] Since inclisiran has not been FDA approved, this review will focus on the findings for bempedoic acid. The authors of this review compared the efficacy, safety and effectiveness of bempedoic acid to maximally tolerated lipid-lowering therapy (placebo arm). A pairwise meta-analysis for primary and secondary outcomes was conducted. Five Phase III RCTs including bempedoic acid were included. LDL-C was the primary outcome for all included trials. [30] Three of the studies were good quality based on the United States Preventive Services Task Force (USPSTF) criteria and two were fair quality because of differential loss to follow-up. The authors found a significant reduction in LDL-C from baseline with bempedoic acid compared to placebo in patients on maximally tolerated lipid lowering therapy (difference -19.5%; 95% CI -22.7 to -16.4; $p<0.0001$; $I^2=69\%$) with high heterogeneity due to different populations studied and differences in the intervention and comparison group. [30] There are insufficient data evaluating bempedoic acid on clinical outcomes. A five-year ongoing clinical outcome study is expected to be completed in 2022. However, all-cause mortality and CV outcomes were included in the safety analysis in two studies. An analysis of this data found nonsignificant increases in all-cause mortality (RR 2.25; 95% CI 0.76 to 6.67) and CV mortality (RR 1.52; 95% CI 0.41 to 5.70) and decreases in non-fatal MI (RR 0.54; 95% CI 0.25 to 1.15) and major adverse cardiovascular events (MACE) (RR 0.79; 95% CI 0.58 to 1.07). [30] Number of events were very small for all outcomes and results are imprecise. There was a slightly higher incidence of serious adverse events and discontinuations due to adverse events with bempedoic acid compared to placebo in all trials. The most common events that led to discontinuation were diarrhea, muscle related events, elevated liver enzymes and headache.

New Guidelines:
No new high-quality guidelines identified.

New Formulations or Indications:
In April 2021, alirocumab was FDA approved as an adjunct to other LDL-C lowering therapies in adults with HoFH to reduce LDL-C.[31] Approval was based on data from the ODYSSEY HoFH trial (**Table 3).** [2] Previous FDA labeling included patients with established CVD and HeFH. The ODYSSEY HoFH trial demonstrated a significant reduction in LDL-C in adults with HoFH on background statin therapy (97%) compared to placebo. There is no data evaluating CV outcomes or all-cause mortality in HoFH. There were no differences in serious adverse events and no discontinuations due to adverse events in either group.

New FDA Safety Alerts:
No new FDA Safety Alerts

Randomized Controlled Trials:
A total of 13 citations were manually reviewed from the initial literature search. After further review, 8 citations were excluded because of wrong study design (e.g., observational, post-hoc analysis)[32-35], comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[36.37-39] Trials identified which evaluated evinacumab are included below. The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
ODYSSEY HoFH[2] MC, PC, PG, DB, RCT	Alirocumab 150 mg SC Q 2 weeks vs. placebo 12 weeks	Adults with HoFH and LDL-C ≥70 mg/dl on background statin therapy or intolerance (n=69)	Percent change in LDL-C from baseline to week 12	<u>% Change in LDL-C:</u> Alirocumab: -26.9% Placebo 8.6% Difference -35.6 (95% CI -51.2% to -19.9%) P<0.0001
STRENGTH[3] DB, MC, RCT	Omega-3 fatty acids (carboxylic acid formulation) 4gm/day vs. matching corn oil 3 years	Adults at high risk for CV event on statin therapy (n=33,047)	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina	<u>CV Composite outcome:</u> Omega-3: 785 (12%) Corn Oil: 795 (12.2%) HR 0.99; 95% CI 0.90 to 1.09
Prespecified analysis of ODYSSEY OUTCOMES RCT[40]	Alirocumab versus placebo	Adults with recent ACS on maximally tolerated statin (n=18,924)	PAD and VTE events	<u>PAD Events:</u> Alirocumab: 101 (1.1%) Placebo: 145 (1.5%) HR 0.69; 95% CI 0.54 to 0.89 <u>VTE events:</u> Alirocumab: 37 (0.4%) Placebo: 55 (0.6%) HR 0.67; 95% CI 0.44 to 1.01

Abbreviations: ACS: acute coronary syndrome; CV = cardiovascular; DB=double blind; HoFH: homozygous familial hypercholesteremia; HR = hazard ratio; LDL-C: low density lipoprotein cholesterol; MC = multicenter; MI = myocardial infarction; PAD = peripheral artery disease; PC= placebo controlled; PG = parallel group; RCT = randomized controlled trial; SC= subcutaneous; VTE= venous thromboembolism

<u>NEW DRUG EVALUATION:</u> Evinacumab (Evkeeza)

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

Clinical Efficacy:
Evinacumab is a fully human recombinant monoclonal antibody that inhibits angiopoietin-like 3 (ANGPTL3), an enzyme involved in lipid metabolism. Inhibition of ANGPTL3 allows enhanced lipoprotein lipase activity, resulting in a reduction in LDL-C independent of the LDL-C receptor. It is indicated as an adjunct to other LDL-C lowering therapies for the treatment of adult and pediatric patients aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH).[41]

It was FDA approved based on a single 24-week double-blinded, multicenter, placebo-controlled, randomized trial in adult and adolescent patients with HoFH as defined by genotyping or clinical criteria, LDL-C ≥70 mg/dL, and on maximally tolerated lipid lowering therapy **(Table 6).**[4] Lipid lowering therapy was defined as daily statin, ezetimibe, and a PCSK9 inhibitor. The genetic diagnosis included a variant in two *LDLR* alleles or the presence of variants in apolipoprotein B (APOB) or PCSK9. Clinical criteria were defined as total cholesterol > 500 mg/dl with or without the presence of xanthomas. A single trial was considered acceptable by FDA due to the rarity of HoFH and the magnitude of effect with evinacumab compared to placebo.[15] After an 8-week run-in period for genotyping and stabilization of background lipid lowering therapy, patients were randomized 2:1 to receive evinacumab 15 mg/kg intravenously (IV) every 4 weeks or placebo.[4] The primary outcome was the percent reduction from baseline to Week 24 in calculated LDL-C.

Patients treated with evinacumab experienced a 47% reduction in LDL-C compared to an increase by 2% in the placebo group (difference -49%; 95% CI -65 to -33.1).[4] The difference was observed as early as Week 4. The absolute change from baseline in calculated LDL-C was -134.7 mg/dl with evinacumab and -2.6 mg/dl with placebo. Fifty-six percent of patients on evinacumab had a 50% or greater reduction from baseline LDL compared to 5% on placebo (OR 24.2; 95% CI 3 to 195.6).[4] However, this finding was imprecise with an extremely wide confidence interval. There were no obvious effects on LDL-C lowering ability based on HoFH mutation, baseline LDL-C or background lipid lowering therapy. Patients in the evinacumab also had significantly lower levels of apolipoprotein B, non-HDL cholesterol and total cholesterol compared to those in the placebo group. Patients were entered in a 48-week open-label extension study after completion of the 24-week double-blinded period. Efficacy was maintained from 24 weeks to 48 weeks in those previously treated with evinacumab.[15]

Risk of bias was low to unclear. Given the small sample size, there were differences in baseline characteristics between the two groups. More patients with null-null LDL-receptor variants (< 15% activity) were in the evinacumab group (35%) compared to placebo (27%), which is expected to be a more difficult to treat population. There was a higher baseline LDL-C in evinacumab compared to placebo (260 mg/dl vs. 247 mg/dl) and more individuals 65 years of age and older in the evinacumab group (19%) compared to placebo (0%). There were also imbalances in background lipid lowering therapy between groups, with 70% of patients in the evinacumab group on at least three lipid lowering therapies and only 50% in the placebo group.

Only 2 pediatric patients were randomized and enrolled. The clinical diagnostic criteria used for enrollment was more liberal than typically used in practice (total cholesterol > 500 mg/dl vs. LDL-C > 500 mg/dl). Therefore, the trial likely included patients with less severe disease than what would be seen in practice. Older patients and pediatric patients were poorly represented in the study, and it is difficult to generalize results to these populations. The FDA review notes that an additional 11 pediatric participants were enrolled in an ongoing open-label study. Efficacy and safety have not been established in patients with HeFH or established ASCVD who require additional LDL-C lowering and it should not be used off-label for these indications at this time.

Clinical Safety:
Evinacumab was generally well tolerated and there were no differences in overall or mild adverse events between evinacumab and placebo. Antidrug antibodies did not develop during the treatment period in any of the patients in the primary 24-week efficacy trial. In the FDA pooled safety analysis, more serious adverse events were experienced by patients exposed to evinacumab compared to placebo (9.9% vs. 1.9%). There appears to be a dose-dependent relationship of serious adverse events with increasing evinacumab exposure. However, only one serious adverse event, anaphylactic reaction, was determined to be drug

related. In the pooled analysis, 3.4% of evinacumab patients discontinued the drug due to adverse events compared to 1.9% of placebo-treated patients. The most common adverse reactions that occurred more frequently than placebo is included in **Table 4**. Evinacumab is associated with hypersensitivity, including infusion reactions and anaphylaxis. Infusion reactions were reported in 6 (7%) of patients treated with evinacumab and 2(4%) of patients treated with placebo. There were no reports of rhabdomyolysis, significant creatine kinase (CK) elevations, or hepatic dysfunction. However, there is not enough safety data or sample size to detect low risk adverse events. Transient increases in blood pressure and heart rate during infusion were also observed. Based on nonclinical data, evinacumab is teratogenic and this is included as a warning and precaution in drug labeling.

Table 4: Adverse Reactions Occurring in >3% of Patients and Greater than Placebo[41]

Reactions	**Placebo (N = 54) %**	**Evinacumab (N = 81) %**
Nasopharyngitis	13%	16%
Influenza like illness	6%	7%
Dizziness	0%	6%
Rhinorrhea	0%	5%
Nausea	2%	5%

Comparative Endpoints:

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

Primary Study Endpoint:
1) Percent change in LDL-C from baseline to week 24

Table 5. Pharmacology and Pharmacokinetic Properties.[41]

Parameter	
Mechanism of Action	Evinacumab is a recombinant human monoclonal antibody that binds to and inhibits ANGPTl3, which is expressed in the liver and plays a role in the regulation of lipid metabolism by inhibiting lipoprotein lipase and endothelial lipase. Inhibition of ANGPTL3 leads to reduction in LDL-C, HDL-C and TG independent of the presence of LDL receptor by promoting VLDL processing and clearance upstream of LDL formation.
Oral Bioavailability	N/A: administered intravenously
Distribution and Protein Binding	4.8 L
Elimination	At higher concentrations, elimination is primarily through a non-saturable proteolytic pathway. At lower concentrations, eliminated through non-linear pathways.
Half-Life	Approximately 19 weeks
Metabolism	Not been characterized; expected to be degraded into small peptides and amino acids via catabolic pathways
Abbreviations: ANGPTL3: angiopoietin-like 3; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; VLDL: very low density lipoprotein	

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. ELIPSE HoFH[4] Part 1: DB, PC, PG, MC, RCT	1. Evinacumab (EVB) 15 mg/kg IV Q4W 2. Placebo 24 weeks	Demographics: 74% white Mean age 42 y/o 94% on statin 77% PCSK9 inhibitor 75% on ezetimibe Mean LDL 255 mg/dl 52% CVD Key Inclusion Criteria: ≥12 years of age with HoFH (genetic confirmation or clinical criteria) Key Exclusion Criteria: Tanner stage <2, LDL-C < 70 mg/dl, unstable background therapy, uncontrolled endocrine disease, unstable weight, HbA1c > 9%, recent CV event, NYHA class IV heart failure, SBP > 160 mm Hg, active malignancy, eGFR < 30 ml/min, AST/ALT > 3x ULN, CPK > 3 x ULN, TSH > 1.5x ULN, pregnant or breastfeeding, of childbearing potential unwilling to practice effective birth control	ITT: 1. 43 2. 22 PP: 1. 44 2. 21 Attrition: 1. 0 2. 0	Primary Endpoint: Percent change in LDL-C from baseline to week 24 1. -47.1% 2. + 1.9% LS mean difference -49%; 95% CI -65 to -33) P<0.001 Secondary Endpoints: Patients with ≥50% reduction from baseline in LDL-C 1. 24 (56%) 2. 1 (5%) OR 24.2; 95% CI 3.0-195.6 P=0.003	NA ARR 51%/ NNT 2	Discontinuations due to adverse events: 1. 0 2. 0 Serious adverse events: 1. 2 (5%) 2. 0 (0%)	NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear; randomized using an interactive voice response system. More patients > 65 y/o in EVB arm versus placebo (19% vs. 0%), differences in baseline genotype and background therapy. Performance Bias: low; double-blinded, double dummy design. Potential unblinding due to hypersensitivity reactions but low incidence. Detection Bias: unclear; objective outcomes, but unclear if outcome assessors blinded Attrition Bias: low; efficacy analyses performed on ITT population; missing data imputed using mixed model repeated measured Reporting Bias: low; outcomes reported as prespecified Other Bias: unclear; Sponsored by Regeneron Pharmaceuticals who designed the trial protocol, selected participating sites. **Applicability**: Patient: Only 2 adolescent patients were included in the trial. Data cannot be generalized to high-risk CV populations who do not have HoFH. Intervention: Dose selection based on phase 2 data Comparator: placebo appropriate comparator with background lipid lowering therapy. Outcomes: Data on LDL-C only, which is a surrogate outcome. Study was not powered or designed to evaluate CV outcomes. Setting: multicenter study in 30 centers in 11 countries; majority outside of the U.S. (85%). 6 participating sites in the U.S. with 10 enrolled patients.

Abbreviations [alphabetical order]:ALT = alanine transaminase; AST = aspartate transaminase; ARR = absolute risk reduction; CI = confidence interval; CPK = creatine phosphokinase; CV = cardiovascular; CVD = cardiovascular disease; DB = double blind; eGFR = estimated glomerular filtration rate; HoFH = homozygous familial hypercholesterolemia; ITT = intention to treat; IV = intravenously; LDL-C = low density lipoprotein cholesterol; LS = least squares; mITT = modified intention to treat; N = number of subjects; MC = multicenter; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NYHA = new York heart association; OR = odds ratio; PC = placebo controlled; PCSK9 = proprotein convertase subtilsin-kexin type 9; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; TSH = thyroid stimulating hormone; ULT = upper limit of normal; Q4W = every 4 weeks; y/o = years old.

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Appendix 1: Current Preferred Drug List

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

colesevelam HCl	COLESEVELAM HCL	ORAL	TABLET	N
colesevelam HCl	WELCHOL	ORAL	TABLET	N
colestipol HCl	COLESTID	ORAL	GRANULES	N
colestipol HCl	COLESTIPOL HCL	ORAL	GRANULES	N
colestipol HCl	COLESTID	ORAL	PACKET	N
colestipol HCl	COLESTIPOL HCL	ORAL	PACKET	N
colestipol HCl	COLESTID	ORAL	TABLET	N
colestipol HCl	COLESTIPOL HCL	ORAL	TABLET	N
fenofibrate	FENOFIBRATE	ORAL	CAPSULE	N
fenofibrate	LIPOFEN	ORAL	CAPSULE	N
fenofibrate	FENOFIBRATE	ORAL	TABLET	N
fenofibrate	FENOGLIDE	ORAL	TABLET	N
fenofibric acid	FENOFIBRIC ACID	ORAL	TABLET	N
fenofibric acid	FIBRICOR	ORAL	TABLET	N
gemfibrozil	GEMFIBROZIL	ORAL	TABLET	N
gemfibrozil	LOPID	ORAL	TABLET	N
icosapent ethyl	ICOSAPENT ETHYL	ORAL	CAPSULE	N
icosapent ethyl	VASCEPA	ORAL	CAPSULE	N
inositol	INOSITOL	ORAL	TABLET	N
lomitapide mesylate	JUXTAPID	ORAL	CAPSULE	N
niacin	NIACIN	ORAL	CAPSULE ER	N
niacin	NIACIN ER	ORAL	TAB ER 24H	N
niacin	NIASPAN	ORAL	TAB ER 24H	N
niacin	NIACIN	ORAL	TABLET	N
choline	CHOLINE	ORAL	TABLET	
niacin	NIACIN	ORAL	TABLET ER	
niacin	NIADELAY	ORAL	TABLET ER	
niacin (inositol niacinate)	NIACIN INOSITOL	ORAL	CAPSULE	
niacinamide	NIACINAMIDE	ORAL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

- Blom D, Harada-Shiba M, Rubba P, et al. Efficacy and Safety of Alirocumab in Adults with Homozygous Familial Hypercholesterolemia: The ODYSSEY HoFH Trial. J Am Coll Cardiol. 2020 Jul 14;76(2):131-142. doi: 10.1016/j.jacc.2020.05.027.

  Background: Homozygous familial hypercholesterolemia (HoFH) is characterized by extremely elevated low-density lipoprotein-cholesterol (LDL-C) levels and early onset atherosclerotic cardiovascular disease despite treatment with conventional lipid-lowering treatment.

  Objectives: This study was designed to assess LDL-C reduction with the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab in adult patients with HoFH.

  Methods: This randomized, double-blind, placebo-controlled, parallel-group, phase 3 study evaluated efficacy and safety of alirocumab 150 mg every 2 weeks. The primary endpoint was percent reduction from baseline in LDL-C versus placebo after 12 weeks of treatment.

  Results: Patients (N = 69) were randomized 2:1 to alirocumab or placebo. At baseline, background lipid-lowering treatment included 67 patients receiving statin (59 patients on high-intensity statin); 50 patients on ezetimibe; 10 patients on lomitapide; and 10 patients undergoing apheresis. Mean baseline LDL-C was 259.6 mg/dl in the placebo group and 295.0 mg/dl in the alirocumab group. At week 12, the least squares mean difference in LDL-C percent change from baseline was -35.6% (alirocumab [-26.9%] vs. placebo [8.6%]; $p < 0.0001$). Reductions (least squares mean difference) in other atherogenic lipids at week 12 were: apolipoprotein B, -29.8%; non-high-density lipoprotein cholesterol, -32.9%; total cholesterol, -26.5%; and lipoprotein(a), -28.4% (all $p < 0.0001$). No serious adverse events, permanent treatment discontinuations, or deaths due to treatment-emergent adverse events were reported during the double-blind treatment period.

  Conclusions: In the largest randomized controlled interventional trial in HoFH patients to date, alirocumab resulted in significant and clinically meaningful reductions in LDL-C at week 12. Alirocumab was generally well tolerated, with a safety profile comparable to that of placebo. (Study in Participants With Homozygous Familial Hypercholesterolemia [HoFH] [ODYSSEY HoFH] NCT03156621.).

- Schwartz G, Steg P, Szarek M, et al. Peripheral Artery Disease and Venous Thromboembolic Events After Acute Coronary Syndrome: Role of Lipoprotein(a) and Modification by Alirocumab: Prespecified Analysis of the ODYSSEY OUTCOMES Randomized Clinical Trial. 2020 May 19;141(20):1608-1617. doi: 10.1161/CIRCULATIONAHA.120.046524. Epub 2020 Mar 29.

  Background: Patients with acute coronary syndrome are at risk for peripheral artery disease (PAD) events and venous thromboembolism (VTE). PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors reduce lipoprotein(a) and low-density lipoprotein cholesterol (LDL-C) levels. Our objective was to ascertain whether PCSK9 inhibition reduces the risk of PAD events or VTE after acute coronary syndrome, and if such effects are related to levels of lipoprotein(a) or LDL-C.

  Methods: This was a prespecified analysis of the ODYSSEY OUTCOMES randomized clinical trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome), which was conducted in 18 924 patients with recent acute coronary syndrome on intensive or maximum-tolerated statin treatment who were randomized to the PCSK9 inhibitor alirocumab or placebo. In a prespecified analysis, PAD events (critical limb ischemia, limb revascularization, or

amputation for ischemia) and VTE (deep vein thrombosis or pulmonary embolism) were assessed. LDL-C was corrected (LDL-Ccorrected) for cholesterol content in lipoprotein(a).

Results: At baseline, median lipoprotein(a) and LDL-Ccorrected were 21 and 75 mg/dL, respectively; with alirocumab, median relative reductions were 23.5% and 70.6%, respectively. PAD events and VTE occurred in 246 and 92 patients, respectively. In the placebo group, risk of PAD events was related to baseline quartile of lipoprotein(a) (Ptrend=0.0021), and tended to associate with baseline quartile of LDL-Ccorrected (Ptrend=0.06); VTE tended to associate with baseline quartile of lipoprotein(a) (Ptrend=0.06), but not LDL-Ccorrected (Ptrend=0.85). Alirocumab reduced risk of PAD events (hazard ratio [HR], 0.69 [95% CI, 0.54-0.89]; P=0.004), with nonsignificantly fewer VTE events (HR, 0.67 [95% CI, 0.44-1.01]; P=0.06). Reduction in PAD events with alirocumab was associated with baseline quartile of lipoprotein(a) (Ptrend=0.03), but not LDL-Ccorrected (Ptrend=0.50). With alirocumab, the change from baseline to Month 4 in lipoprotein(a), but not LDL-Ccorrected, was associated with the risk of VTE and the composite of VTE and PAD events.

Conclusions: In statin-treated patients with recent acute coronary syndrome, risk of PAD events is related to lipoprotein(a) level and is reduced by alirocumab, particularly among those with high lipoprotein(a). Further study is required to confirm whether risk of VTE is related to lipoprotein(a) level and its reduction with alirocumab. Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01663402.

- Nicholls S, LIncoff M, Garia M, et al. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. 2020 Dec 8;324(22):2268-2280. doi: 10.1001/jama.2020.22258.

  Objective: To determine the effects on cardiovascular outcomes of a carboxylic acid formulation of EPA and DHA (omega-3 CA) with documented favorable effects on lipid and inflammatory markers in patients with atherogenic dyslipidemia and high cardiovascular risk.

  Design, setting, and participants: A double-blind, randomized, multicenter trial (enrollment October 30, 2014, to June 14, 2017; study termination January 8, 2020; last patient visit May 14, 2020) comparing omega-3 CA with corn oil in statin-treated participants with high cardiovascular risk, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C). A total of 13 078 patients were randomized at 675 academic and community hospitals in 22 countries in North America, Europe, South America, Asia, Australia, New Zealand, and South Africa.

  Interventions: Participants were randomized to receive 4 g/d of omega-3 CA (n = 6539) or corn oil, which was intended to serve as an inert comparator (n = 6539), in addition to usual background therapies, including statins.

  Main outcomes and measures: The primary efficacy measure was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization.

  Results: When 1384 patients had experienced a primary end point event (of a planned 1600 events), the trial was prematurely halted based on an interim analysis that indicated a low probability of clinical benefit of omega-3 CA vs the corn oil comparator. Among the 13 078 treated patients (mean [SD] age, 62.5 [9.0] years; 35% women; 70% with diabetes; median low-density lipoprotein [LDL] cholesterol level, 75.0 mg/dL; median triglycerides level, 240 mg/dL; median HDL-C level, 36 mg/dL; and median high-sensitivity C-reactive protein level, 2.1 mg/L), 12 633 (96.6%) completed the trial with ascertainment of primary end point status. The primary end point occurred in 785 patients (12.0%) treated with omega-3 CA vs 795 (12.2%) treated with corn oil (hazard ratio,

0.99 [95% CI, 0.90-1.09]; P = .84). A greater rate of gastrointestinal adverse events was observed in the omega-3 CA group (24.7%) compared with corn oil-treated patients (14.7%).

Conclusions and relevance: Among statin-treated patients at high cardiovascular risk, the addition of omega-3 CA, compared with corn oil, to usual background therapies resulted in no significant difference in a composite outcome of major adverse cardiovascular events. These findings do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in high-risk patients.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to June 11, 2021>

1 ezetimibe.mp. or Ezetimibe/ 3797
2 bile acid sequestrants.mp. 472
3 colestipol.mp. or Colestipol/ 546
4 cholestyramine.mp. or Cholestyramine Resin/ 3548
5 colesevelam.mp. or Colesevelam Hydrochloride/ 318
6 alirocumab.mp. 735
7 evolocumab.mp. 799
8 PCSK9 inhibitors.mp. 1052
9 fenofibrate.mp. or Fenofibrate/ 3932
10 gemfibrozil.mp. or Gemfibrozil/ 2222
11 icosapent ethyl.mp. 206
12 omega-3 fatty acids.mp. or Fatty Acids, Omega-3/ 17791
13 niacin.mp. or Niacin/ 13716
14 bempedoic acid.mp. 132
15 evinacumab.mp. 56
16 nonstatin.mp. 324
17 cardiovascular disease.mp. or Cardiovascular Diseases/ 246719
18 atherosclerotic cardiovascular disease.mp. 4366
19 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 45776
20 17 or 18 246719
21 19 and 20 4490
22 limit 21 to (english language and humans and yr="2020 -Current" and (clinical trial, all or meta analysis or randomized controlled trial or "systematic review")) 71
23 from 22 keep 2-5,7,11,16,18,20,23-25,36,40-42,44,46,49,52-54,56 23

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

EVKEEZA™ (evinacumab-dgnb) injection, for intravenous use

Initial U.S. Approval: 2021

INDICATIONS AND USAGE

EVKEEZA is an ANGPTL3 (angiopoietin-like 3) inhibitor indicated as an adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH). (1)

Limitations of Use:

- The safety and effectiveness of EVKEEZA have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH). (1)
- The effects of EVKEEZA on cardiovascular morbidity and mortality have not been determined. (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of EVKEEZA is 15 mg/kg administered by intravenous (IV) infusion once monthly (every 4 weeks). (2.1)
- See the Full Prescribing Information for preparation instructions for the intravenous infusion. (2.2)
- Administer the diluted solution via IV infusion over 60 minutes through an IV line containing a sterile, in-line or add-on, 0.2 micron to 5 micron filter. (2.3)
- Do not mix other medications with EVKEEZA or administer other medications concomitantly via the same infusion line. (2.3)
- The rate of infusion may be slowed, interrupted or discontinued if the patient develops any signs of adverse reactions, including infusion or hypersensitivity reactions. (2.3).

DOSAGE FORMS AND STRENGTHS

- Injection: 345 mg/2.3 mL (150 mg/mL) and 1,200 mg/8 mL (150 mg/mL) solution in single-dose vials. (3)

CONTRAINDICATIONS

- History of serious hypersensitivity reactions to evinacumab-dgnb or to any of the excipients in EVKEEZA. (4)

WARNINGS AND PRECAUTIONS

- *Serious Hypersensitivity Reactions*: Have occurred with EVKEEZA in clinical trials. If a serious hypersensitivity reaction occurs, discontinue EVKEEZA, treat according to standard-of-care and monitor until signs and symptoms resolve. (5.1)
- *Embryo-Fetal Toxicity*: EVKEEZA may cause fetal harm based on animal studies. Advise patients who may become pregnant of the risk to a fetus. Consider obtaining a pregnancy test prior to initiating treatment with EVKEEZA. Advise patients who may become pregnant to use contraception during treatment and for at least 5 months following the last dose. (5.2, 8.1, 8.3)

ADVERSE REACTIONS

Common adverse reactions (≥ 5%) were nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-833-385-3392 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 02/2021

Appendix 5: Key Inclusion Criteria

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

Evinacumab

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

- Evinacumab (Evkeeza™) – pharmacy and provider administered claims

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code; go to #2	
2. Is the patient 12 years or older with a diagnosis of homozygous or familial hypercholesterolemia (HoFH) diagnosed by genetic testing or the following clinical criteria? • Untreated LDL-C > 500 mg/dl or treated LDL-C > 300 mg/dl	**Yes:** Go to #3	**No:** Pass to RPh; deny for medical appropriateness
3. Does the patient still have an LDL-C of ≥ 100 mg/dl while taking a maximally tolerated: • statin and • ezetimibe and • PCSK9 inhibitor (alirocumab or evolocumab)?	**Yes:** Go to #4 Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness.
4. Is the patient of childbearing potential?	**Yes:** Go to #5	**No:** Approve for up to 12 months

Approval Criteria		
5. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh; deny for medical appropriateness.	**No:** Go to #6
6. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh; deny for medical appropriateness.

P&T / DUR Review: *08/21 (MH)*
Implementation:

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 an 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*

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

Approval Criteria		
8. 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*

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