Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR025.0625	**CARDIOVASCULAR AGENTS** **VASCEPA®** (Icosapent ethyl capsules)
Effective Date: 8/1/2025	**Review/Revised Date**: 08/13, 10/14, 10/15, 09/16, 08/17, 10/18, 09/19, 12/19, 07/20, 05/21, 05/22, 05/23, 05/24, 05/25 (SAB)
Original Effective Date: 09/13	**P&T Committee Meeting Date**: 08/13, 10/14, 10/15, 10/16, 10/17, 10/18, 10/19, 12/19 (cv), 02/20, 10/20, 06/21, 06/22, 06/23, 06/24, 06/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For **Hypertriglyceridemia** all the following must be met:
1. A fasting triglyceride level within the past six months that is greater than 500 mg/dL.
2. Trial and failure (defined as at least two months of therapy), intolerance, or contraindication to one of the following formulary agents to treat very high triglycerides: fenofibrate or gemfibrozil.

For **ASCVD Risk Prevention** all of the following must be met:
1. One of the following:
    a. Established atherosclerotic heart disease as defined as one or more of the following:
        i. Acute coronary syndromes
        ii. History of myocardial infarction
        iii. Stable/unstable angina
        iv. Coronary or other arterial revascularization
        v. Stroke or transient ischemic attack
        vi. Peripheral arterial disease presumed to be of atherosclerotic origin
        i. Clinically significant coronary heart disease of atherosclerotic origin identified by diagnostic catheterization, imaging (CT angiogram or

cardiac MRI), or stress testing (nuclear stress test or stress echocardiogram)

b. Diabetes mellitus and two or more of the following additional risk factors for cardiovascular disease:
    i. Age 50 years or older
    ii. Hypertension
    iii. High-density lipoprotein cholesterol (HDL-C) equal to or less than 40 mg/dL for men or equal to or less than 50 mg/dL for women
    iv. High-sensitivity C-reactive protein (hs-CRP) greater than 3.0 mg/dL
    v. Reduced kidney function (eGFR less than 60 mL/min per 1.73m2)
    vi. Current cigarette smoker or recently quit smoking cigarettes within the past three months
    vii. Retinopathy
    viii. Micro- or macro-albuminuria
    ix. Ankle-brachial index less than 0.9 without symptoms of intermittent claudication

2. One of the following:
    a. Provider attestation of trial and failure of at least eight weeks of therapy with a high-intensity statin therapy (specifically, atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily), defined as failure to achieve desired LDL-C lowering

    OR

    b. Provider attestation of statin intolerance, defined as one of the following:
        i. Rhabdomyolysis
        ii. Skeletal muscle related symptoms while receiving separate trials of at least two different statins with resolution of symptoms after discontinuation
        iii. Elevated liver enzymes while on separate trials of at least two different statins with resolution after discontinuation

    OR

    c. The patient has an FDA labeled contraindication to a statin
3. A triglyceride level within the past six months that is equal to or greater than 150 mg/dL.

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:

Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Vascepa® (icosapent ethyl) is indicated as an adjunct to diet to reduce very high (≥500mg/dL) triglyceride levels in adult patients. Icosapent ethyl is the first omega-3 fatty acid product that only contains eicosapentaenoic acid (EPA). Other omega-3 products are a combination of ethyl esters of EPA and docosahexaenoic acid (DHA). Some evidence suggests that DHA can increase low-density lipoprotein (LDL) cholesterol plasma concentrations. By eliminating the DHA component from the icosapent ethyl product it is postulated that the intended benefit of lowering triglycerides could be achieved without adversely affecting LDL levels.

FDA APPROVED INDICATIONS:

Vascepa® is indicated:

1. as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (greater than or equal to 150 mg/dL) and
    a. established cardiovascular disease or
    b. diabetes mellitus and two or more additional risk factors for cardiovascular disease
2. as an adjunct to diet to reduce triglyceride levels in adult patients with very high (more than 500 mg/dL) triglyceride levels.

Limitations of Use: The effect of icosapent ethyl on the risk of pancreatitis in patients with severe hypertriglyceridemia has not been determined

POSITION STATEMENT:
Two pivotal Phase III trials demonstrated the safety and efficacy of icosapent ethyl when compared to placebo. They are the ANCHOR and MARINE trials. The ANCHOR trial evaluated the efficacy and safety of icosapent ethyl in a multicenter, placebo-controlled, randomized, double-blinded, 12-week clinical trial. High-risk statin-treated patients with residually high TG levels (≥200 and <500 mg/dl) despite LDL cholesterol control were recruited for the trial. Patients (n = 702) on a stable diet were randomized to icosapent 4 gram/day, 2 gram/day, or placebo. The primary end point was median percent change in TG levels from baseline versus placebo at 12 weeks. Icosapent ethyl 4 gram/day significantly decreased TG levels by 21.5%. Icosapent ethyl was generally well tolerated, with safety profiles similar to placebo.

The MARINE trial was a multicenter, placebo-controlled, randomized, double-blind, parallel-group 12-week study. Patients whose baseline TG levels were between 500 and 2,000 mg/dL were enrolled in this study. Patients (N = 229) were randomized to three treatment groups: icosapent ethyl 4grams/day, icosapent ethyl 2 grams/day or placebo. Results indicated patients receiving icosapent ethyl 4 gram/day demonstrated a statistically significant placebo-adjusted median triglyceride reduction of 33% and did not show an increase in LDL levels relative to placebo. The authors concluded icosapent ethyl is effective for the reduction of triglyceride levels in adult patients with severe hypertriglyceridemia. The reduction in TG observed with icosapent ethyl was not associated with elevations in LDL levels relative to placebo.

The effect of icosapent ethyl on patients with atherosclerotic cardiovascular disease (ASCVD) risk on a stable dose of a statin was studied in the REDUCE-IT trial. The REDUCE-IT trial evaluated the efficacy and safety of icosapent ethyl compared to placebo in a multicenter, randomized, double-blind, placebo-controlled, median duration 4.9-year study. Patients with established atherosclerotic heart disease, or diabetes and an additional risk factor, on pre-existing statin therapy with residual hypertriglyceridemia of levels of 200 to 449 mg/dL (initial enrollment included patients with triglyceride levels of 150 to 449 mg/dL with a protocol allowing a 10% lower triglyceride level from the target lower limit, extending the lower triglyceride level to 135 mg/dL) were enrolled in this study. Patients (N = 8,179) were randomized to either icosapent ethyl 4 grams/day or placebo. The primary end point, a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, demonstrated a statistically significant lower occurrence of 17.2% of patients in the icosapent ethyl group as compared with 22.0% of the patients in the placebo group. Hospitalization for atrial fibrillation or flutter as well as serious bleeding was observed to be higher in the

icosapent ethyl patient treatment group as compared to the placebo group (3.1% vs 2.1%, p = 0.004 and 2.7% vs 2.1%, p = 0.006 respectively).

To treat severe hypertriglyceridemia, nonpharmacologic interventions (weight loss, exercise, diet, elimination of medications that raise serum triglyceride levels and glycemic control in diabetics) should be first-line therapy. Per the AHA/ACC (American Heart Association/ American College of Cardiology) lipid guidelines (2018), severe hypertriglyceridemia should be diagnosed with a fasting triglyceride value; while for general triglyceride screening both fasting and non-fasting results are acceptable.[7] Further, they recommend nonpharmacologic interventions such as implementing a very low-fat diet and adding fibrates or omega-3 fatty acids for patients with persistently elevated severe hypertriglyceridemia.[6] However, AHA/ACC states that in patients with ASCVD risk on maximally tolerated statin therapy, the use of ezetimibe initially and then PCSK9 inhibitory therapy for patients judged to be very high risk can be considered. There is no mention of omega-3 fatty acid use in patients with ASCVD risk after statin step therapy as the 2018 AHA/ACC lipid guidelines were developed prior to the REDUCE-IT trial. The National Lipid Association released a statement in November 2019 stating icosapent ethyl as a class I recommendation to reduce cardiovascular risk in patients aged 45 years or older with clinical ASCVD or patients 50 years or older with diabetes mellitus and one additional risk factor, already on a high or moderate intensity statin, with fasting triglycerides 135-499 mg/dL, and with or without ezetimibe.

The 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia[10] recommend that first line treatment for everyone is diet and lifestyle management. ASCVD risk should be assessed and statin therapy optimization is priority for lowering ASCVD risk. For those with diabetes, glycemic control should also be optimized. Recommendations for when icosapent ethyl may be considered is for those with established ASCVD and for those 50 years of age and older with diabetes and at least one ASCVD high-risk feature as per the REDUCE-IT trial. For TG 500 – 999 mg/dL, fibrates (fenofibrate preferred) or either icosapent ethyl or omega-3 acid ethyl esters can be considered to reduce risk of pancreatitis.

The efficacy of omega 3 fatty acids in reducing triglycerides has been demonstrated, but more definitive trials are needed to ascertain the role of EPA-DHA omega 3 fatty acid formulations in primary or secondary prevention of major coronary events in patients with CHD. Fenofibrate or gemfibrozil can reduce triglyceride levels by 20 to 50 percent. High doses of nicotinic acid (1500 to 2000 mg/day) can reduce triglyceride levels by 15-25%. Omega 3 fatty acid supplements (such as Lovaza®) can lower triglycerides by 23-45%. The FDA limited approval of omega-3 fatty acids

to the treatment of severe hypertriglyceridemia (≥500 mg/dL) because of concerns that it appears to increase LDL levels.

Table 1. Effects of different classes of lipid-lowering drugs on lipid parameters

Statins*	Ezetimibe*	PCSK9 Inhibitors*	Fibric acids*	Bile Acid sequestrants*	Omega-3-fatty acids	Niacin	Bempedoic acid*
LDL ↓20-60%	LDL ↓17%	LDL ↓38-72%	LDL ↓6-20%	LDL ↓15-30%	LDL ↑4-49%	LDL ↓10-25%	LDL ↓ 15-19%
HDL ↑5-10%	HDL ↑1%	HDL ↑4-9%	HDL ↑5-20%	HDL 0% to slight increase	HDL ↑5-9%	HDL ↑15-35%	HDL no change to ↓ 4.5
TRIG ↓10-33%	TRIG ↓7-8%	TRIG ↓2-23%	TRIG ↓35-53%	No change	TRIG ↓23-45%	TRIG ↓25-30%	TRIG no change

*At least one agent in this class has shown clear ASCVD benefit in clinical trials

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