Vascepa® (icosapent ethyl)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Vascepa® (isosapent ethyl) policy is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Vascepa (icosapent ethyl) is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA) and is indicated:

- 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 (≥150 mg/dL) and
  - established cardiovascular disease or
  - diabetes mellitus and 2 or more additional risk factors for cardiovascular disease
- as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia

Limitations of Use:

- The effect of Vascepa on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

POLICY

Criteria for Approval

A. Vascepa (icosapent ethyl) may be considered **medically necessary** for reducing the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients when ALL the following criteria are met:
   1.) Must be prescribed by, or in consultation with, a cardiologist, endocrinologist, or lipid specialist
   2.) Patient meets at least ONE of the following:
      a. 45 years of age or older with established cardiovascular (CV) disease [See Appendix A]
         OR
      b. 50 years of age or older with ALL of the following:
         i.) Diabetes mellitus
         ii.) Two additional risk factors for CV disease [See Appendix B]
   3.) Patient is engaging in healthy lifestyle changes (i.e., a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and exercise regimen)
   4.) Patient has, or did have prior to the start of treatment with Vascepa, a triglyceride (TG) level of ≥150 mg/dL
   5.) Patient is currently receiving maximally tolerated statin therapy unless the patient has a documented contraindication (e.g., active liver disease, pregnancy, breastfeeding), or medically justifiable reason that precludes statin use (e.g., patient has experienced rhabdomyolysis, CK elevations ≥ 10x ULN, or statin intolerance)
      a. Statin intolerance shall be defined in accordance with the National Lipid Association definition [See Appendix C]
   6.) Will not to be used in combination with Juxtapid
   7.) If the request is for Vascepa 0.5 gram capsules, a medically justifiable reason for why the patient cannot take Vascepa 1 gram capsules is required

Approval will be for **12 months**

B. Vascepa (icosapent ethyl) may be considered **medically necessary** for reducing triglyceride levels in patients with severe hypertriglyceridemia when ALL the following criteria are met:
   1.) Must be prescribed by, or in consultation with, a cardiologist, endocrinologist, or lipid specialist
   2.) Patient is 18 years of age or older
   3.) Patient is engaging in healthy lifestyle changes (i.e., a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and exercise regimen)
   4.) Triglyceride (TG) level of >500 mg/dL prior to initiating therapy with Vascepa
   5.) For requests for continuation of therapy with Vascepa, patient must have a documentation of a positive clinical response to therapy as defined by triglyceride (TG) level of <500 mg/dL
   6.) Patient has experienced an inadequate response, intolerance, or contraindication to a fibrate medication (e.g., fenofibrate)
   7.) Patient is currently receiving maximally tolerated statin therapy unless the patient has a documented contraindication (e.g., active liver disease, pregnancy, breastfeeding), or medically justifiable reason that precludes statin use (e.g., patient has experienced rhabdomyolysis, CK elevations ≥ 10x ULN, or statin intolerance)
      a. Statin intolerance shall be defined in accordance with the National Lipid Association definition [See Appendix C]
   8.) Will not to be used in combination with Juxtapid
   9.) If the request is for Vascepa 0.5 gram capsules, a medically justifiable reason for why the patient cannot take Vascepa 1 gram capsules is required

Approval will be for **12 months**

Vascepa is considered **not medically necessary** for patients who do not meet the criteria set forth above.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limit

Trade Name	Generic Name	Quantity Limit
Vascepa®	Icosapent ethyl	4 grams per day

APPENDICES

APPENDIX A: Criteria for Establishing Cardiovascular (CV) Disease

Criteria for Establishing CV Disease
Defined as men and women ≥45 years of age with one or more of the following:
1. Documented coronary artery disease (CAD; one or more of the following): • Documented multi-vessel CAD (≥50% stenosis in at least two major epicardial coronary arteries – with or without antecedent revascularization); • Documented prior MI; • Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (with objective evidence of ischemia: ST-segment deviation or biomarker positivity).
2. Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied): • Documented prior ischemic stroke; • Symptomatic carotid artery disease with ≥50% carotid arterial stenosis; • Asymptomatic carotid artery disease with ≥70% carotid artery stenosis per angiography or duplex ultrasound; • History of carotid revascularization (catheter-based or surgical).
3. Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied): • Ankle-brachial index (ABI) <0.9 with symptoms or intermittent claudication; • History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).

APPENDIX B: Risk-Enhancing Factors for Cardiovascular (CV) Disease

Risk-Enhancing Factors
Family history of premature ASCVD (males, age <55 y; females, age <65 y)
Primary hypercholesterolemia (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*
Metabolic syndrome (increased waist circumference [by ethnically appropriate cutpoints], elevated triglycerides [>150 mg/dL, nonfasting], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; a tally of 3 makes the diagnosis)
Chronic kidney disease (eGFR 15–59 mL/min/1.73 m2 with or without albuminuria; not treated with dialysis or kidney transplantation)
Chronic inflammatory conditions, such as psoriasis, RA, lupus, or HIV/AIDS
History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia
High-risk race/ethnicity (e.g., South Asian ancestry)

Lipids/biomarkers: associated with increased ASCVD risk
Persistently elevated* primary hypertriglyceridemia (≥175 mg/dL, nonfasting)
If measured:
Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).
Elevated apoB (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
ABI (<0.9)

APPENDIX C: National Lipid Association definition of Statin intolerance

Inability to tolerate at least two statins (one at any dose, one at lowest daily dose) due to objectionable symptoms or abnormal biomarkers temporally related to statin use, reversible upon statin discontinuation and reproducible by re-challenge while excluding other known determinants. Other known determinants include low body mass index (BMI), acute infection, untreated or undertreated hypothyroidism, severe renal or hepatic dysfunction, organ transplant, recent severe trauma, HIV infection, Vitamin D deficiency, history of creatine kinase elevation, history of preexisting or unexplained muscle or joint pain, high level of physical activity, illicit drug abuse, excess alcohol use. Each statin trial, both initial and re-challenge shall be at least two weeks duration.

CLINICAL RATIONALE

Background

Cardiovascular disease is the leading cause of death in the United States, contributing to more than 600,000 deaths annually. The link between elevated lipid parameters, including triglycerides, LDL-C, non-HDL-C, TC, HDL-C, VLDL-C, and Apo B and cardiovascular risk is well-established, and clinical guidelines recommend pharmacological therapy in combination with diet and exercise to lower elevated lipid parameters and reduce cardiovascular risk.

Vascepa (icosapent ethyl) forms an active metabolite, eicosapentaeonic acid (EPA), which is subsequently absorbed in the small intestine. Studies suggest that EPA reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and/or secretion and enhances TG clearance from circulating VLDL particles. Potential mechanisms of action include increased β-oxidation; inhibition of acyl-CoA; 1,2-diacylglycerol acyltransferase (DGAT); decreased lipogenesis in the liver; and increased plasma lipoprotein lipase activity. The mechanisms of action contributing to reduction of cardiovascular events with Vascepa are not completely understood but are likely multi-factorial. Increased EPA lipid composition from carotid plaque specimens and increased circulating EPA/arachidonic acid ratio have been observed following EPA treatment. EPA inhibits platelet aggregation under some ex vivo conditions. However, the direct clinical meaning of individual findings is not clear.

Efficacy

The efficacy of Vascepa in preventing cardiovascular events in patients with elevated triglyceride levels and other risk factors for cardiovascular disease was evaluated in the REDUCE-IT phase 3, multinational, randomized, double-blind, placebo-controlled, event-driven clinical trial. The REDUCE-IT trial enrolled 8,179 adult patients who were statin-treated, had a baseline LDL-C >40 mg/dL and ≤100 mg/dL and elevated triglyceride levels, and who had established cardiovascular disease or diabetes and other risk factors for cardiovascular disease. Patients with established cardiovascular disease were defined as being at least 45 years of age and having a documented history of coronary artery disease, cerebrovascular or carotid disease, or peripheral artery disease. Patients with other risk factors for cardiovascular disease were defined as being at least 50 years of age with diabetes and at least one additional risk factor.

In the REDUCE-IT trial, patients were randomized to receive Vascepa (n = 4,089) 4 grams daily or placebo (n = 4,090) and were followed for a median of 4.9 years. Overall, 99.8% of patients were followed for vital status until the end of the trial or death. The primary composite endpoint measured was time to first occurrence of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina and the key secondary composite endpoint measured was time to first occurrence of cardiovascular death, myocardial infarction, or stroke. Overall, Vascepa significantly reduced the risk for both the primary composite endpoint ($p<0.001$) and the key secondary composite endpoint ($p<0.0001$).

The efficacy of Vascepa in the treatment of severe hypertriglyceridemia was evaluated in a randomized, placebo-controlled, double-blind, parallel-group study. The study enrolled adult patients with severe hypertriglyceridemia (baseline TG levels between 500 and 2,000 mg/dL), randomized them 1:1 to receive either Vascepa 4 grams daily (n = 76) or placebo (n = 75), and followed them for 12 weeks. The primary efficacy endpoint measured was the difference in the median percentage change from baseline in TG levels between the Vascepa and placebo groups. Secondary efficacy endpoints measured were the differences in the median percentage change from baseline in LDL-C, non-HDL-C, TC, HDL-C, VLDL-C, and Apo B levels between the Vascepa and placebo groups. Overall, Vascepa 4 grams daily demonstrated a statistically significant reduction in the median percentage change from baseline in TG ($p<0.001$), VLDL-C ($p<0.05$), and Apo B ($p<0.05$) levels. Vascepa 4 grams daily did not demonstrate a statistically significant reduction in the median percentage change from baseline in LDL-C, non-HDL-C, TC, or HDL-C levels.

Safety

Vascepa was associated with an increased risk of atrial fibrillation or atrial flutter requiring hospitalization and bleeding in double-blind, placebo-controlled trials. The incidence of atrial fibrillation was greater in patients with a history of atrial fibrillation or atrial flutter and the incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin. Some published studies with omega-3 fatty acids have also demonstrated prolongation of bleeding time, and patients receiving Vascepa and concomitant anticoagulants and/or antiplatelet agents should be monitored for bleeding.

Vascepa contains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to Vascepa. Patients receiving Vascepa who have a known hypersensitivity to fish and/or shellfish should be informed of the potential for allergic reactions and advised to discontinue Vascepa and seek medical attention if any reactions occur.

The most common adverse events reported in subjects treated with Vascepa during the cardiovascular outcomes clinical trial (incidence ≥ 3% and ≥ 1% more frequent than placebo) were musculoskeletal pain, peripheral edema, constipation, gout, and atrial fibrillation. In the hypertriglyceridemia clinical trials, the most common adverse events reported in subjects treated with Vascepa (incidence ≥ 1% and more frequent than placebo) were arthralgia and oropharyngeal pain.

Vascepa is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to Vascepa or any of its components.

Other

In their 2019 Final Evidence Report, the Institute for Clinical and Economic Review (ICER) concluded that there is high certainty that Vascepa (icosapent ethyl) provides a small-to-substantial net health benefit for adults with established cardiovascular disease or at high risk of cardiovascular events who are being treated with statins. Overall, they assigned Vascepa with a grade of a 'B+' for its comparative clinical effectiveness

vs. optimal medical management. This grade was given despite the uncertainty ICER noted on whether the use of mineral oil may have caused some harm to the placebo group, and it was not believed that the theory could account for the entire benefit observed in the REDUCE-IT trial. Additionally, ICER concluded that Vascepa provides gains in quality-adjusted survival and overall survival over optimal medical management. They also noted that costs for treatment with Vascepa would fall below commonly cited thresholds for cost effectiveness, assuming clinical signals within the REDUCE-IT trial and current net prices hold.

Other proposed mechanisms for how Vascepa (icosapent ethyl) provides clinical benefit is through its anti-atherosclerotic effects, particularly in patients with known coronary atherosclerosis. The EVAPORATE trial was a multi-center, randomized, double-blind, placebo-controlled clinical trial that evaluated the anti-atherosclerotic effects of diet, exercise, and statin therapy with or without ezetimibe plus either Vascepa or placebo. To be included in the trial, patients had to have known coronary atherosclerosis (narrowing of ≥ 20% in 1 coronary artery by either invasive angiography or CCTA), elevated fasted triglyceride levels (135-499 mg/dL), and low-density lipoprotein levels (LDL-C) between ≥ 40 and ≤ 115 mg/dL. Patients were followed for a total of 18 months and randomized 1:1 to receive either Vascepa 4 gm/day (n = 31) or placebo (n = 37). Patients in the placebo group were given 1 gm soft gelatin capsules that consisted of pharmaceutical grade mineral oil, to mimic the composition of Vascepa capsules. The primary endpoint was the change in low-attenuation plaque (LAP) volume measured by multidetector computed tomography (MDCT) angiography, and secondary endpoints included changes in total plaque (TP), total non-calcified plaque (TNCP), fibrofatty (FF), fibrous (F), and calcified plaque (CP). Basic lipid measures (changes in total cholesterol, LDL-C, HDL-C, and TG) from baseline to follow-up were also measured in both groups. Overall, the EVAPORATE trial demonstrated that Vascepa plus statin therapy were associated with slowed plaque progression compared with statin plus placebo and there was a statistically significant difference between the two groups from baseline to follow-up for all endpoints except the change in CP levels. The EVAPORATE trial did not, however, demonstrate any statistically significant differences in lipid measures from baseline to follow-up for either of the two groups.

Additionally, the investigators in the EVAPORATE study looked at the rates of change of patients in the EVAPORATE study who were subject to mineral oil (the placebo cohort) and compared with a second study that used a cellulose-based placebo. Their goal was to evaluate if mineral oil resulted in faster plaque progression rates, which may lead to overestimates of the beneficial plaque changes seen with Vascepa. After their review, the investigators found no difference in plaque progression between mineral oil and cellulose-based placebos.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD-CM diagnostic codes.

- Not applicable

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POLICY HISTORY

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