PHARMACY COVERAGE GUIDELINE

LOVAZA® (omega-3-acid ethyl esters) oral
VASCEPA® (icosapent ethyl) oral
Icosapent ethyl oral

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

LOVAZA (omega-3 acid ethyl esters)

- **Criteria for initial therapy:** Lovaza (omega-3 acid ethyl esters) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Individual is 18 years of age or older.

  2. Individual has a confirmed diagnosis of **hypertriglyceridemia (≥ 500 mg/dL).**

  3. Individual is compliant with a lipid-lowering diet and exercise program.

4. Documented failure, contraindication per FDA label or intolerance to omega-3-acid ethyl esters (generic Lovaza).

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Lovaza (omega-3 acid ethyl esters) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

1. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
    a. Triglyceride level is within the normal limits or has dropped at least by 50%
    b. No episodes of pancreatitis
    c. No evidence of disease progression

2. Individual has been adherent with the medication

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

VASCEPA (icosapent ethyl)
Icosapent ethyl

- **Criteria for initial therapy:** Vascepa (icosapent ethyl) or icosapent ethyl is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Individual 18 years of age or older with severe (≥500 mg/dL) hypertriglyceridemia with **ONE** of the following:
        i. Has failure, contraindication per FDA label or intolerance to omega-3-acid ethyl esters (generic Lovaza)

        ii. Use of a prescription omega-3 fatty acid product has resulted in an increase in LDL-C (documentation of use of other product and that an increase has occurred is required and must be submitted with request)

b. **ONE** of the following:
   i. Individual 45 years of age or older with established cardiovascular disease (see Definitions section) on stable dose of statin for at least 4 weeks (with or without ezetimibe) with a fasting LDL-C between 41-100 mg/dL **AND** a triglyceride level between 135-499 mg/dL

   ii. Individual 50 years of age older with diabetes that requires treatment and has at least **one** or more additional risk factor for cardiovascular disease (see Definitions section) on stable dose of statin for at least 4 weeks (with or without ezetimibe) with a fasting LDL-C between 41-100 mg/dL **AND** a triglyceride level between 135-499 mg/dL

2. Individual is compliant with a lipid-lowering diet and exercise program.

3. **For brand Vascepa**: Documented failure, contraindication per FDA label or intolerance to generic icosapent ethyl.

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Vascepa (icosapent ethyl) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

1. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
   a. Severe hypertriglyceridemia response is defined as:
      i. Triglyceride level is within the normal limits or has dropped at least by 50%
      ii. No episodes of pancreatitis
      iii. No evidence of disease progression
   b. Cardiovascular risk reduction response is defined as:
      i. No evidence of disease progression
      ii. Documented evidence of efficacy, disease stability and/or improvement

2. Individual has been adherent with the medication.

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

3. **Off-Label Use of Non-Cancer Medications**

4. **Off-Label Use of Cancer Medications**

PHARMACY COVERAGE GUIDELINE

LOVAZA® (omega-3-acid ethyl esters) oral
VASCEPA® (icosapent ethyl) oral
Icosapent ethyl oral

Description:

Omega-3 acid ethyl esters (Lovaza brand and generic) and icosapent ethyl (Vascepa brand and generic) are omega-3 fatty acids indicated as an adjunct to diet and exercise to reduce triglyceride levels in adults with severe (500 mg/dL or more) hypertriglyceridemia. Icosapent ethyl (Vascepa brand and generic) is also 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 levels (150 mg/dL or more) and established cardiovascular disease or diabetes mellitus with two or more additional risk factors for cardiovascular disease.

The Endocrine Society guidelines for the treatment of hypertriglyceridemia recommends that omega-3 fatty acids may be considered for triglyceride levels greater than 1,000 mg/dL and may be used alone or in combination with HMG-CoA reductase inhibitors (or statin). Secondary causes of hyperlipidemia should be ruled out prior to therapy. The effect, if any, of omega-3 fatty acids on the risk of pancreatitis or cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia is not known.

In general, omega-3 fatty acids are a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Lovaza (brand & generic) omega-3 acid ethyl esters capsules contain at least 900 mg of ethyl esters of omega-3 fatty acids sourced from fish oil, which are predominantly EPA (approximately 465 mg) and DHA (approximately 375 mg). Epanova is a carboxylic acid free fatty acid composed of a combination of polyunsaturated fatty acids. It includes 50-60% EPA, 15-25% DHA, and other omega-3 fatty acids. Omtryg is an omega-3 fatty acid ethyl esters A containing $\geq$ 75% EPA and DHA. Icosapent ethyl is an ethyl ester of EPA obtained from fish oil; however, it contains at least 96% EPA and does not contain DHA.

Several clinical studies have demonstrated that icosapent ethyl and prescription omega-3 acid ethyl esters can effectively lower triglycerides, as well as positively impact other lipid parameters when used as monotherapy or in combination with fenofibrate or a statin.

Recommendations in clinical guidelines regarding the use of omega-3 fatty acids are varied. Older guidelines suggest omega-3 fatty acids may reduce the risk of cardiovascular disease and may be reasonable for cardiovascular disease risk reduction, while newer guidelines do not address the use or recommend against the use of omega-3 fatty acids for reducing the risk of cardiovascular disease due to limited data. In general, therapeutic lifestyle changes, including diet, exercise, and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial treatment with a statin is recommended and considered first line therapy for patients with established coronary heart disease (CHD) or CHD equivalents.

The exact mechanism by which these agents reduce triglyceride levels is not completely understood. Possible mechanisms include inhibition of acyl CoA: 1,2 diacylglycerol acyltransferase (DGAT), increased hepatic mitochondrial and hepatic peroxisomal beta-oxidation, reduction in the hepatic synthesis of triglycerides, or an increase in plasma lipoprotein lipase activity. They may also reduce the hepatic synthesis of triglycerides because EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis, and EPA and DHA inhibit esterification of other fatty acids.

The majority of EPA circulating in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, and <1% is present as the unesterified fatty acid. Greater than 99% of unesterified EPA is bound to plasma

proteins. Icosapent ethyl is de-esterified during absorption to its active metabolite EPA. EPA is mainly metabolized by the liver via beta-oxidation similar to dietary fatty acids. Beta oxidation splits the long carbon chain of EPA into acetyl Coenzyme A, which is converted into energy via the Krebs cycle. Cytochrome P450-mediated metabolism is a minor pathway of elimination of EPA.

Definitions:

Established Cardiovascular Disease (CVD):

Man or woman ≥ 45 years of age with **one or more** of the following:

- Documented coronary artery disease (CAD; **one** of the following primary criteria must be satisfied):
  - Documented multi-vessel CAD (**one** with > 50% stenosis in two major epicardial coronary arteries – with or without antecedent revascularization)
  - Documented prior MI
  - Hospitalization for high-risk NSTE ACS (with objective evidence of ischemia: ST-segment deviation or biomarker positivity)
- 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 arterial stenosis per angiography or duplex ultrasound
  - History of carotid revascularization (catheter-based or surgical)
- Documented peripheral arterial disease (PAD; **one** of the following primary criteria must be satisfied):
  - Ankle-brachial index (ABI) < 0.9 **with** symptoms of intermittent claudication
  - History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical)
- Documented diabetes with, as defined above, CAD, PVD, or cerebrovascular or carotid disease

Cardiovascular Disease (CVD) Risk Factors:

- Man or woman ≥ 50 years of age **AND**
- Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication **AND**
- **One** of the following at Visit 1 (***additional risk factor for CVD***):
  - Man ≥ 55 years of age and Woman ≥ 65 years of age
  - Cigarette smoker or stopped smoking within 3 months before Visit 1
  - Hypertension (blood pressure ≥ 140 mmHg systolic **OR** ≥ 90 mmHg diastolic) or on antihypertensive medication
  - HDL-C ≤ 40 mg/dL for men or ≤ 50 mg/dL for women
  - hs-CRP > 3.0 mg/L
  - Renal dysfunction: creatinine clearance (CrCl) > 30 and < 60 mL/min
  - Retinopathy, defined as any of the following: non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation
  - Micro- or macro-albuminuria. Micro-albuminuria is defined as either a positive micral or other strip test, an albumin/creatinine ratio ≥ 2.5 mg/mmol or an albumin excretion rate on timed collection ≥ 20 mg/min all on at least two successive occasions; macro-albuminuria, defined as albustix or other dipstick evidence of gross proteinuria, an albumin/creatinine ratio ≥ 25 mg/mmol or an albumin excretion rate on timed collection ≥ 200 mg/min all on at least two successive occasions

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Icosapent ethyl oral

ABI < 0.9 **without** symptoms of intermittent claudication

Resources:

Lovaza (omega-3-acid ethyl esters) product information, revised by Woodward Pharma Services, LLC 02-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 03, 2022.

Omega-3-acid ethyl esters product information, revised by Major Pharmaceuticals 12-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 03, 2022.

Vascepa (icosapent ethyl) product information, revised by Amarin Pharma Inc. 09-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 03, 2022.

Icosapent ethyl product information, revised by Hikma Pharmaceuticals USA, Inc. 01-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 03, 2022.