BlueCross BlueShield Arizona

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| **PHARMACY COVERAGE GUIDELINES** | **ORIGINAL EFFECTIVE DATE: 1/21/2016** |
| **SECTION: DRUGS** | **LAST REVIEW DATE: 8/19/2021** |
| | **LAST CRITERIA REVISION DATE: 8/19/2021** |
| | **ARCHIVE DATE:** |

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

**Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.**

**This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.**

**The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.**

**The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.**

**State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.**

**Pharmacy Coverage Guidelines are subject to change as new information becomes available.**

**For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.**



This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

**PHARMACY COVERAGE GUIDELINES**
**SECTION: DRUGS**

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

## 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** of the following criteria are met:

  1. Individual is 18 years of age or older
  2. A confirmed diagnosis of **hypertriglyceridemia (≥ 500 mg/dL)**
  3. Individual is compliant with a lipid-lowering diet and exercise program
  4. 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** of the following criteria are met:

  1. Individual's condition responded while on therapy
     a. 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
  2. Individual has been adherent with the medication, lipid-lowering diet, and exercise

  **Renewal duration**: 12 months

## Vascepa (icosapent ethyl)

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

  1. A confirmed diagnosis of **ONE** of the following:
     a. As an adjunct to diet to reduce triglyceride levels in adults 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. Cardiovascular risk reduction in **ONE** of the following:
   i. Individual 45 years of age or older with established cardiovascular disease (see Definition 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** other risk factor for cardiovascular disease (see Definition 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

**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** of the following criteria are met:

1. Individual's condition responded while on therapy
   a. Prevention of pancreatitis 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, lipid-lowering diet, and exercise

**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 a Non-cancer Medications**

2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

**Description:**

Omega-3 acid ethyl esters (Lovaza brand and generic) and Vascepa (icosapent ethyl) 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. Vascepa (icosapent ethyl) 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.

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

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

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**Resources:**

Lovaza (omega-3-acid ethyl esters) product information, revised by GlaxoSmithKline LLC 09-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on July 10, 2021.

Omega-3-acid ethyl esters product information, revised by Amneal Pharmaceuticals LLC 09-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on July 10, 2021.

Vascepa (icosapent ethyl) product information, revised by Amarin Pharma Inc. 12-2019. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on July 10, 2021.