Instructions for Use
VASCEPA® (icosapent ethyl)
Prior Authorization Letter

Note to requesting physician: This letter provides a suggested format for a medical necessity letter if payers impose a prior authorization requirement for VASCEPA® (icosapent ethyl). This letter is focused on explaining the rationale and clinical decision-making for choosing this particular prescription drug for a specific patient. Also see the Prescribing Information for VASCEPA.

NOTE: Some payers have not yet updated their plans to acknowledge the expanded indication that FDA approved in late 2019. This letter includes details on the data supporting that new indication that makes VASCEPA particularly well-suited for some patients.

The provider must ensure that the information included in the letter is accurate and reflective of the patient's medical condition and medical history. Amarin makes no representation or guarantee concerning coverage or reimbursement for any service or item.

Below is a listing of ICD-10 Codes that may be appropriate when submitting this PA.

These codes are not all-inclusive. Appropriate codes can vary by patient, payer, and setting of care. The provider is responsible for ensuring correct coding. Please check with the payer to verify codes and special billing requirements. Amarin does not make any representation or guarantee concerning reimbursement or coverage.

Please see next page for VASCEPA® PA Letter

[Use Physician Letterhead]

[Date]

[Payer Name]

Attn: [Contact Title/Medical Director]

[Name]

[Address]

RE: VASCEPA® (icosapent ethyl) Capsules, for oral use [Include in Reference: Patient's full name]

[D/O/B] [Insurance ID#] [Insurance Group ID#] [Case ID# (if known)] [Date of Service]

Dear [Insert Contact Name or Title/Medical Director] ,

I am the prescribing physician for [Patient Name] . I am writing to request Prior Authorization of, and document the medical necessity for, VASCEPA. This letter provides information about my patient's medical history and diagnosis. And a summary of the treatment plan.

My patient has the demonstrated medical need for VASCEPA based on the following diagnosis. Check one below:

☐ established cardiovascular disease or

☐ diabetes plus two or more additional cardiovascular risk factors.

The patient is [Male/Female] and is [XX] years old and their triglyceride level is [YYY] mg/dL. The patient is on a maximally tolerated dose of a statin.

Because of the patient's clinical history and their elevated triglycerides, this patient is at a high risk of experiencing a CV event.

In my clinical judgment, this patient requires VASCEPA as the most suitable therapy based on the available evidence from clinical trials. *VASCEPA is the only non-cholesterol-lowering therapy that has demonstrated cardiovascular risk reduction as an adjunct to maximally tolerated statin therapy.* As outlined in more detail below, DHA-containing omega-3-acid ethyl esters (generic Lovaza®), fibrates, and niacin have all failed to demonstrate a reduction in cardiovascular events as an adjunct to statin therapy. These therapies would, therefore, not be clinically appropriate for my patient.

VASCEPA received an additional FDA-approved indication on December 13, 2019, and 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 (≥ 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.

As documented above, this patient clearly falls within the scope of the new FDA-approved indication for VASCEPA.

The CV benefits of VASCEPA based on the REDUCE-IT® study cannot be generalized to any other product. There is no AB-Rated alternative for VASCEPA.

ESTABLISHED CARDIOVASCULAR DISEASE.[2] Check all that apply:

- ☐ I21.0 ST elevation (STEMI) myocardial infarction of anterior wall
- ☐ I21.1 ST elevation (STEMI) myocardial infarction of inferior wall
- ☐ I21.2 ST elevation (STEMI) myocardial infarction of other sites
- ☐ I21.3 ST elevation (STEMI) myocardial infarction of unspecified site
- ☐ I21.4 Non-ST elevation (NSTEMI) myocardial infarction
- ☐ I25.10 Atherosclerotic heart disease of native coronary artery without angina pectoris
- ☐ I25.118 Atherosclerotic heart disease of native coronary artery with other forms of angina pectoris
- ☐ I25.2 Old myocardial infarction
- ☐ I25.700 Atherosclerosis of coronary artery bypass graft(s), unspecified, with unstable angina pectoris
- ☐ I25.810 Atherosclerosis of coronary artery bypass graft(s) without angina pectoris
- ☐ I25.83 Coronary atherosclerosis due to lipid rich plaque
- ☐ I25.84 Coronary atherosclerosis due to calcified coronary lesion
- ☐ I63.9 Cerebral infarction, unspecified
- ☐ I67.9 Cerebrovascular disease, unspecified
- ☐ I73.9 Peripheral vascular disease, unspecified
- ☐ Z95.1 Presence of aortocoronary bypass graft
- ☐ Z98.61 Coronary angioplasty status
- ☐ Other_____

DIABETES AND 2 OR MORE ADDITIONAL RISK FACTORS.[2] Check all that apply:

- ☐ E10 Type 1 diabetes mellitus
- ☐ E10.29 Type 1 diabetes mellitus with other diabetic kidney complication
- ☐ E11 Type 2 diabetes mellitus
- ☐ E11.29 Type 2 diabetes mellitus with other diabetic kidney complication
- ☐ E13.22 Other specified diabetes mellitus with diabetic chronic kidney disease
- ☐ E66.01 Morbid (severe) obesity due to excess calories
- ☐ E66.9 Obesity, unspecified
- ☐ E78.0 Pure hypercholesterolemia
- ☐ E78.2 Mixed hyperlipidemia
- ☐ E78.5 Hyperlipidemia, unspecified
- ☐ I10 Essential (primary) hypertension
- ☐ N18.9 Chronic kidney disease, unspecified
- ☐ R79.82 Elevated C-reactive protein (CRP)

- ☐ Z72.0 Tobacco use
- ☐ Z82.3 Family history of stroke
- ☐ Z82.49 Family history of ischemic heart disease and other diseases of the circulatory system
- ☐ Other _____

1. Need to reduce cardiovascular (CV) events in patient with residual risk in the REDUCE-IT trial

VASCEPA was proven to reduce CV events as an adjunct to maximally tolerated statins in adults with elevated triglyceride (TG) levels ≥150 mg/dL and established CV disease or diabetes and 2 or more additional risk factors for CV disease: Primary composite endpoint (5-point MACE of nonfatal myocardial infarction [MI], nonfatal stroke, CV death, coronary revascularization, hospitalization for unstable angina) demonstrated a highly statistically significant (*P*=0.00000001) 25% relative risk reduction (RRR) (4.8% absolute risk reduction [ARR]), with a number needed to treat (NNT) of 21 over 4.9 years. Key secondary composite endpoint (3-point MACE of nonfatal MI, nonfatal stroke, CV death) demonstrated a highly statistically significant (*P*=0.0000006) 26% RRR (3.6% ARR) with an NNT of 28 over 4.9 years.[3]

Significant reductions in prespecified secondary endpoints were also demonstrated, including a 31% reduction in MI, a 28% reduction in stroke, and a 20% reduction in CV death.[3] Additionally, large and clinically meaningful reductions in total (first and subsequent) ischemic events were seen for both the primary (30% RRR, *P*=0.00000000036) and key secondary (28% RRR, *P*=0.00000071) endpoints with icosapent ethyl over placebo.[4] Recurrent event exploratory analysis reflects a series of prespecified statistical models, one of which was *post hoc*. Data not opined on by the FDA.

2. Fenofibrates are inappropriate for reducing my patient's persistent cardiovascular risk

- Fenofibrate is <u>not</u> indicated or approved for concomitant or adjunctive use with a statin[5]
  - — In April of 2015, the FDA removed the following indication from the Trilipix® package insert (PI): Trilipix is indicated as an adjunct to diet in combination with a statin to reduce TG and increase high-density lipoprotein cholesterol (HDL-C) in patients with mixed dyslipidemia and coronary heart disease (CHD) or a CHD risk equivalent who are on optimal statin therapy to achieve their low-density lipoprotein cholesterol (LDL-C) goal
  - — In addition, in April 2016, the FDA announced the removal of the indication for co-therapy with statin from all generic Trilipix products. The reason the Agency gave was that the "FDA has determined that the benefits of niacin ER tablets and fenofibric acid DR capsules for coadministration with statins no longer outweigh the risks, and the approvals for this indication should be withdrawn"
- Fibrates have been shown to increase LDL-C by approximately 45% in some patients with very high triglyceride (VHTG) levels—complicating efforts to improve overall lipid health and requiring added or stronger-dose statin intervention in eligible patients[6]
- Side effects reported for fenofibrate include serious conditions such as myopathy (e.g., muscle weakness), cholelithiasis (i.e., gallstones) and rhabdomyolysis (i.e., muscle breakdown that can result in kidney damage)—the muscle-related risks may be increased when taken with a statin, which patients with persistent high TGs may require. Myopathy and rhabdomyolysis have been reported in patients taking fenofibrate. The risks for myopathy and rhabdomyolysis are

increased when fibrates are co-administered with a statin, particularly in elderly patients and patients with diabetes, renal failure, or hypothyroidism[6]
- For the reasons listed above, fenofibrates are not, in my opinion, the most appropriate therapy for this patient
- Fenofibrates and extended-release niacin are not FDA-approved for co-administration with statins to affect lipid, lipoprotein, or inflammation parameters with the aim of reducing CV mortality or morbidity[5-7]
- No head-to-head, randomized, well-controlled studies have been conducted to compare the effects of VASCEPA with other FDA-approved TG-lowering therapies

3. Docosahexaenoic acid (DHA)-containing omega-3 combination products are inappropriate for reducing my patient's persistent cardiovascular risk

- DHA-containing omega-3 combination products do not currently have cardiovascular (CV) outcomes trials showing reduction in CV events[8]
- DHA-containing omega-3 combination products tend to increase levels of LDL-C in some patients with VHTG, by approximately 45%[8]
- A meta-analysis published in March 2018 in *JAMA* titled "Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks" reported that most of the included studies utilized mixed EPA and DHA omega-3 products administered daily at a low dose, and were not positive, including prescription therapy and dietary supplements[9]
- The ASCEND trial, which used Lovaza® (named Omacor in Europe)—a prescription omega- 3 mixture of EPA, DHA, and other ingredients—administered at a low dose of 1 gram/day in the omega-3 arms of the study, did not find a reduction of serious vascular events in patients with diabetes and without diagnosed CV disease[10]
- Similar analyses have been conducted and published by other sources, including a Cochrane review.[11] Failed results with omega-3 mixtures on top of statin therapy was again demonstrated in the VITAL study published in November 2018 in the *NEJM*, in which Lovaza failed to demonstrate CV benefit[12]
- *Most recently, on January 13, 2020, AstraZeneca announced that, following the recommendation from an independent Data Monitoring Committee, it has discontinued the Phase III STRENGTH trial for Epanova (omega-3 carboxylic acids), a prescription omega-3 mixture of DHA and EPA, due to its low likelihood of demonstrating a benefit to patients with mixed dyslipidaemia who are at an increased risk of cardiovascular events*[13]
- For the reasons listed above, DHA-containing omega-3 combination products, including omega-3-acid ethyl esters, are not, in my medical opinion, the most appropriate therapy for this patient

4. Fish oil dietary supplements are inappropriate for reducing my patient's persistent cardiovascular risk

- As reflected in the Orange Book (www.fda.gov/cder/ob), there are no FDA-approved "OTC" omega-3 dietary supplements available to treat medical conditions[14]
- Dietary supplements are not regulated as drugs by the FDA; they are regulated as food. Therefore, supplements do not have to meet stringent FDA drug standards, and the FDA does not review any clinical trial data before supplements are sold to patients making any omega-3 supplement efficacy claims regarding lowering triglycerides unverified[14]
- The quantity and quality of ingredients in omega-3 dietary supplements are reported to be highly variable.[14] Top-selling supplements contain only ~30% omega-3,[15] and many contain lower omega-3 amounts than specified on the label.[16] Many supplements contain DHA, which

has the potential to raise LDL-C levels in some patients.[17,18] Remaining ingredients are unknown/uncharacterized on the label,[15,19] and some supplements may contain up to one-third saturated fat.[16] In addition, if fish oil is exposed to air during poor manufacturing conditions, it may oxidize.[20] There is a significant pill burden to attempt to achieve 4 grams of EPA. Given that the most commonly sold omega-3 dietary supplements are only ~30% omega-3, patients would need to ingest 10 or more capsules per day to achieve the equivalent 4 grams of pure EPA found in one daily dose of prescription VASCEPA[15,17]

- The health benefits of dietary supplements are unproven. Dietary supplements may contain oxidized components that interfere with their potential biological benefits[17]
- Organizations such as the American Heart Association, American Diabetes Association, American Society of Health-System Pharmacists, and American Association of Clinical Endocrinologists do not recommend omega-3 supplements to treat disease[21-24]
- For the reasons listed above, omega-3 dietary supplements are not, in my medical opinion, the most appropriate therapy for this patient

5. Extended-release (ER) niacin and ER niacin-statin combinations are inappropriate for reducing my patient's persistent cardiovascular risk

- Although extended-release niacin can be used for the treatment of persistent high TGs, the tolerability profile of this class of products may make it difficult for compliance and meaningful clinical use[7]
- In April of 2015, the FDA removed the following indication from the Niaspan® PI[5]:
  - Niaspan in combination with simvastatin or lovastatin is indicated for the treatment of primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb) when treatment with Niaspan, simvastatin, or lovastatin monotherapy is considered inadequate
- In addition, in April 2016, the FDA announced the removal of the indication for co-therapy with statin from all generic Niaspan products. The reason the Agency gave was that the "FDA has determined that the benefits of niacin ER tablets and fenofibric acid DR capsules for coadministration with statins no longer outweigh the risks, and the approvals for this indication should be withdrawn"[5]
- Further, in April 2016, the FDA publicly announced that Advicor® & Simcor® (niacin XR + lovastatin and niacin XR + simvastatin, respectively) have also been removed from the market. In an entry published within the *Federal Register*, the FDA stated that it has determined that "benefits of ADVICOR and SIMCOR no longer outweigh the risks, and approval should be withdrawn"[25]
- For the reasons listed above, Niacin is not, in my medical opinion, the most appropriate therapy for this patient

Please see Indications, Limitations of Use, and Important Safety Information below.

In my medical judgment, VASCEPA is the best option for this patient. I appreciate your consideration to approve my request for [Patient Name Here] . Please contact me at [xxx-xxx-xxxx] if I can be of further assistance.

Sincerely,

[Physician Name]

INDICATIONS AND LIMITATIONS OF USE

• VASCEPA® (icosapent ethyl) 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

• VASCEPA is indicated as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia

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

IMPORTANT SAFETY INFORMATION

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

• VASCEPA was associated with an increased risk (3% vs 2%) of atrial fibrillation or atrial flutter requiring hospitalization in a double-blind, placebo-controlled trial. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or atrial flutter

• It is not known whether patients with allergies to fish and/or shellfish are at an increased risk of an allergic reaction to VASCEPA. Patients with such allergies should discontinue VASCEPA if any reactions occur

• VASCEPA was associated with an increased risk (12% vs 10%) of bleeding in a double-blind, placebo-controlled trial. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel or warfarin

• Common adverse reactions in the cardiovascular outcomes trial (incidence ≥3% and ≥1% more frequent than placebo): musculoskeletal pain (4% vs 3%), peripheral edema (7% vs 5%), constipation (5% vs 4%), gout (4% vs 3%) and atrial fibrillation (5% vs 4%)

• Common adverse reactions in the hypertriglyceridemia trials (incidence ≥1% more frequent than placebo): arthralgia (2% vs 1%) and oropharyngeal pain (1% vs 0.3%)

• Adverse Events, Product Complaints, or Special Situations may be reported by calling 1-855-VASCEPA or the FDA at 1-800-FDA-1088

• Patients receiving VASCEPA and concomitant anticoagulants and/or anti-platelet agents should be monitored for bleeding

Please see full Prescribing Information for more information on VASCEPA.

VAS-02654 04/20

References: 1. VASCEPA [package insert]. Bedminster, NJ: Amarin Pharma, Inc.; 2019. **2.** Centers for Medicare & Medicaid Services. 2020 ICD-10-CM. https://www.cms.gov/Medicare/Coding/ICD10/2020-ICD-10-CM. Accessed April 2, 2020. **3.** Bhatt DL, Steg PG, Miller M, et al; for the REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22. Bhatt DL. AHA 2018, Chicago. **4.** Bhatt DL, Steg PG, Miller M, et al; on behalf of the REDUCE-IT Investigators. Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT. *J Am Coll Cardiol*. 2019;73(22):2791-2802. Bhatt DL. ACC 2019, New Orleans. **5.** Department of Health and Human Services. [Docket no. FDA–2016–N–1127]: AbbVie Inc., et al; Withdrawal of approval of indications related to the coadministration with statins in applications for niacin extended-release tablets and fenofibric acid delayed-release capsules. *Federal Register*. 2016;81(74):22612-22613. **6.** Trilipix [package insert]. North Chicago, IL: AbbVie; 2018. **7.** Niaspan [package insert]. North Chicago, IL: AbbVie; 2018. **8.** Lovaza [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2019. **9.** Aung T, Halsey J, Kromhout D, et al. Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77 917 Individuals. *JAMA Cardiol*. 2018;3(3):225-234. **10.** ASCEND Study Collaborative Group; Bowman L, Mafham M, Wallendszus K, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379(16):1540-1550**. 11.** Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2018;7:CD003177. **12.** Manson JE, Cook NR, Lee IM, et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *N Engl J Med*. 2018. 2019;380(1):23-32. **13.** Update on Phase III STRENGTH trial for Epanova in mixed dyslipidaemia. https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/update-on-phase-iii-strength-trial-for-epanova-in-mixed-dyslipidaemia-13012020.html. Accessed April 3, 2020. **14.** Hilleman D, Smer A. Prescription omega-3 fatty acid products and dietary supplements are not interchangeable. *Manag Care*. 2016;25(1):46-52. **15.** Davidson MH. Omega-3 fatty acids: new insights into the pharmacology and biology of docosahexaenoic acid, docosapentaenoic acid, and eicosapentaenoic acid. *Curr Opin Lipidol*. 2013;24(6):467-474. **16.** Kleiner AC, Cladis DP, Santerre CR. A comparison of actual versus stated label amounts of EPA and DHA in commercial omega-3 dietary supplements in the United States. *J Sci Food Agric*. 2015;95(6):1260-1267. **17.** Mason RP, Sherratt SCR. Omega-3 fatty acid fish oil dietary supplements contain saturated fats and oxidized lipids that may interfere with their intended biological benefits. *Biochem Biophys Res Commun*. 2017;483(1):425-429. **18.** Jacobson TA, Glickstein SB, Rowe JD, Soni PN. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: A review. *J Clin Lipidol*. 2012;6(1):5-18. **19.** Zargar A, Ito MK. Long chain omega-3 dietary supplements: a review of the National Library of Medicine Herbal Supplement Database. *Metab Syndr Relat Disord*. 2011;9(4):255-271. **20.** Albert BB, Cameron-Smith D, Hofman PL, Cutfield WS. Oxidation of marine omega-3 supplements and human health. *Biomed Res Int*. 2013;2013:464921. **21.** Skulas-Ray AC, Wilson PWF, Harris WS, et al. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. *Circulation*. 2019;140(12):e673-e691. **22.** Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2013;36(11):3821-3842. **23.** American Society of Health-System Pharmacists. ASHP statement on the use of dietary supplements. *Am J Health-Syst Pharm*. 2004;61(16):1707-1711**. 24.** Jellinger PS, Handlesman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for

Management of Dyslipidemia and Prevention of Atherosclerosis. *Endocr Pract*. 2017;23(suppl 2)1-87. **25.** Department of Health and Human Services. [Docket no. FDA–2016–N–1097]: AbbVie Inc.; Withdrawal of approval of new drug applications for ADVICOR and SIMCOR. *Federal Register*. 2016;81(74):22608-22609.