Omega-3-acid ethyl esters (Lovaza)

Summary

Omega-3-acid ethyl esters (Lovaza) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (greater than or equal to 500 mg/dL) hypertriglyceridemia. Omega-3-ethyl esters contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-3-acid ethyl esters can reduce triglycerides by more than 50%, but may also increase low-density cholesterol (LDL-C) by 30 to 49%.

Hypertriglyceridemia occurs when the body has a higher than normal level of triglyceride (a type of lipid). It is usually discovered after performing a routine test for different lipid levels in the body. Causes of high lipid levels (or high cholesterol) include high-fat diet, lack of physical exercise, and medical conditions such as diabetes, hypothyroidism (a condition in which the body does not make enough thyroid hormone), liver disease, and other conditions. People with triglyceride levels between 150 mg/dL and 499 mg/dL are considered to have moderate hypertriglyceridemia. Severe hypertriglyceridemia is defined as having a fasting TG level greater than or equal to (≥) 500 mg/dL. People with hypertriglyceridemia can have a higher risk of heart attacks, strokes, inflammation in the pancreas (i.e., pancreatitis), and other health problems. The ultimate goal of treating hypertriglyceridemia is to reduce the risk of pancreatitis and Atherosclerotic cardiovascular disease (ASCVD).

Hypertriglyceridemia treatment options include lifestyle and dietary changes, and medications such as statins (such as atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, and fluvastatin), fibrates (fenofibrate, fenofibric acid, and gemfibrozil) and fish oil supplements (omega-3-acid ethyl esters and icosapent ethyl). Fibrate therapy can reduce triglyceride level by as much as 50% or more. Patients may receive a fibrate alone or in combination with a statin. Adding Vascepa [icosapent ethyl] can further reduce cardiovascular risk.

The ACC/AHA guidelines should be reviewed for the most current recommendations. Please refer to the ACC website at https://www.acc.org/guidelines for more information.

Definitions

"ASCVD" or "Atherosclerotic cardiovascular disease" is a chronic condition caused by plaque buildup in the arterial walls. ASCVD refers to conditions that include: coronary heart disease, myocardial infarction (heart attack), coronary artery stenosis, cerebrovascular disease (such as a stroke or transient ischemic attack), carotid artery stenosis, peripheral artery disease (e.g., claudication), and aortic atherosclerotic disease (e.g., abdominal aortic aneurysm).

"Fibrates" refer to a class of medications used to lower triglyceride levels and increase high density lipoproteins and include drugs like fenofibrate (TriCor), or gemfibrozil (Lopid).

"Hypertriglyceridemia" is a medical condition in which triglyceride levels are elevated.

"Lipids" are several types of fats found in the body. They are essential for the body to make hormones, vitamin D, and substances that help with digestion.

"Omega-3 Polyunsaturated Fatty Acids (PUFAs)" are a type of fat beneficial for heart health, found in certain types of fish, algae, and supplements.

"Statin" refers to medications that lower cholesterol levels in the blood, which are often prescribed to prevent cardiovascular disease.

"Triglycerides" are a type of lipid in the body.

Medical Necessity Criteria for Initial Authorization

The Plan considers omega-3-acid ethyl esters (Lovaza) medically necessary when ALL of the following criteria are met for the following indication:

For the treatment of severe hypertriglyceridemia with triglyceride level 500 mg/dL or above:

1. The member is 18 years of age or older; *AND*
2. The member has documented diagnosis of severe hypertriglyceridemia with pre-treatment (baseline) triglyceride level of ≥500 mg/dL; *AND*
3. The member is unable to use, or has adequately tried and failed maximally tolerated statin OR fibrate therapy (including reason for treatment failure); *AND*
4. The requesting provider submits documentation or attestation indicating nutritionist or provider education about lifestyle modifications (dietary changes and exercise) has been performed and that the patient has been on and will continue an appropriate lipid-lowering diet and exercise regimen*; AND*
5. Chart documentation and supporting lab work are provided for review to substantiate the above listed requirements.

<u>If the above prior authorization criteria is met, Lovaza (omega-3-acid ethyl esters) will be approved for up to 12 months.</u>

Medical Necessity Criteria for Reauthorization:

Reauthorization for up to 12 months will be granted if the member meets ALL of the following criteria:

1. The member still meets the applicable initial criteria; *AND*
2. The member has a documented therapeutic response to the requested therapy as evidenced by recent lab work (dated within the last 3 months) and clinical chart documentation showing ONE of the following:
    a. The member has shown a reduction in triglyceride (TG) levels since starting the requested medication; *or*
    b. The member has reached and maintained their triglyceride (TG) level goal; *AND*

The member maintains adherence to the prescribed dosing regimen as evidenced by pharmacy claims record.

Experimental or Investigational / Not Medically Necessary

Omega-3-acid ethyl esters (Lovaza) for any other indication are considered not medically necessary by the Plan, as this is deemed to be experimental, investigational, or unproven.

Appendix

<u>Prevention of Cardiovascular Events</u>

The inclusion of omega-3-acid ethyl esters (Lovaza) for the prevention of cardiovascular events is not supported at this time due to several key factors:

1. The effectiveness of marine- and plant-derived omega-3 fatty acids in preventing cardiovascular events remains uncertain. While some studies suggest a potential risk reduction in cardiovascular events and mortality related to coronary heart disease (CHD) with higher omega-3 fatty acid

intake, the available evidence lacks consistency and conclusive results. Therefore, it is challenging to establish clear criteria for the use of Lovaza in preventing cardiovascular events.

2. Current guidelines from the American Heart Association/American College of Cardiology (AHA/ACC) prioritize lifestyle modifications, including dietary changes and exercise, as the primary approach for reducing cardiovascular risk. For patients with clinical atherosclerotic cardiovascular disease (ASCVD) or diabetes mellitus, statin therapy is the recommended treatment alongside lifestyle modifications to lower LDL cholesterol, a significant contributor to ASCVD. The guidelines also suggest considering other established therapies such as ezetimibe and PCSK9 inhibitors in specific cases. However, omega-3-acid ethyl esters (Lovaza), specifically, is not recommended by the guidelines for primary or secondary prevention of cardiovascular events.
3. While a cardiovascular outcomes study showed a reduction in ASCVD risk with an omega-3 fatty acid preparation containing EPA in statin-treated patients with hypertriglyceridemia and established ASCVD or high risk of ASCVD (RECUDE-IT, icosapent ethyl [Vascepa]), it is crucial to note that this evidence cannot be applied universally to other omega-3 fatty acid preparations that contain a mixture of EPA and DHA. Different types of omega-3 fatty acids may have distinct effects on lipids and lipoproteins, making it challenging to generalize the findings to medications like omega-3-acid ethyl esters (Lovaza).

There is some literature to support that there is a relationship between lowering triglyceride and reducing the risk of major vascular events. A systematic review and meta-analysis found a relative risk (RR) of 0.80 (95% CI, 0.76-0.85; *P*<0.0001) per 1-mmol/L reduction in LDL-cholesterol (0.79 per 40 mg/dL) and 0.84 (95% CI, 0.75-0.94; *P*=0.0026) per 1-mmol/L (0.92 per 40 mg/dL) reduction in triglycerides. However, the REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial) significantly influenced these outcomes. When removed, the RRs became 0.79 (95% CI, 0.76-0.83; *P*<0.0001) per 1-mmol/L (0.78 per 40 mg/dL) reduction in LDL-C and 0.91 (95% CI, 0.81-1.006; *P*=0.06) per 1-mmol/L (0.96 per 40 mg/dL) reduction in triglycerides. It also appears that EPA has a higher associated with cardiovascular risk reduction, in the same study they found that each 1 g/day of EPA was associated with a 7% RR reduction (RR0.93, [95% CI, 0.91-0.95], p<0.0001), but the same was not true of DHA dosing (RR 0.96, [95% CI, 0.89-1.03]). The REDUCE-IT study assessed the effects of an EPA-only marine omega-3, and this may contribute it's significant cardiovascular risk reduction when combined with a statin. A 2024 systematic review and meta-analysis also found a reduction in cardiovascular events, cardiac death, myocardial infarction, and revascularization risk; however findings were significantly influenced by the REDUCE-IT trial and there was significant heterogeneity between studies (i.e., $I^2 > 25\%$).

<u>Review of Clinical Trials:</u>

Clinical trials evaluating marine omega-3 fatty acids have yielded mixed results. Low-dose mixtures of EPA and DHA did not significantly reduce cardiovascular endpoints in recent trials such as ASCEND, VITAL, and OMEMI. The JELIS trial demonstrated a reduction in major coronary events with EPA, but concerns were raised about its trial design. The REDUCE-IT trial, using high-dose icosapent ethyl (IPE), and EPA-only product, showed a significant reduction in cardiovascular events. However, the STRENGTH trial with omega-3 carboxylic acids did not demonstrate cardiovascular benefits. Differences in trial

design, patient populations, formulations of omega-3 fatty acids, and placebo comparators may contribute to these varying outcomes.

Potential Limitations and Considerations:

- *The use of mineral oil as a placebo in the REDUCE-IT trial has raised questions about its impact on LDL cholesterol and inflammatory markers, potentially influencing the observed cardiovascular benefits.*
- *Additionally, increased incidences of atrial fibrillation have consistently been observed in active treatment groups across recent omega-3 therapy trials.*

References

1. Abdelhamid, A. S., T. J. Brown, J. S. Brainard, P. Biswas, G. C. Thorpe, H. J. Moore, K. H. Deane et al. "Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Systematic Review, 3." (2020).
2. American College of Endocrinology Guidelines for the Management of Dyslipidemia and Prevention of Cardiovascular Disease- 2017. Endocrine Practice - 2017 April; 23(Supplement 2): S97-S115.
3. American Diabetes Association. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes - 2020. Diabetes Care 2020 Jan; 43(Supplement 1): S111-S134.
4. American Diabetes Association. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes – 2025. Diabetes Care. 2025;48(Suppl 1):S207-S238.
5. ASCEND Study Collaborative Group; Bowman L, Mafham M, et al,. Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus. N Engl J Med. 2018 Oct 18;379(16):1540-1550. doi: 10.1056/NEJMoa1804989. Epub 2018 Aug 26.
6. Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2012;97:2969-89 (erratum in J Clin Endocrinol Metab 2015;100:4685).
7. Bhatt D.L., Steg G., Miller M., et al. Effects of Icosapent Ethyl on Total Ischemic Events: From
8. Bhatt DL, Steg G, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019; 380:11-22.
9. Bhatt, D. L., Steg, P. G., Miller, M., Brinton, E. A., Jacobson, T. A., Ketchum, S. B., ... & Jiao, L. (2019). Reduction in first and total ischemic events with icosapent ethyl across baseline triglyceride tertiles. Journal of the American College of Cardiology, 74, 1159-1161.
10. Bowman, L., Mafham, M., Wallendszus, K., Stevens, W., Buck, G., Barton, J., ... & HPS Collaborative Group. (2018). Effects of n-3 fatty acid supplements in diabetes mellitus. New England Journal of Medicine, 379, 1540-1550.
11. Dong S, Wang Y, Bian J, et al,. The effect of omega-3 Polyunsaturated Fatty Acid (PUFA) prescription preparations on the prevention of clinical cardiovascular disease: a meta-analysis of RCTs. Nutr J. 2024 Dec 6;23(1):157. doi: 10.1186/s12937-024-01051-y.
12. DM Lloyd-Jones et al. 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2022 August 25 (epub).
13. Kalstad, A. A., Myhre, P. L., Laake, K., Tveit, S. H., Schmidt, E. B., Smith, P., ... & Seljeflot, I. (2021). Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: A randomized, controlled trial. Circulation, 143, 528-539.
14. Lovaza (omega-3-acid ethyl esters) [prescribing information]. Wixom, MI: Woodward Pharma Services LLC; February 2021.
15. Manson JE., Cook NR., Lee IM., et al,.Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. New England Journal of Medicine. 2019;380(1), 23-32. Epub 2018 Nov 10.

16. Marston NA, Giugliano RP, Im K, et al,. Association Between Triglyceride Lowering and Reduction of Cardiovascular Risk Across Multiple Lipid-Lowering Therapeutic Classes: A Systematic Review and Meta-Regression Analysis of Randomized Controlled Trials. Circulation. 2019 Oct 15;140(16):1308-1317. doi: 10.1161/CIRCULATIONAHA.119.041998. Epub 2019 Sep 18.
17. Nicholls, S. J., Lincoff, A. M., Bash, D., Ballantyne, C. M., Barter, P. J., Davidson, M. H., ... & Kastelein, J. J. (2018). Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: Rationale and design of the STRENGTH trial. Clinical Cardiology, 41, 1281-1288.
18. Nicholls SJ, Lincoff AM, Garcia M, et al,. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. JAMA. 2020 Dec 8;324(22):2268-2280. doi: 10.1001/jama.2020.22258.
19. Orringer CE, Jacobson TA, Maki KC. National Lipid Association Scientific Statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk. J Clin Lipidol. 2019;13(6):860-872.
20. Pearson GJ, Thanassoulis G, Anderson TJ, et al,. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. Can J Cardiol. 2021 Aug;37(8):1129-1150. doi: 10.1016/j.cjca.2021.03.016. Epub 2021 Mar 26.
21. Preston Mason R. New insights into mechanisms of action for omega-3 fatty acids in atherothrombotic cardiovascular disease. Curr Atheroscler Rep. 2019;21:2 doi: 10.1007/s11883-019-0762-1Sharma, G., Martin, S. S., & Blumenthal, R. S. (2020). Effects of omega-3 fatty acids on major adverse cardiovascular events: What matters most: The drug, the dose, or the placebo? JAMA, 324, 2262-2264.
22. SM Grundy et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol 2019; 73:e285.
23. US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults. US Preventive Services Task Force recommendation statement. JAMA 2022; 328:746.
24. Vascepa (omega-3-acid ethyl esters) [prescribing information]. Bridgewater, NJ: Amarin Pharma Inc; December 2019.
25. Virani SS, Newby LK, Arnold SV, Bittner V, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2023;148:e9–e119. doi: 10.1161/CIR.0000000000001168
26. Virani SS, Morris PB, Agarwala A, et al. 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021;78:960-93.
27. Wu, H., Xu, L., & Ballantyne, C. M. (2020). Dietary and pharmacological fatty acids and cardiovascular health. The Journal of Clinical Endocrinology & Metabolism, 105, 1030-1045.
28. Yokoyama, M., Origasa, H., Matsuzaki, M., Matsuzawa, Y., Saito, Y., Ishikawa, Y., ... & Kita, T. (2007). Effects of eicosapentaenoic acid on major coronary events in hypercholesterolemic patients (JELIS): A randomized open-label, blinded endpoint analysis. The Lancet, 369, 1090-1098.

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