Brand Name: Vascepa™

Generic Name: Icosapent ethyl (eicosapentaenoic acid)

Manufacturer: Amarin Pharmaceuticals

Drug Class[1,2]: Antihyperlipidemic; Omega-3 Fatty Acid

Uses[1,2,3,4,5]: Severe hypertriglyceridemia (≥500mg/dl)

Mechanism of Action[1,2,3,5]: Mechanism of action not clearly known; possible mechanisms of the metabolite eicosapentaenoic acid (EPA) include inhibition of acyl coenzyme A, 1,2: 1,2 diacylglycerol acyltransferase, increased hepatic beta-oxidation, a reduction in hepatic synthesis of very low-density lipoprotein triglycerides, or an increase in plasma lipoprotein lipase activity.

Pharmacokinetics[1,2,3,4,5]:

Absorption:	De-esterified to active metabolite (EPA) which is absorbed in the small intestine. The effect of food on absorption has not been studied; recommended to be given with or following a meal.
Distribution:	V_d=88 hours, >99% plasma protein binding (incorporated into phospholipids, triglyceride, and cholesterol esters)
Metabolism:	Mainly by hepatic beta-oxidation of EPA to acetyl coenzyme A; minor CYP450. Icosapent's metabolite EPA is the active entity.
Half-life Elimination:	EPA half-life elimination about 89 hours
Excretion:	Not renally excreted. Total plasma clearance of EPA at steady state is 684ml/hr.
Time to peak:	5 hours

Efficacy:

Citation:

Ballantyne CM, Bays HE, Kastelein JJ, Stein E, Isaacsohn JL, Braeckman RA, Soni PN. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol. 2012 Oct 1;110(7):984-92.

Study design:
A multicenter, placebo-controlled, randomized, double blind study

Description of study:

This was a 12 week trial studying the effect of icosapent-ethyl in statin-treated patients with high triglycerides (≥200 and <500mg/dl) and low LDL-C (≥40 and <100mg/dl). Treatment groups were 4g/day, 2g/day or placebo. Primary measure was median percent change in triglyceride levels from baseline and after 11 and 12 weeks. Secondary outcome measures included median percent change in non HDL-C, LDL-C, apolipoprotein B, VLDL-C, and lipoprotein-associated phospholipase A_2.

Triglycerides were reduced by 34.5% and 31% from baseline in both 2g/day and 4g/day groups, respectively. All other measures, including post hoc secondary measures were significantly lower than placebo for both groups except for the following: LDL-C in 2g/day vs. placebo, HDL-C in 2g/day vs. placebo, and high-sensitivity CRP in 2g/day vs. placebo. Significant reductions in triglycerides were seen in both diabetic and non-diabetic groups, and patients with higher baseline triglycerides showed greater reduction.

The only adverse events occurring more often in treatment group (by percentage) were musculoskeletal and connective tissue disorders, including arthralgias. There was no statistical difference in the number of serious adverse events between groups.

Limitations:

While many outcomes were seen as statistically significant, the clinical relevance of the changes seen is inconclusive. The authors focus on absolute reduction instead of relative reduction, which is not always the goal of therapy. There were no statistical analyses on the differences between the end of treatment and baseline, only end results of treatment groups versus placebo. It would have been prudent for the study to include patients with triglycerides >500mg/dl as well.

Conclusions:

Icosapent may be helpful in lowering triglycerides in patients already on multidrug therapy for dyslipidemia. From this data, it is not possible to say that patients would be able to reach treatment goals in the absence of other triglyceride lowering agents. It may play a role in the replacement of current prescription omega 3 fatty acid medications since it was not associated with increases in LDL-C. Icosapent decreases triglycerides in patients on statins and those not on statins; however, the effects on LDL-C are not exactly known for patients not receiving statins.

Citation:

Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized,double-blINd, 12-week study with an open-label Extension [MARINE] trial). Am J Cardiol. 2011 Sep 1;108(5):682-90

Study Design:
Multi-center, placebo-controlled, randomized, double blind study with an open-label extension

Description of Study:

This 12 week study took place in 9 different countries around the world. Participants had triglyceride levels of ≥500mg/dl to ≤2,000mg/dl. Treatment groups were 4g/day, 2g/day or placebo. Primary measure was median percent change in triglyceride levels from baseline average and after 11 and 12 weeks. Secondary measures were percent

change from randomization baseline for VLDL-C, apolipoprotein B, lipoprotein-associated phospholipase A_2, and post hoc measures of total cholesterol, LDL-C, HDL-C, VLDL-TG, and non HDL-C.

Placebo-corrected median triglyceride levels were reduced by 33.1% ($p<0.0001$) and 19.7% ($p=0.0051$) for 4g/day and 2g/day, respectively. Triglycerides were significantly reduced in both statin and non-statin groups, although the statin group had a much a larger reduction (4g/day, 65%, $p=0.0001$; 2g/day, 40.7%, $p=0.0276$) than the non-statin group (4g/day, 25.8%, $p=0.0002$; 2g/day, 16.4%, $p=0.0360$).

No adverse events were seen more often in treatments groups as compared to placebo. No differences were noted in vital signs, EKG parameters, hemoglobin A1c, ALT, AST, or CK.

Limitations:

While many outcomes were seen as statistically significant, the clinical relevance of the changes seen in the secondary measures is inconclusive

Conclusions:

This study provided a statistical analysis of the baseline versus the end of treatment levels in each group, instead of only comparing it with placebo, and included patients with triglycerides ≥500mg/dl. The trial supports the claim that icosapent can provide major reduction in triglycerides in patient with or without statin use, while not significantly affecting LDL-C.

Contraindications[1,2,3]**:** Hypersensitivity to icosapent ethyl or any component of the formulation

Precautions[1,2,3,5]**:** Patients with fish or shellfish allergies, coagulopathy or anticoagulation therapy, hepatic impairment, medications known to worsen hypertriglyceridemia (beta blockers, thiazides, estrogens). In patients with hepatic impairment, monitor ALT and AST during therapy.

Adverse Effects[1,2,3,4,5]**:** 1-10% neuromuscular and skeletal effects (arthralgias 2.3% vs. 1% in placebo); 1% oropharyngeal pain (pain in throat or dental pain); hemorrhagic diathesis[4]; and epistaxis or ecchymosis when given with antiplatelet or anticoagulant agents[3].

Drug Interactions[1,2,3,4]**:** Antiplatelet agents, warfarin: omega-3 fatty acids inhibit platelet aggregation, therefore may increase antiplatelet and anticoagulant effects, respectively. Some instances report a change in INR[3], but no major bleeding events occurred. Monitor therapy.

Dosing/Administration[1,2,3,4,5]**:** Adults 4g/day given as 2 capsules orally twice daily with food. Rule out other causes of hypertriglyceridemia (e.g. diabetes mellitus, hypothyroidism, medications, etc) before prescribing.

Use in Special Circumstances[1,2,3,5]**:**

Pregnancy: Category C; no studies in humans have been done, but developmental abnormalities have been seen in rat fetuses when pregnant females were given doses 6 to 40 times greater than recommended human dosing[5].

*Breastfeeding: E*xcreted into breast milk, potentially at 6 to 14 times higher concentrations than in plasma as seen in rats[5].

Special Populations: No adjustments needed in geriatric or renally impaired patients. No adjustments needed for hepatic impairment; however, ALT and AST monitoring is recommended. Dosing in pediatric patients (<18 years of age) has not been established.

Conclusion:

Icosapent ethyl provides an alternative to fibrates and other prescription omega-3 fatty acids for the treatment of hypertriglyceridemia (≥500mg/dl). A benefit of icosapent ethyl over the alternatives includes its minimal effects on LDL cholesterol. Patients on statins have had more significant decreases in triglycerides while on icosapent ethyl; however, non-statin users have also had a significant reduction in triglycerides. There is not enough evidence to predict the effect of icosapent ethyl on LDL cholesterol in patients that are not receiving statins, specifically.

Recommended References (6)

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5. Vascepa [package insert]. St. Peterburg, FL. Amarin Pharma Inc, Dublin, Ireland: 2012.
6. Ballantyne CM, Bays HE, Kastelein JJ, Stein E, Isaacsohn JL, Braeckman RA, Soni PN. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol. 2012 Oct 1;110(7):984-92.
7. Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized,double-blINd, 12-week study with an open-label Extension [MARINE] trial). Am J Cardiol. 2011 Sep 1;108(5):682-90

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