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Class Update: Other lipid Lowering Agents

Month/Year of Review: September 2013
PDL Classes: Other Lipid Lowering Agents
New Drug Evaluation: Icosapent Ethyl (ICP)
Manufacturer: Amarin Pharma Inc

Date of Last Review: May 2012
Source Document: OSU College of Pharmacy
Brand Name: Vascepa®
Dossier Received: Yes

Current Status of PDL Class:

- **Preferred Agents:** CHOLESTYRAMINE POWDER, FENOFIBRATE TABLETS, GEMFIBROZIL TABLET, NIACIN TABLET, NIACIN ER (NIASPAN®)
- **Non-Preferred Agents:** OMEGA-3 ACID ETHYL ESTERS (LOVAZA®), EZETIMIBE (ZETIA®), COLESEVELAM HCL (WELCHOL®), FENOFIBRIC ACID (TRILIPIX, FIBRICOR), COLESTIPOL HCL, MICRONIZED FENOFIBRATE (ANTARA, LOFRIBA)

Previous Conclusions and Recommendation:

- Add other non-statin lipotropics as a class to the PDL
- Make cholestyramine a preferred bile acid sequestrant, which has shown improved cardiovascular (CV) related or stroke outcomes.
- Include gemfibrozil as a preferred lipotropic which as demonstrated improved CV related or stroke outcomes.
- There is no clinical evidence of superiority of one fenofibrate agent over another.
- Make Niaspan and Niacor preferred due to a demonstrated reduction in cardiovascular outcomes.
- Make ezetimibe a non-preferred agent due to insufficient outcome data, and implement the non-PDL prior authorization criteria for use.
- Make Lovaza a non-preferred agent and use the non-PDL prior authorization criteria due to its use as an alternative to a fibric acid derivative and niacin for hypertriglyceridemia.

Research Questions:

- Is there any new comparative evidence for other lipid lowering agents, in reducing cardiovascular mortality or stroke in adult patients?
- Is there any new evidence about comparative harms of other lipid lowering agents in adult patients being treated for hyperlipidemia?
- Are there subpopulations of patients for which one lipid lowering agent is more effective or associated with less harm?
- Is icosapent ethyl (ICP) more effective or safer than other lipid lowering agents in reducing cardiovascular mortality or stroke in adult patients with hypertriglyceridemia?

Conclusions:

- There is insufficient evidence to compare the long-term clinical benefits of combined lipid-modifying therapy with any other lipid lowering class with statin therapy to intensification of statin monotherapy. There is recent evidence that niacin or fibrates in addition to statins has neutral effects on CV outcomes.
- There remains insufficient comparative evidence for drugs within each class.
- There is moderate quality evidence that gemfibrozil may reduce the risk for stroke and CV mortality.
- There is insufficient evidence that the use of omega-3 fatty acids reduces cardiovascular outcomes. They remain a treatment alternative to fibric acid derivatives and niacin for the treatment of high triglycerides.
- There is insufficient evidence to suggest that ICP at a dose of 2g BID when compared to placebo is effective in decreasing risk for pancreatitis and cardiovascular (CV) outcomes in patients with TG levels exceeding 500 mg/dL. The trials have been of insufficient duration to attain sufficient long-term safety and efficacy outcomes.
- There is insufficient evidence comparing ICP to any of the current therapies. When compared to the efficacy of current treatments such as fibrates or niacin, ICP has similar TG lowering ability but there is insufficient data to compare CV risk lowering or pancreatitis risk lowering in any of these therapies. ICP is at least as safe as fibrates or niacin and has significantly fewer treatment-associated adverse effects.

Recommendations:

- Make isocapent ethyl a non-preferred lipotropic agent and use the non-PDL prior authorization criteria due to its use as an alternative to a fibric acid derivative and niacin for hypertriglyceridemia.
- No significant changes in comparative efficacy or safety were found for the other lipid lowering agents. Continue to prefer gemfibrozil and Niaspan due to a demonstrated reduction in cardiovascular outcomes.
- Evaluate comparative costs of other agents in executive session.

Background:

Cardiovascular disease (CVD) includes coronary heart disease, stroke, heart failure, arrhythmias, heart valve disease, congenital heart disease, and hypertension. Abnormal lipid levels can lead to the development of atherosclerosis. There is a known association of elevated low-density lipoprotein (LDL) levels with CVD.[1] Therefore, there has been a strong strategy to focus on LDL reduction to decrease the risk of CVD. Statin therapy has the most robust therapy in preventing CVD events.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III includes guidelines on when to start lipid-lowering therapy and LDL targets for coronary heart disease (CHD) risk reduction.[2] High risk individuals include those with established CHD, other clinical atherosclerotic CVD, or multiple risk factors. These individuals have a 10-yuear CHD risk greater than 20% and their LDL target is less than 100 mg/dl, with an optional goal of less than 70 mg/dl. An update of these guidelines (ATP IV) is anticipated to be released shortly. Statins are the most widely prescribed lipid-lowering agents and are often used as monotherapy. Statins can be combined with other medications, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acids, nicotinic acid, and omega-3 fatty acids. Evidence has demonstrated that combination therapy can lead to better lipid outcomes, but does not reduce cardiovascular death, MI, revascularization, or stroke.[1] There has also been a demonstrated correlation between raised triglycerides and CV disease.[3] However, the reduction of triglycerides has not been shown consistently to be beneficial for stroke or other CV mortality. There has been some controversy as to whether hypertriglyceridemia is an independent risk factor of CHD since patients with these elevated levels often have other CHD risk factors such as central obesity,

diabetes and tobacco or alcohol use.[2,4–6] The Endocrine Society suggests that mild or moderate TG levels put a patient at greater risk for CVD and by treating severe or very severe hypertriglyceridemia in order to decrease risk for pancreatitis, we may be increasing the risk of CHD in these patients though there is no source cited.[7] A meta-analysis and review showed that CV events were significantly increased in patients with hypertriglyceridemia as was incidence of CV death and MI; however all-cause mortality was not significant.[8]

Fibric acid derivatives such as fenofibrate and gemfibrozil have been examined in several studies looking at CHD risk reduction including the FIELD trial, the Helsinki Heart Study and the ACCORD trial.[9] The FIELD study showed a non-significant decrease in coronary events collectively when fenofibrate was compared to placebo, however when non-fatal MI was examined separately from CHD death, there was a significant decrease in non-fatal MI, a non-significant increase in CHD death, and a significant decrease in total CVD events and coronary revascularization.[10] The Helsinki Heart Study looked at gemfibrozil and prevention of CHD risk in patients with borderline high TGs.[11,12] Patients who were originally placed on gemfibrozil had significantly less risk of CHD mortality, but all cause mortality was not statistically significant. [11,12] Gemfibrozil had a significant effect on total cholesterol, HDL-c, LDL-c and TGs therefore correlation between TG levels and cardiac endpoints are difficult to assess as independent risk factors and patients.[11] The ACCORD trial examined CV risk in patients on combination statin and fenofibrate therapy vs statin alone.[9] TG levels were significantly lower in the fenofibrate group though there was no significant difference between the two groups at the follow up in the primary outcome of major fatal or nonfatal CV event or any of the secondary outcomes such as stroke, non-fatal MI or death from any cause.

Niacin has inconsistent LDL-c lowering, requiring high doses which may increase incidence of adverse reactions such as hepatotoxicity, hyperuricemia and hyperglycemia therefore it has historically been most often used in lower doses (<2g) to target TGs with or without a statin.[2,7] Recent evidence from the AIM-HIGH trial, compared coronary heart disease (CHD) risk reduction with niacin/simvastatin combination therapy, indicated that the addition of niacin may actually increase incidence of ischemic strokes and investigators saw no reduction in the primary endpoint of composite death from CHD, non-fatal myocardial infarction(MI), ischemic stroke, hospitalization for acute coronary syndrome and symptom driven coronary or cerebral revascularization.[13]

Prescription omega-3 fatty acids (POM3) with a combination of DHA and EPA (such as Lovaza) have shown to effectively lower serum TG levels, however elevated LDL-c levels have also been observed, the clinical significance of this is unknown.[14,15] In the Japan EPA Lipid Intervention Study (JELIS), increases in LDL-c associated with fish oil was determined to be primarily associated with the DHA component and not EPA.[15,16] Primary endpoints in JELIS included major coronary events, sudden cardiac death, fatal and non-fatal myocardial infarction and other non-fatal events including unstable angina, angioplasty, stenting or coronary artery bypass grafting.[16] Incidence of major coronary events in all patients statistically favored the use of EPA compared to placebo, however when primary and secondary prevention patients were separated the results were insignificant. LDL-c goals were reached in approximately equal proportions of both the EPA and non-EPA group whereas more patients in the EPA group reached non-HDL-c goals.[17] There was lower incidence of CAD in patients who were on EPA and/or who were at their LDL-c and non-HDL-c goal indicating that there may be some protective effect of EPA in patients who have not met non-HDL-c and LDL-c goals but this requires further study. Incidence of CAD did not appear to be directly affected by lowering TGs. ICP contains only EPA instead of both EPA and DHA like most supplements and therefore theoretically doesn't increase LDL as much as EPA/DHA combinations, but also seems less effective for lowering TGs. Omega 3 fatty acid therapy research has produced some evidence of benefit of these agents, and the increase in LDL-c may not be clinically relevant, however further data is required before these agents could be strongly recommended as an alternative to, or adjunct to, standard statin or fibrate therapy.

Methods:

A MEDLINE Ovid search was conducted using all lipid lower agents including: hyperlipidemia, hypercholesterolemia, cardiovascular disease, hydroxyl-3-methyglutaryl coenzyme A (HMG COA) reductase inhibitors, statin, ezetimibe, fibrates, nicotinic acid, niacin, bile acid sequestrant (BAS) and omega-3 fatty acids.

The search was limited to randomized controlled trials and meta-analysis, English language, and to studies conducted in humans from May 2012 to present. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic reviews:

Agency for Healthcare Research and Quality:
At the time of this review, a draft AHRQ review comparing the benefits and harms of combination of statin and other lipid-modifying medication to intensification of statin monotherapy was available, including studies through January 2013.[1] Studies in adults with moderate or high cardiovascular disease risk were included. Fifty-eight RCTs were included in the analysis. The strength of evidence was overall variable across comparisons. Only one comparison had high strength of evidence for serious adverse events and nine comparisons had moderate strength of evidence for LDL and HDL outcomes. All other comparisons and outcomes had low or insufficient evidence, including clinical outcomes of mortality, acute coronary events, and revascularization procedures. Other conclusions related to LDL and HDL outcomes are defined below:

Bile acid sequestrants plus statin therapy
- There is moderate quality evidence that combination therapy with bile acid sequestrants and low potency statin therapy lowers LDL cholesterol up to 14% more compared to intensification of statin monotherapy.
- There was insufficient evidence to compare combined bile acid sequestrant and statin therapy with statin monotherapy on the rates of serious adverse events.

Ezetimibe plus statin therapy
- There is moderate quality evidence that combination therapy with ezetimibe in combination with mid potency statin improves LDL-c compared to high potency statin monotherapy and low quality evidence that it improves HDL-c compared with statin monotherapy.
- There is high quality evidence that high potency statin m monotherapy produces fewer serious adverse events than combination of mid potency statin with ezetimibe.
- In patients with preexisting coronary heart disease and in patients with diabetes, there is moderate quality evidence that ezetimibe in combination with mid potency statin more effectively lowers LDL and low quality evidence for raising HDL as compared to high potency statin monotherapy.

Fibrate plus statin therapy
- There is moderate quality evidence that high potency statin monotherapy lowers LDL up to 15% more than mid potency statin in combination with fibrate.
- Moderate quality evidence demonstrates that mid potency statin in combination with fibrate raises HDL up to 10% more than high potency statin monotherapy.

- There is insufficient evidence to compare fibrate plus statin combination therapy to statin monotherapy on the rates of serious adverse events.

Niacin plus statin therapy
- There is low quality evidence that high potency statin monotherapy lowers LDL up to 12% more than mid potency statin in combination with niacin.
- There is low quality evidence that mid potency statin in combination with niacin raises HDL more than high potency statin monotherapy.
- There is insufficient evidence to compare the combination of niacin and statin to statin monotherapy on the rates of serious adverse events.

Omega-3 Fatty Acid plus statin therapy
- There is insufficient evidence to compare the benefits or serious adverse events of combined lipid-modifying therapy with an omega-3 fatty acid and statin to statin monotherapy on LDL-c and HDL-c, regardless of statin potency.

The authors concluded that the evidence suggests that some combination therapy regimens may confer benefits with respect to lowering LDL levels, including bile acid sequestrants and ezetimibe. However, intensification of statin monotherapy provided benefits or showed little difference with respect to LDL lowering in comparison to combination therapy with fibrates or niacin. There is insufficient evidence to address whether LDL lowering benefits achieved with these medications leads to decreased rates of CV disease. The evidence suggests that providers should tailor therapy based on individual patient needs and concerns for adverse events.

Zhou et al:
A recent systematic review and meta-analysis of RCT's evaluated the effects of fibrate therapy on stroke.[3] Studies were reviewed by 2 authors and quality was assessed using the Jadad score. The analysis included 10 RCTs consisting of 37,791 patients. Pooling the trials showed that fibrate therapy had no effect on the risk of stroke (RR 1.02; 95% CI 0.90 to 1.16). Six trials demonstrated no evidence that fibrate therapy protected against fatal stroke (RR 0.790; 95% CI 0.51 to 1.23) with little heterogeneity. An inverse relationship between total cholesterol lowering and incidence of stroke was observed. Subgroup analysis showed that gemfibrozil therapy was associated with a statistically significant difference on the risk of stroke (RR 0.72; 95% CI 0.53 to 0.98, p=0.04), however this was based on a small subset of patients. Study participants included those with a history of stroke, diabetes, myocardial infarction, coronary disease, or high levels of cholesterol.

Lavigne, et al.:
A systematic review assessed the efficacy of niacin for reducing CVD events.[18] A literature search identified 11 RCTs reporting clinical CVD event data with a minimum of 6 months of follow-up. The quality of each study was assessed using the Jadad scale. The primary analysis looked at the effect of niacin, as monotherapy or as adjunctive treatment, on the composite endpoint of any CVD event (cardiac death, nonfatal MI, hospitalization for acute coronary syndrome, stroke, or revascularization procedure). Overall, the primary composite endpoint of any CV event was significantly less frequent in niacin-treated patients compared with controls (OR 0.66; 95% CI 0.49-0.89; p=0.007, I2=59%). There was no significant difference in stroke risk (OR 0.88; 95% CI 0.5 to 1.54; p=0.65). There was no significant difference in CVD events when analysis was limited to studies in which treatment and control arms differed only with respect to the addition of niacin therapy. Results need to be interpreted with caution as there were significant differences between studies, including comparators, dosing, and population characteristics.

Kotwal, et al.:
Another systematic review evaluated the effect of omega3 fatty acids on CV outcomes.[19] Two investigators reviewed all abstracts and the quality of the studies was assessed using the Jadad criteria. The primary outcome was a composite of CV events (MI, stroke, and CV death). A total of 20 studies were included in a meta-analysis, with a total of 62,851 patients. Twelve studies showed no benefit of omega 3 fatty acids on the primary outcome (RR 0.96, 95% CI 0.90-1.03; p=0.24; I2=47.2%). The definition of composite CV outcome differed slightly between studies. Treatment with omega 3 fatty acids did show to protect against vascular death (RR 0.86, 95% CI 0.75-0.99; p=0.03) but not against sudden death. There was no evidence that treatment with omega 3 fatty acids reduced total mortality or nonvascular mortality. The use of omega-3 fatty acids was associated with an increased risk of side effects (RR .18; 95% CI 1.02-1.37; p=0.03) which were mainly gastrointestinal in nature.

Horizon Scan:
A recent AHRQ Horizon Scan report identified 2 cholesterol ester transfer protein inhibitors currently in Phase III trials for lipid management in coronary artery disease.[20] One human monoclonal antibody for the treatment of hypercholesterolemia is also being studied to decrease CV events in those with hypercholesterolemia.

New Guidelines:
American Diabetes Association (ADA):
The ADA recommendations state combination therapy for lipid-lowering has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended (level A recommendation).[21] The guidelines state that nicotinic acid has been shown to reduce CVD outcomes, but the study was done in a nondiabetic cohort and gemfibrozil has been shown to decrease rates of CVD in patients without diabetes. In one large trial specific to diabetic patients, fenofibrate did not reduce overall cardiovascular outcomes.

Canadian Cardiovascular Society:
The 2009 Canadian Cardiovascular Society Dyslipidemia guidelines have been updated using the GRADE system for recommendations and process.[22] This update recommends using apolipoprotein B or non-HDL cholesterol as alternate lipid markers and introduces the concept of cardiovascular age. No new recommendations on nonstatin pharmacotherapy were made in the 2012 update. Authors state that no studies have demonstrated a decrease in CVD event rate with the addition of lipid modulating drugs to statin therapy. For subjects who do not tolerate statin therapy, favorable LDL effects can be achieved with ezetimibe, bile acid sequestrants, or niacin.

The Endocrine Society Clinical Practice Guidelines:
Clinical practice guidelines were developed for hypertriglyceridemia by an endocrine society task force.[7] The task force used the GRADE approach to develop recommendations. The guidelines recommend that a fibrate be used as a first-line agent for reduction of triglycerides in patients at risk of triglyceride-induced pancreatitis (low quality evidence). They suggest that three drug classes (fibrates, niacin, omega 3 fatty acids) alone or in combination with statins be considered as treatment options in patients with moderate to severe triglyceride levels (low quality evidence).

New Drug Evaluation: Icosapent Ethyl (Vascepa®)

FDA approved indications: ICP is an ethyl ester of eicosapentaenoic acid (EPA) indicated as an adjunct to dietary therapy in the treatment of adult patients with severe hypertriglyceridemia (>500 mg/dL).

Clinical Efficacy Data:
Two pivotal Phase 3, placebo controlled, randomized, double blind trials (MARINE and ANCHOR) led to the approval of Vascepa™ (icosapent ethyl), an omega-3 fatty acid product that is ≥96% EPA, by the FDA on July 26th of 2012. ICP is approved for the treatment of hypertriglyceridemia at a dose of 2g twice daily to be used as an adjunct to diet and exercise in patients with very high TGs (≥500 gm/dL).[23,24] The MARINE and ANCHOR trials looked at two distinctly different populations of patients with differing degrees of hypertriglyceridemia.[23–25]

MARINE Trial
The MARINE trial was evaluated as being of poor-fair quality due to lack of transparency in the randomization and blinding process, short duration and lack of relevant clinical endpoints. This a phase 3, multi center, placebo-controlled, randomized, double-blind study examined patients with TG levels ranging from 500-2000 mg/dL, with or without background statin therapy, who were placed on 4 g QD ICP, 2g QD ICP or placebo for a duration of 12 weeks with a 40 week open label extension period.[23] Patients were predominantly Caucasian and male, 88% and 76% respectively, with a mean age of 52.9+/-9.34 years, and a mean BMI of 30.8+/-4.25 kg/m^2. 28% of patients were diabetic, 25% of patients were on a statin. The primary endpoint for the MARINE trial was placebo-corrected median percentage of change in TG from baseline to week 12 (study end). There was a statistically significant decrease in TGs in the Intent-to-treat (ITT) population; however there was no mention of how missing data was treated (i.e. last observation carried forward, mean of available values etc.). Results showed a significant percent placebo corrected decrease in TGs from baseline in both the 2 g daily and the 4 g daily groups (-19.7 and -33.1 $p<0.01$ for both). The change in LDL-c and HDL-c was non-significant in both cases. The results of the MARINE study showed that ICP is effective at decreasing TGs without the statistically significant LDL-c increase seen with other fish oil products but there is no efficacy data regarding whether this drug prevents pancreatitis or CV events. The ICP 4 g daily dose is what the FDA has approved (2 g BID) and this dose resulted in a greater mean % change from baseline with all study endpoints than the 2 g daily doses though not all of the differences were statistically significant.

ANCHOR Study
The ANCHOR study was a fair quality study due to lack of relevant clinical endpoints, a change in inclusion criteria part-way through the trial, low external validity due to primarily white cohort, and low internal validity due to lack of transparency with blinding, treatment allocation, non-adherence and contamination.[24] This phase 3, multi center, placebo-controlled, randomized, double-blind study looked at patients with TG levels ranging from 200-500 mg/dL despite being at their LDL-c goal with background statin therapy. Patients were placed on 4g QD ICP, 2g QD ICP or placebo for 12 weeks. The population in this trial was primarily Caucasian (96%), with a mean age of 61.4 years and mean BMI of 32.9kg/m^2, 73% of patients had diagnoses of diabetes mellitus, A1c range of 6.5-6.7% and the mean TG level was 259.0 mg/dL. Of the 702 patients who met the eligibility criteria and were randomized, 94.4% of patients completed the trial per protocol, 97.8% were included in the primary analysis, and 100% were included in the safety analysis. [24] This trial developed a protocol amendment after randomization had begun to facilitate enrollment: A1c was increased to >9.5% from 9.0%, the mean of 2 TG qualifying values was ≥185 ,g/dL with ≥1 or the 2 values ≥200 mg/dL, and the upper limit LDL-c was increased to ≤115 mg/dL.[25] Several subgroup analyses were conducted looking at various statin therapies, diabetes and degree of TG elevation. [24] Significant decreases in TG levels were seen with the 4g per day group taking simvastatin, atorvastatin and rosuvastatin as well as the patients in the 2 g per day group taking simvastatin. Higher baseline TG levels (≥289.5 mg/dL) appeared to result in greater TG decreases but

there was no significant difference in TG decrease in patients with diabetes or with low to moderate TG levels (<289.5).[12] Results showed a significant percent placebo corrected decrease in TGs from baseline in both the 2 g daily and the 4 g daily groups but the percent placebo corrected change in LDL-c and HDL-c from baseline was non-significant.[12] Results were assessed based upon an ITT basis and missing data was inputted using the last-observed-carried-forward method. The results of the ANCHOR study reinforce the results of the MARINE study in ICP's ability to decrease TG levels significantly without risk of increased LDL-c levels but as with the MARINE study, there is no data assessing the CV implications of this drug.

REDUCE-IT Study

The REDUCE-IT study is an ongoing trial looking at ICP in patients with TG levels between 150-500 mg/dL who are at high risk for CVD. The primary endpoint for this trial will be composite endpoint of CV death, MI, stroke, coronary revascularization, and hospitalization for unstable angina.[26] Whereas these endpoints are clinically relevant, there is no endpoint of pancreatitis and the patient population is not relevant for the indication of hypertriglyceridemia treatment in patients with serum TG levels ≥500 mg/dL. This trial is more likely an attempt to expand the indications of this drug rather than to illuminate its efficacy in prevention relevant clinical endpoints.

Data from the ICP clinical trials have demonstrated a significant decrease in TG levels without any LDL-c increase, however there are no published studies looking at this drug that have examined outcomes more directly related to patient long term survival, pancreatitis risk or CV events. The JELIS trial showed that EPA (EPA purity of >98%, similar to ICP purity of ≥96%) may have some promise in prevention of some CV events; however the significant limitations of this study beg further examination. Until more studies looking at ICP and its efficacy in relevant clinical outcomes such as pancreatitis and CV risk are completed, or until head-to-head superiority trials can be performed, it is difficult to determine the clinical efficacy of this drug.

<u>Clinical Safety:</u>

The pivotal trials, ANCHOR and MARINE, provide minimal safety outcomes data and are limited to the duration of the trials since there are no follow up safety analyses for these trials. In the short term safety analysis, patients experienced minimal side effects mostly involving GI symptoms and no serious side effects were associated with the study drug.[23,24] In the MARINE trial, 35% of the 4g group and 34% of the 2g group developed a treatment emergent adverse event and 37% of the placebo indicating no difference in incidence of adverse events in patients on the study drug.[11] The only adverse events that occurred in >3% of patients were diarrhea, nausea and eructation, all of which were more common in the placebo group with the exception of nausea which was more common in the 2g group, however it is unclear if these differences were significant. Four patients discontinued the study medication due to treatment emergent adverse events: 1 patient in the 2g group and 3 in the placebo group. Only 2 serious adverse events occurred; coronary artery disease and noncardiac chest pain, however the study investigators concluded that these events were unrelated to the study drug though no details are provided regarding this conclusion. There were no significant changes in vital signs, ECG parameters, ALT/AST, or creatinine kinase in either of the study groups. The ANCHOR trial showed only one adverse event, arthralgia, that occurred in more than 3% of patients with increased incidence in the study groups when compared to placebo, all other adverse events (diarrhea, nausea and nasopharyngitis) were more common in placebo. An important note here is that arthralgia was not a dose dependent adverse event and it was not observed in the MARINE trial, and the ANCHOR trial patient baseline characteristics were outside of the current FDA indications of TG levels >500 mg/dL therefore this adverse event requires further study.

The integrated summary of safety data from Amarin Pharma (May 2012) was derived from 15 clinical studies: 2 phase 1 studies in healthy subjects; 2 phase 3 clinical studies in hypertriglyceridemic patients (MARINE and ANCHOR); 3 drug interaction studies and 8 clinical studies in patients with CNS disorders which are no longer under development due to lack of efficacy.[25] Patients included in the dataset received doses of 0.5-4 g daily (particularly wide dose ranges) and took at least 1 dose of ICP during blinded and open label periods. 55.5% of patients reported all causality treatment emergent adverse events the most common

(occurred in ≥3% of patients) were: diarrhea (6.4%), depression (3.7%), falls (3.7%) and nausea (3.3%). Most treatment emergent adverse events were mild to moderate and considered unrelated to treatment and 4.5% of patients reported a serious adverse event. Most commonly reported adverse events were as follows: non-cardiac chest pain (0.3%), aggression (0.2%), depression (0.2%), psychotic disorder (0.2%), overdose of dothiepin (0.2%), irritability (0.2%), and CAD (0.2%). There were 3 serious adverse events that occurred in the CNS population (there was no information regarding the reason for looking at this population; however omega 3 fatty acids are occasionally used by the psychiatric community to treat depression) that were considered to be treatment related: completed suicide, subdural hematoma and iron deficiency though there were no percentages reported.[14] Two deaths occurred in patients taking ICP, one was a completed suicide in a Huntington's disease patient taking 2 g/day that was considered possibly related and an accidental dothiepin overdose in the 1 g per day group that was determined to be unrelated to treatment. 2.9% of patients reported treatment emergent adverse events that led to discontinuation of the study drug; however there were no individual events that occurred in >1% of patients. When the hypertriglyceridemia placebo controlled integrated data set was examined, a total of 622 patients were treated with ICP and 309 patients received placebo and the incidence of all cause treatment emergent adverse events was reported in 45.8% of ICP patients and 48.9% of placebo patients.[14] Most common side effects (occurring in ≥3% of patients) were: diarrhea (3.7% ICP, 3.9% placebo), nausea (2.6% ICP, 3.9% placebo), and arthralgia (2.6% ICP, 1.3% placebo). There were no significant differences in the subgroups of gender, race, smoking status, age, statin use or alcohol use in the overall integrated summary of safety and there were no dose related trends observed in the incidence of patients with treatment emergent adverse events (TEAEs), treatment related TEAEs, serious adverse events or TEAEs leading to discontinuation.[14] In the hypertriglyceridemia placebo controlled integrated dataset, there were no significant differences in TEAEs in patients due to vital signs, laboratory values, gender, age, race, smoking status or alcohol use.[14] In addition there was no significant increase in fasting plasma glucose, or A1c in diabetic patients when compared with placebo.[14] There was no indication of any increased risk of bleeding with ICP compared to placebo. Liver transaminase levels and cutaneous adverse reactions were similar in both the treatment group and placebo and the incidence was small in both groups.

Overall, ICP was well tolerated and no serious adverse events were significantly associated with the study drug in either of the pivotal trials, MARINE or ANCHOR, other than arthralgia which was seen in some of the phase II trials described in the integrated data set but the current evidence is not sufficient to conclusively attribute this to ICP and will require further investigation.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1. Acute Pancreatitis
2. CV events
3. Hospitalizations
4. Mortality

Primary Study Endpoints:

1. TG levels (% change from baseline to week 12)

Secondary Endpoints:

2. LDL, VLDL, HDL, non-HDL, ApoB, Lp-PLA_2, and C reactive protein % change from baseline to week 12
3. Incidence of adverse events
4. Change in laboratory, vitals and physical assessments.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N=229 patients	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns

MARINE Trial Phase III RCT, DB, MC, PC 12 weeks with an open extention	1. ICP 4 g daily 2. ICP 2 g daily 3. Placebo Permitted concomitant medications: Antihypertensive, antidiabetes drug therapies, tamoxifen, estrogens, and progestins as long as doses were stable ≥4 weeks before screening and were unchanged throughout the study. Statins with or without ezetimibe but only if patient was deemed high risk of CHD Duration: 4-6 week lead-in period followed by a 2-3 week qualifying period. 12 week safety and efficacy period with a 40 week open label extension with all patients getting 4 g daily.	**Demographics (4g/2g/placebo):** Age (yrs) mean: 51.9/53.4/53.4 Age <65 yrs (%): 91/92/93 Men (%): 77/76/76 White (%): 87/88/90 BMI mean (kg/m^2): 30.4/30.8/31.0 Statin use (%): 26/25/24 Baseline TG >750 mg/dL (%): 38/38/42 Diabetes mellitus (%): 29/26/28 **Inclusion Criteria:** ->18 years old -willing to maintain a stable diet -willing to maintain normal current physical activity level -TG ≥500 mg/dL and ≤2000 mg/dL **Exclusion Criteria:** -women who were pregnant or planning to become pregnant or breastfeeding -women of childbearing potential not willing to use accepted birth control methods throughout study -history of pancreatitis BMI >45 kg/m^2 -weight change >3 kg during lead in period -Hgb A1c >9.5% (Patients with diabetes were required to be on stable therapy) -History of stroke /MI/life threatening arrhythmia -TSH >1.5 X ULN or Hx of hypothyroidism or hyroid hormonal therapy not stable for ≥6 weeks before screening -AST/ALT >3xULN or elevated CK -Hx of gall stone within 1 year without cholecystectomy Known nephritic syndrome or >3g daily proteinuria	**Randomized: (4g/2g/placebo)** 77/76/76 **ITT:** 76/73/75 **PP:** 74/70/71 **Attrition (%):** 3.9/7.9/6.6	**No Relevant endpoints linked to patient outcomes** Primary study Endpoint: Placebo corrected median percentage of change in TG from baseline to week 12 I 4g: -33.1%* I 2g:-19.7%^ P<0.0001* P<0.01^	NA NA	Safety Endpoints Any treatment emergent adverse event I 4g:35% I2g:34% P: 37% No p values provided Patients discontinued drug due to treatment related adverse event I 4g: 0% I 2g: 1.3% P: 3.9% No p values provided	NA NA	**Quality Rating: Poor-fair** **Internal Validity: RoB** Selection: Patients participated in a 4-6 week lead-in and a 2-3 week qualifying period in which disease state was assessed. There was a 12 week safety and efficacy period which was followed by an open label 40 week extension. Randomization was not described in the text and there were no supplemental materials provided. Baseline characteristics were similar. Performance: No details regarding dosage forms, cross-over or contamination. Detection: Patients and investigators were blinded per statement that study was double blinded but treatment allocation methodology was not specified. Unclear if data analysis group was blinded as well. Attrition: Attrition rates appear to be similar between the groups. The 4 g subgroup was 3.9% but the 2g and placebo groups were 7.9% and 6.6% respectively. Overall attrition was 6.11% which was acceptable as other omega 3 studies looking at hypertriglyceridemia have attrition rates ranging between 1% and 17%. **External Validity:** Recruitment: Not reported. Multicenter study took place in 10 countries. Patient Characteristics: 76% male 86% white 92% <65 yrs old Mean age 52.9 +/- 9.34 Setting: 4-6 week lead in and 2-3 week qualifying periods prior to randomization. Outcomes Significance was set at p=0.01 for the primary endpoint Primary endpoint: placebo corrected median TG % change from baseline Not linked to patient centered outcomes such as fewer hospitalizations, CV data, and incidence of acute pancreatitis or morbidity/mortality. **Statistical Analysis:** STD of 45% in TG measurements and p<0.01 significance level required a sample size of 69 completed patients per treatment group to provide ≥90% power to detect a difference of 30% between treatment and placebo. Primary efficacy analysis was performed using a Wilcoxon rank sum test with the Hodges-Lehmann median and interquartile range.

ANCHOR Trial Phase III RCT, DB, MC, PC	1. ICP 2 g BID 2. ICP 1 g BID 3. Placebo Permitted Concomittant Medications: Atorvastatin, rosuvastatin, simvastatin and ezetimibe. No statement regarding medications allowed for other comorbidities. Duration: A 4-6 week lead in period followed by a 2-3 week qualifying period followed by a 12 week double blind period	**Demographics: (4g/2g/placebo):** Age (yrs mean) 61.1/61.8/61.2 Men (%) 39/40/37 White (%) 97/96/96 BMI (kg/m^2 mean) 32.7/32.9/33.0 Diabetes(%) 73/73/73 A1c (value % n=226/234/227) ** 6.6/6.7/6.5 Statin use Atorvastatin (%) 19/18/19 Simvastatin (%) 58/58/57 Rosuvastatin (%) 24/24/24 Statin efficacy regimens Lower (%) 7/7/6 Medium (%) 64/63/62 Higher (%) 30/30/32 **Inclusion Criteria:** >18 years old, at high risk for CVD per NCEP ATPIII guidelines, willing to maintain stable diet and exercise routine, by first TG qualifying visit > 4 weeks stable statin therapy with optimal LDL potential (>40 mg/dL and <100 mg/dL), TG value ≥200 mg/dL and <500 mg /dL**. **Exclusion Criteria:**** A1c>9.5%, LDL≥115 mg/dL, BMI>45 kg/m^2, weight change of >3 kg from the first visit to the end of the qualifying period, non-HDL <100 mg/dL, proteinuria >3g/day, malignancy, bariatric surgery, long term treatment with antihypertensive and antidiabetic medications, treatment with weight loss drugs, TSH >1.5 x ULN, ALT/AST >3xULN, unexplained creatinine kinase concentrations >3xULN or elevated CK due to known muscle disease. **Demographics were different at the beginning of the trial as there was a follow up change in exclusion criteria to "facilitate enrollment" after the beginning of randomization. A1c, LDL, TG criteria changed. This number is the final criteria.	**Randomized: (4g/2g/placebo)** 233/236/233 **ITT:** 226/234/227 **PP:** 221/225/217 **Attrition (%):** 5.15/4.66/6.86	**No Relevant endpoints linked to patient outcomes**** **Primary study endpoint:** Median placebo adjusted % change in TG levels from baseline to week 12. I 4g: -21.5%* I 2g:-10.1%^ P<0.0001* P=0.0005^	NA NA	**Safety Endpoint:** Any treatment emergent adverse event during double blind treatment period I 4g:45.5% I2g:44.9% P: 48.1% No p values provided Patients discontinued drug due to treatment related adverse event I 4g: 2.14% I 2g:1.69% P: 3.43% No p values provided Arthralgia: I 4g:1.7% I 2g:3.4% P:0.4%	NA NA	**Quality Rating: Poor-Fair** **Internal Validity: RoB** Selection: Patients participated in a 4-6 week lead-in and a 2-3 week qualifying period and there was a 12 week double blind period. Randomization was not described in the text and there were no supplemental materials provided. Baseline characteristics were similar. Performance: No details regarding dosage forms, cross-over or contamination Detection: Patients and investigators were blinded per statement that study was double blinded but treatment allocation methodology was not specified. Unclear if data analysis group was blinded as well. Attrition: The 4 g subgroup was 5.15% but the 2g and placebo groups were 4.66% and 6.86% respectively. Attrition rates appear to be similar. Overall attrition was 5.56% which was acceptable as other omega 3 studies looking at hypertriglyceridemia have attrition rates ranging between 1% and 17%. **External Validity:** Recruitment: Not reported. This was a multi center study taking place in 97 sites across the US. Patient Characteristics: White 96% Male 61% mean age of 61.4 years Setting: 4-6 week lead in and 2-3 week qualifying periods prior to randomization. Outcomes Primary endpoint: TG median placebo adjusted % change from baseline. Not linked to patient centered outcomes such as fewer hospitalizations, CV data, incidence of acute pancreatitis or morbidity/mortality. The study population was not the population of interest for this medication and therefore renders the data from this study somewhat irrelevant. **Statistical Analysis:** STD of 45% in TG measurements and p<0.05 significance level required a sample size of 194 completed patients per treatment group to provide ≥90.6% power to detect a difference of 15% between treatment and placebo and an 80% power to demonstrate non-inferiority with a significance level of p<0.025 of the LDL response between treatment and placebo. Using a Shapiro-Wilk test, p<0.01, the median and interquartile range would be calculated for each treatment group and median differences and Hodges-Lehmann 2 tailed 95% CI would be calculated for each comparison between treatment and placebo. Nonparametric analysis p values were planned using Wilcoxon rank-sum test for each comparison.

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

PHARMACOKINETICS[25,26]

Parameter	Result
Oral Bioavailability	Not described
Volume of distribution	88L
Protein Binding	>99%
Excretion	Not renally excreted,
Plasma elimination Half-Life	~89 Hours
Metabolism	Mainly hepatic via beta-oxidation with some minor Cyp 450
Time to peak plasma concentration	5 hours

DOSE & AVAILABILITY[25,26]

STRENGTH	ROUTE	FREQUENCY	DOSAGE FORM:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
1 Gram	By Mouth	2 capsule Twice daily	1 g oral liquid gel capsule	No dosage adjustments provided in manufacturer's labeling	No dosage adjustments provided in manufacturer's labeling	No studies have been conducted in children	Refer to adult dosing	Drug is not renally eliminated Monitoring of ALT and AST is recommended in patients with hepatic impairment.

DRUG SAFETY[25,26]

Contraindications*:* Hypersensitivity/anaphylactic reaction to ICP or any component of the formulation

Black Box Warning/REMS*:* N/A

Warnings and Precautions*:*

- Hypersensitivity reactions: Ethyl esters of EPA obtained from fish oil. Cross sensitivity to fish or shell fish is unknown. Use with caution in patients with these allergies

- Hepatic function impairment: monitor ALT and AST periodically
- Fertility impairment: ethyl EPA caused some infertility in rats but no human examples. BSA based dosing in rats was 7 times the human systemic exposure with 4 g per day. Pregnancy Category C. Lactation safety undefined-excreted in breast milk use caution.
- Children: Not defined
- Elderly: 33% of patients studied in clinical trials were 65 years old or greater and no difference in safety or effectiveness was observed in these patients.
- Concomitant use of drugs that may exacerbate hypertriglyceridemia should be avoided (i.e. beta blockers, thiazides, estrogen)
- Risk of prolonged bleeding time has been reported with omega-3 fatty acids therefore patients on drugs affecting platelet aggregation and coagulation should be closely monitored
- Appropriate use: ICP should be used as an adjunct to diet and exercise modifications and only in patients with TGs exceeding 500 mg/dL. Secondary causes of hypertriglyceridemia should be ruled out prior to initiating therapy.
- The effects of ICP risk of pancreatitis and CV morbidity and mortality in patients with severe hypertriglyceridemia is unknown.