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**Month/Year of Review:** September 2014
**PDL Classes:** Other Lipotropics

**Date of Last Review:** September 2013
**Source Document:** OSU College of Pharmacy

**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), ICOSAPENT ETHYL (VASCEPA®)

**PA criteria:** Prior Authorization Criteria is in place for Omega-3 Fatty Acids (Lovaza® and Vascepa®) to promote the safe and effective use of these lipid lowering agents (Appendix 1).

**Previous Conclusions and Recommendation:**

- Make cholestyramine a preferred bile acid sequestrant, which has shown improved cardiovascular (CV) related or stroke outcomes.
- There is moderate quality evidence that gemfibrozil may reduce the risk for stroke and CV mortality. Include gemfibrozil as a preferred medication.
- There is no clinical evidence of superiority of one fenofibrate agent over another.
- Make Niaspan and Niacor preferred due to a demonstrated reduction in CV outcomes.
- Make ezetimibe a non-preferred agent due to insufficient outcome data, and implement the non-PDL prior authorization criteria for use.
- 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. Maintain as non-preferred and prior authorize omega-3 fatty acids including the following:
    - Clinically diagnosed hypertriglyceridemia with triglyceride levels > 500
    - Failure or contraindication to a fibric acid derivative and niacin OR
    - The patient is taking a statin and is unable to take a fibric acid derivative or niacin due to an increased risk of myopathy.

**Conclusions and Recommendations:**

- There remains insufficient evidence for improved Atherosclerotic Cardiovascular Disease (ASCVD) outcomes for non-statin lipid lowering agents.
- For high risk patients, it may be reasonable to add a nonstatin cholesterol-lowering medication in high-risk patients who have a less than anticipated response to statins, who are unable to tolerate a less than recommended intensity of a statin or who are completely statin intolerant.
- There is no new relevant evidence supporting changes to PDL; evaluate comparative costs 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 including the medications and diagnoses as search terms. The search was limited to English language articles of controlled trials and systematic reviews conducted on humans published from 2013 to August week two 2014.

The Cochrane Collection, Dynamed, National Institute for Health and Care Excellence (NICE) and Agency for Healthcare Research and Quality (AHRQ) were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

**New Systematic Reviews:**
*Agency for Healthcare Research and Quality:*

A 2014 AHRQ review compared 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.[18,19] 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.

Another publication focused only on adults at high risk for atherosclerotic cardiovascular disease (ASCVD).[19] This review was done in response to the new ACC/AHA guidelines recommending moderate- or high-intensity statin monotherapy as first line therapy. For patients who cannot tolerate the recommended intensity of statin therapy, lower-intensity combination therapy could still be an option. Thirty six RCTs were included in this analysis. Overall, there was insufficient evidence to compare long-term clinical outcomes, including mortality acute coronary events, cerebrovascular events, and revascularization procedures, for all combination therapy and statin intensity comparisons. 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.

**Guidelines:**

In November, 2013, the ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic CV risk in adults was released.[20,21] The new guidelines abandon specific cholesterol treatment goals and instead focus on four high-risk groups that are most likely to benefit from statin therapy. The new guidelines also emphasize that overall risk of heart disease and stroke should be evaluated on an individual basis and recommend only using medications that have been proven to reduce ASCVD risk. Therefore, moderate- to high-intensity statins are the focus of the recommendations. The panel could not find data supporting the routine use of nonstatin drugs combined with statin therapy to further reduce ASCVD events and no RCTs that assessed ASCVD outcomes in statin-intolerant patients were found. In regards to other lipid-modifying agents, the 2013 ACC/AHA guidelines suggest that clinicians consider "moderated" combination therapy with a lower-intensity statin and another lipid-modifying medication among high-risk

patients (LDL cholesterol level _4.91 mmol/L [_190 mg/dL], preexisting ASCVD, or DM) who are intolerant of or unresponsive to statins. This recommendation is only based on expert opinion (Evidence grade E). Other recommendations regarding non-statin therapies include:

- Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are greater than or equal to 500 mg/dl are judged to outweigh the potential risk for adverse events (Expert opinion; E).
- Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabomyolysis (Moderate SOE; B).

The Institute for Clinical Systems Improvement (ICSI) released guidelines for the lipid management in adults in November 2013.[22] Evidence-based recommendations, which could only be provided for statin use and lifestyle habits. Recommendations for other lipid-lowering agents were provided throughout the document, but only as a result of work group consensus and not evidence-based.

**New drugs:**
None

**New Formulations/Indications:**
None

**New FDA safety alerts:**
None

**New Trials:**
No head to head trials or relevant placebo-controlled trials were identified.

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**Appendix 1: Prior Authorization Criteria**

# Omega-3 Fatty Acids

**Goal(s):**

- Promote safe and effective therapies for lipid lowering agent.

**Length of Authorization: 1 year**

**Requires PA :** Omega-3-Acid Ethyl Esters (Lovaza®)
Icosapent Ethyl (Vascepa®)

**Covered Alternatives**: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

| Approval Criteria | | |
|---|---|---|
| **1.** What is the diagnosis? | Record ICD-9 code | |
| **2.** Is the diagnosis an OHP covered diagnosis? | **Yes:** Go to #3. | **No:** Pass to RPh, Deny for OHP Coverage. |
| **3.** Will the prescriber consider a change to a preferred product?<br>Message:<br>• Preferred products do not require PA.<br>• Preferred products have received evidence-based reviews for comparative effectiveness and safety by the Pharmacy & Therapeutics Committee | **Yes:** Inform provider of covered alternatives in class http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html | **No:** Go to #4 |
| 4. Does the patient have clinically diagnosed hypertriglyceridemia with triglyceride levels ≥ 500 mg/dl? | **Yes:** Go to #5 | **No:** Pass to RPh; Deny for Medical Appropriateness |
| 5. Has the patient failed or have a contraindication to an adequate trial (at least 8 weeks) of a fibric acid derivitave (fenofibrate or gemfibrozil) at maximum tolerable dose (as seen in dosing table below).<br>**AND**<br>niacin 1-2 mg/day<br>**OR**<br>Is patient taking a statin and is unable to take a fibric acid derivative or niacin due to an increased risk of myopathy. | **Yes:** Approve up to 1 year. | **No:** Deny for Medical Appropriateness. Recommend untried agent(s). |

**Table 1: Dosing of fenofibrate and derivatives for hypertriglyceridemia**

| Drug | Recommended dose | Maximum dose |
|---|---|---|
| Antara (micronized) | 43-130 mg once daily | 130 mg once daily |
| Fenoglide | 40-120 once daily | 120 mg once daily |
| Fibricor | 25-105 mg once daily | 105 mg once daily |
| Lipofen | 50-150 mg once daily | 150 mg once daily |
| Lofibra (micronized) | 67-200 mg once daily | 200 mg once daily |
| Lofibra (tablets_ | 54-160 mg once daily | 160 mg once daily |
| TriCor | 48-145 mg once daily | 145 mg once daily |
| Triglide | 50-160 mg once daily | 160 mg once daily |
| Trilipix | 45-135 mg once daily | 135 mg once daily |
| Gemfibrozil | 600 mg twice daily | 600 mg twice daily |

*P&T Action: 3-27-2014 (MH/KK)*
*Revision(s):*
*Initiated:*