Prescription Omega-3 Fatty Acid Products and Dietary Supplements Are Not Interchangeable

Daniel Hilleman, PharmD, and Aiman Smer, MBBCh

INTRODUCTION

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain omega-3 fatty acids (OM3-FA) that have important roles and potential benefits in cardiovascular disease, stroke, and dyslipidemia (Arterburn 2006, Connor 2000). Although DHA can be derived from EPA, it is structurally and molecularly distinct from EPA with different functional properties (Arterburn 2006, Jump 2012).

A broad range of cardiovascular effects has been associated with OM3-FA use (with and without concomitant statin therapy), including improvements in autonomic control, endothelial dysfunction, triglycerides, inflammation, thrombosis, and arrhythmia (Mozaffarian 2011). EPA in particular, alone or in addition to statins, has been shown to be beneficial in multiple steps in the cellular and molecular pathogenesis of atherosclerosis, including oxidation (Mason 2011, Mason 2014); endothelial dysfunction (Borow 2015, Sasaki 2012, Toyama 2014); macrophage, monocyte, and foam cell function (Cawood 2010, Nishio 2014, Thies 2003); inflammation (Bays 2013, Cawood 2010); plaque progression, formation, and vulnerability (Ando 2015, Cawood 2010, Domei 2013, Niki 2012, Nishio 2014, Uehara 2013, Yamano 2015), and thrombus formation (Gajos 2010, Nomura 2009).

Results:

Prescription OM3-FA products are supported by robust clinical development and safety monitoring programs, whereas dietary supplements are not required to demonstrate safety or efficacy prior to marketing. There are no over-the-counter OM3-FA products available in the United States. Investigations of OM3-FA dietary supplements show that quantities of EPA and DHA are highly variable within and between brands. Dietary supplements also may contain potentially harmful components, including oxidized OM3-FA, other lipids, cholesterol, and toxins. Prescription OM3-FA products may contain DHA and EPA or EPA alone. All prescription OM3-FA products have demonstrated statistically significant triglyceride reduction as monotherapy or in combination with statins in patients with hypertriglyceridemia. Differential effects between products containing EPA and DHA compared with a high-purity EPA product (icosapent ethyl) have clinical implications: Increases in low-density lipoprotein cholesterol associated with DHA have the potential to confound strategies for managing patients with dyslipidemia. Cardiovascular outcomes studies of prescription OM3-FA products are ongoing.

Conclusions:

OM3-FA dietary supplements should not be substituted for prescription products, and prescription OM3-FA products that contain DHA are not equivalent to or interchangeable with high-purity EPA (icosapent ethyl) and should not be substituted for it.

Keywords:
dietary supplements, docosahexaenoic acid, eicosapentaenoic acid, hypertriglyceridemia, icosapent ethyl, omega-3 fatty acids

Editor’s note

Amarin Pharma, which funded the medical writing assistance of this manuscript, sued the FDA to gain the right to promote its prescription omega-3 fatty acid product, Vascepa, with data on uses not covered by the product’s FDA-approved label. The FDA responded, in part, by saying the company could make a claim regarding potential cardiovascular risk reduction if the product was relabeled as a dietary supplement.

A federal district court judge, citing the First Amendment, made a preliminary ruling in Amarin’s favor on Aug. 7, 2015. The case is being watched closely by the pharmaceutical industry and the FDA because of its implications for off-label promotion.
have demonstrated robust lowering of triglycerides in clinical trials as well as beneficial effects on other lipid parameters, such as non–high-density lipoprotein cholesterol (non–HDL-C), total cholesterol, and very-low-density lipoprotein cholesterol (VLDL-C) (Lovaza 2014, Ballantyne 2012, Bays 2011, Davidson 2007, Harris 1997, Kastelein 2014, Maki 2013, Pownall 1999). In clinical studies, prescription OM3-FA products containing DHA have demonstrated statistically insignificant increases in apolipoprotein B (apoB), while high-purity EPA has shown statistically significant reductions in apoB (Epanova 2014, FDA 2014, Ballantyne 2012, Bays 2011, Kastelein 2014). Differential effects between DHA and EPA on low-density lipoprotein cholesterol (LDL-C) have been investigated in metaanalyses and systematic reviews: EPA was found to minimally reduce or have a neutral effect on LDL-C levels, whereas DHA was found to increase LDL-C (Jacobson 2012, Wei 2011). A potential mechanism underlying these differential effects may be the downregulation of the LDL receptor by DHA (Dawson 2012, Ishida 2013). LDL-C increases associated with DHA may compromise lipid treatment strategies and must be considered when selecting treatment.

This article provides an overview of prescription OM3-FA products and dietary supplements and key considerations for their clinical use.

OMEGA-3 FATTY ACID PRODUCTS

An overview of the types of OM3-FA products is provided in Table 1. Two US Food and Drug Administration (FDA)-approved OM3-FA brand-name prescription products are currently available (Lovaza 2014, Vascepa 2015), as well as many nonprescription OM3-FA products. However, the nonprescription products are dietary supplements and not over-the-counter (OTC) drugs; no OM3-FA products that were approved as drugs are available over the counter in the United States. Additional prescription OM3-FA products have been approved (Epanova 2014, Omtryg 2014), but as of November 2015 were not available.

### Dietary Supplements

In 1994, Congress enacted the Dietary Supplementation Health and Education Act (DSHEA) to amend the Federal Food, Drug, and Cosmetics Act (FDA 2009). The DSHEA designated dietary supplements as a special category under the general umbrella of “foods” rather than under the category of “drugs.” In the decades following this legislation, the dietary supplement industry grew tremendously, and among OM3-FA dietary supplements alone, more than 100 products are now available (Zargar 2011). Product formulations range from soft gels (most common) to liquids, powders, and gummies. OM3-FA dietary supplements are derived from a variety of sources including fish, krill, algae, and plant oils (Weintraub 2013), which may include OM3-FAs as triglycerides or phospholipids, or process OM3-FAs to ethyl esters or re-esterified triglycerides (Bunea 2004, Opperman 2013).

### Table 1

#### Types of omega-3 fatty acid products

<table>
<thead>
<tr>
<th>Prescription products (see Table 2 for additional details)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• DHA + EPA products: Lovaza (generics available), Omtryg*, and Epanova*</td>
</tr>
<tr>
<td>• EPA-only product: Vascepa</td>
</tr>
<tr>
<td>• All are formulated as soft gel capsules</td>
</tr>
<tr>
<td>• Sources: DHA-containing products derived from fish oils; EPA-only product is high-purity icosapent ethyl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTC products</th>
</tr>
</thead>
<tbody>
<tr>
<td>• None approved or available at present</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dietary supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>• More than 100 products: predominantly contain DHA + EPA in varying quantities</td>
</tr>
<tr>
<td>• Formulations include soft gels, liquids, powders, and gummies</td>
</tr>
<tr>
<td>• Sources: fish oils, krill oils, algae oils, plant oils</td>
</tr>
</tbody>
</table>

DHA=docosahexaenoic acid, EPA=eicosapentaenoic acid, OTC=over the counter. *Epanova and Omtryg are approved but not currently available.

Variable Content and Concerns With Product Quality of Omega-3 Fatty Acid Dietary Supplements

Manufacturers of dietary supplements are not required to demonstrate the safety of their product prior to marketing (ACS 2014, Lopez 2010). A commentary in the New England Journal of Medicine underscored the fact that dietary supplements do not require premarketing approval from the FDA, and under the DSHEA of 1994, anything labeled as a dietary supplement is assumed to be safe until proven otherwise (Cohen 2014). The author noted that consumers and physicians cannot be assured that dietary supplements are safe without substantial legal and regulatory reforms.

It is well documented that the actual quantities of EPA and DHA contained in OM3-FA dietary supplements may be substantially lower or greater than quantities specified on the product label (Albert 2015, Kleiner 2015, Ritter 2013, Shim 2003). A recent investigation compared the actual to the stated label amounts of EPA and DHA in OM3-FA dietary supplements commercially available in the United States. Among 47 dietary supplements tested (including those containing krill oil, algae oil, and fish oil), EPA content ranged from 66% to 184% of stated label amounts, and DHA content ranged from 62% to
184% of stated label amounts (Kleiner 2015). Greater than 70% of the dietary supplements tested in this study did not contain the amount of EPA or DHA claimed on the label. Another study of 437 patients with suspected coronary disease found no relationship between the number of fish oil pills that patients reported taking and plasma levels of EPA and DHA (Gurbel 2015), thus emphasizing the challenges in realizing consistent and known OM3-FA dose levels with dietary supplements.

Most dietary supplements contain a mixture of EPA and DHA and also may include other lipids and potentially harmful or unwanted ingredients, such as cholesterol, saturated fats, and contaminating polychlorinated biphenyls (PCBs) (Bernstein 2012, Bunea 2004, Mason 2015, Shim 2003, Truong 2007, Weintraub 2013, Weitz 2010, Zargar 2011). Impurities and other ingredients may be associated with a fishy taste, which may interfere with patient adherence (Bradberry 2013).

Compounding these concerns, testing of OM3-FA dietary supplements has revealed that many products are highly oxidized (Albert 2015, Halvorsen 2011, Mason 2015, Rupp 2014). Oxidized OM3-FA products were recently shown to reduce the ability of omega-3 fatty acids to inhibit small dense LDL oxidation and thus may interfere with the biological activity of EPA and DHA (Mason 2015). The potentially harmful doses of these oxidation products and their possible effects have not been well investigated, and little is known about the dose level that would result in a hazard to the user’s health (Halvorsen 2011). Product testing reveals that increased monitoring of dietary OM3-FA supplement quality by manufacturers and government agencies is needed (Kleiner 2015).

**Prescription Omega-3 Fatty Acid Products**

Prescription OM3-FA products currently approved in the United States are indicated as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia (Table 2) (Epanova 2014, Lovaza 2014, Omtryg 2014, Vascepa 2015). All but one of the approved prescription OM3-FA products contain combinations of DHA and EPA. Lovaza, Omtryg, and Lovaza generics contain omega-3-acid ethyl esters (Lovaza 2014, Omtryg 2014). Epanova (omega-3-carboxylic acids) contains polyunsaturated free fatty acids, including EPA and DHA (Epanova 2014); Epanova has received FDA approval but was not available as of November 2015. The EPA-only product, Vascepa, is a high-purity formulation containing icosapent ethyl, an ethyl ester of EPA (Vascepa 2015) and the only prescription product that is an EPA-only formulation.

**Impact of Prescription Omega-3 Fatty Acid Products on Lipid Parameters**

Prescription OM3-FA products have demonstrated statistically significant triglyceride reductions in patients with very high triglyceride levels when used alone (Lovaza 2014, Bays 2011, Harris 1997, Kastelein 2014, Pownall 1999) or in combination with statin therapy (Lovaza 2013, Ballantyne 2012, Davidson 2007, Maki 2013) (Table 2). Differences in patient baseline triglyceride levels contribute to the wide range of triglyceride reductions reported, with higher baseline triglyceride levels generally associated with larger reductions in triglycerides (Bays 2011, Jacobson 2012, Nieman 2014). Prescription OM3-FA products have beneficial effects on additional lipid parameters, including total cholesterol, non–HDL-C, and VLDL-C. However, important differential effects on LDL-C are evident, as well as potential differences in effect on apoB. While the EPA-only product Vascepa appears to have minimal or neutral effects on LDL-C compared with placebo, products containing DHA may increase LDL-C and apoB levels, which may be problematic in patients managed for dyslipidemia (Epanova 2014, Jacobson 2012, Kastelein 2014, Wei 2011).

**Safety of Prescription Omega-3 Fatty Acid Products**

Prescription OM3-FA products have well-established tolerability and safety profiles. In clinical trials, gastrointestinal effects were the most commonly reported adverse events with DHA-containing products (Epanova 2014, Lovaza 2014, Omtryg 2014). With icosapent ethyl, arthralgia was the only adverse event occurring at an incidence >2.0% and more frequently than placebo (2.3% with icosapent ethyl vs 1.0% with placebo) (Vascepa 2015). Unlike other triglyceride-lowering therapies (Niaspan 2015, Trilipix 2015), when taken alone or in combination with statins, prescription OM3-FA products have not been associated with increased risk of myopathy. While prolonged bleeding time has been reported in some studies of OM3-FAs, it did not exceed normal limits and did not produce clinically significant bleeding episodes, although patients receiving OM3FA products along with drugs affecting coagulation should be monitored periodically (Epanova 2014, Lovaza 2014, Omtryg 2014, Vascepa 2015). Because products containing both EPA and DHA have been associated with increased LDL-C, product labeling recommends periodic monitoring of LDL-C during therapy (Epanova 2014, Lovaza 2014, Omtryg 2014).

**CONSIDERATIONS FOR OMEGA-3 FATTY ACID SUPPLEMENTS AND PRESCRIPTION PRODUCTS**

Key differences between prescription OM3-FA products and OM3-FA dietary supplements are summarized in Table 3.
### Omega-3 Fatty Acid Products

#### TABLE 2
Overview of prescription omega-3 fatty acid products

<table>
<thead>
<tr>
<th>DHA and EPA combination prescription products</th>
<th>EPA-only prescription product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand name</strong> (generic name)</td>
<td></td>
</tr>
<tr>
<td>Lovaza† (omega-3-acid ethyl esters)</td>
<td></td>
</tr>
<tr>
<td>Omtryg† (omega-3-acid ethyl esters A)</td>
<td></td>
</tr>
<tr>
<td>Epanova‡ (omega-3-carboxylic acids)</td>
<td></td>
</tr>
<tr>
<td>Vascepa (icosapent ethyl)</td>
<td></td>
</tr>
</tbody>
</table>

#### References
- Omtryg 2014
- Epanova 2014, Kastelein 2014, Maki 2013
- Vascepa 2015, Ballantyne 2012, Bays 2011

#### FDA indication
In all products, indicated as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia

#### DHA content/capsule
- Lovaza: ~0.375 g
- Omtryg: ~0.375 g
- Epanova: 0.2 g None

#### EPA content/capsule
- Lovaza: ~0.465 g
- Omtryg: ~0.465 g
- Epanova: 0.55 g 1 g

#### Total OM3-FA dose/day (schedule)
- Lovaza: 4 g (4 capsules QD or 2 capsules BID)
- Omtryg: 4 g (4 capsules QD or 2 capsules BID)
- Epanova: 2 g or 4 g (2 or 4 capsules QD)
- Vascepa: 4 g (2 capsules BID)

#### 4 g/day in patients with very high triglycerides at baseline (≥500 mg/dL)†,‡

<table>
<thead>
<tr>
<th>Change vs placebo</th>
<th>Change vs placebo</th>
<th>Change vs placebo</th>
<th>Change vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>triglycerides</td>
<td>−51.6% (P &lt; .05)</td>
<td>−12.2% (P &lt; .05)</td>
<td>−21% (NR)</td>
</tr>
<tr>
<td>total cholesterol</td>
<td>−8.0% (P &lt; .05)</td>
<td>−6.9% (NR)</td>
<td>−9% (NR)</td>
</tr>
<tr>
<td>non–HDL-C</td>
<td>−10.2% (NR)</td>
<td>−8.5% (NR)</td>
<td>−10% (NR)</td>
</tr>
<tr>
<td>apoB</td>
<td>NR</td>
<td>NR</td>
<td>+2% (NR)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>+49.3% (P &lt; .05)</td>
<td>+24.7% (P &lt; .01)</td>
<td>+15% (NR)</td>
</tr>
</tbody>
</table>

#### 4 g/day in patients with high triglycerides at baseline (≥200 and <500 mg/dL)§

<table>
<thead>
<tr>
<th>Change vs placebo</th>
<th>Change vs placebo</th>
<th>Change vs placebo</th>
<th>Change vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>triglycerides</td>
<td>−23.2% (P &lt; .001)</td>
<td>N/A</td>
<td>NR§</td>
</tr>
<tr>
<td>total cholesterol</td>
<td>−3.1% (P &lt; .05)</td>
<td>N/A</td>
<td>NR§</td>
</tr>
<tr>
<td>non–HDL-C</td>
<td>−6.8% (P &lt; .001)</td>
<td>N/A</td>
<td>NR§</td>
</tr>
<tr>
<td>apoB</td>
<td>−2.3% (P &lt; .05)</td>
<td>N/A</td>
<td>NR§</td>
</tr>
<tr>
<td>LDL-C</td>
<td>+3.5% (P = .05)</td>
<td>N/A</td>
<td>NR§</td>
</tr>
</tbody>
</table>

#### Adverse effects
- Gastrointestinal (eructation, dyspepsia, taste perversion)
- Gastrointestinal (eructation, dyspepsia, taste perversion)
- Gastrointestinal (diarrhea, nausea, abdominal pain or discomfort, eructation)
- Arthralgia

#### Drug interactions
No clinically important drug–drug interactions

#### Cardiovascular outcomes studies
- Lovaza: N/A
- Omtryg: N/A
- Epanova: STRENGTH (NCT02104817)
- Vascepa: REDUCE-IT (NCT01492361)

#### Notes:
- apoB: apolipoprotein B, BID: twice daily, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, LDL-C: low-density lipoprotein cholesterol, non–HDL-C: non-high-density lipoprotein cholesterol, N/A: not applicable, NR: not reported, NS: not statistically significant, OM3-FA: omega-3 fatty acids, QD: once daily.
- †Generic formulations of Lovaza available. ‡Epanova and Omtryg were approved, but not available as of Nov. 24, 2015. §Values represent % difference vs placebo. ††Upper limit for triglyceride levels was 2000 mg/dL in studies of Lovaza, Epanova, and Vascepa and 1500 mg in the Omtryg study. *Pooled data reported in Lovaza prescribing information (PI); P values not provided in the PI, but available in the individual studies. ‡Statistical significance not reported in product prescribing information; P values noted to be ≤.05 in corresponding study publication. ‡†The study of Epanova in patients with high triglycerides did not report median % differences vs placebo; however, absolute least-squares geometric mean changes were reported as follows: triglycerides, −20.6%; total cholesterol, −3.8%; non–HDL-C, −6.9%; apoB, −2.1%; LDL-C, +1.3%; changes in triglycerides, total cholesterol, non–HDL-C, and apoB were statistically significant compared with placebo (Maki 2013).
Product Substitution

OM3-FA dietary supplements are not an FDA-approved option for the treatment of high or very high triglyceride levels because the safety and tolerability of dietary supplements is not well characterized or defined, especially when taken at doses aimed at achieving FDA-approved doses of prescription OM3-FA products required to treat severe hypertriglyceridemia. Therefore, OM3-FA dietary supplements should not be substituted for prescription OM3-FA products. To achieve FDA-approved doses of prescription OM3-FA products required to treat hypertriglyceridemia, a high number of servings (by some estimates >10/daily) would be needed with OM3-FA dietary supplements (Bradberry 2013, Zargar 2011). This higher “pill burden” could have a negative impact on patient adherence to treatment and also could be associated with increased intake of unwanted ingredients that may be contained in dietary supplements (eg, saturated fats, cholesterol, PCBs, and oxidation products) (Albert 2015, Halvorsen 2011, Truong 2007, Zargar 2011).

Generic prescription omega-3-acid ethyl ester products, all of which contain both EPA and DHA, are available and may be substituted for branded Lovaza. However, brand name or generic prescription OM3-FA products containing both EPA and DHA should not be substituted for the EPA-only product Vascepa (FDA 2015). From a clinical perspective, the potential LDL-C increase associated with DHA-containing products must be considered when selecting treatment, because such lipid effects may complicate patient management. Also, based on FDA equivalence codes (ie, Orange Book), DHA-containing products are not considered to be therapeutically equivalent to icosapent ethyl (FDA 2015). Of note, the recent findings of the IMPROVE-IT trial demonstrated that add-on therapy in statin-treated patients can further reduce cardiovascular risk, supporting the concept that “lower LDL-C is better” (Cannon 2015, Jarcho 2015). Many patients taking prescription OM3-FA products also may be taking statins; this denotes potential issues with DHA-containing products, as DHA has been shown to raise LDL-C (Jacobson 2012, Wei 2011).

Cost Considerations

Although OM3-FA dietary supplements should not be substituted for prescription OM3-FA products, patients may perceive dietary supplements to be a low-cost option; however, the higher pill burden needed to achieve FDA-approved doses of OM3-FA products required to treat severe hypertriglyceridemia, along with questionable efficacy, would be associated with greater cost than might be expected. According to one study based on the National Library of Medicine Herbal Supplement Database, available OM3-FA dietary supplements require a median 11.2 servings/day to achieve the recommended prescription dose, at median cost of $63 per month (ranging from $15 to $700 per month) (Zargar 2011). Generic prescription OM3-FA options for omega-3-acid ethyl esters are available, but are still higher in cost compared with dietary supplements. When cost is a barrier, savings programs are in place for the available prescription OM3-FA products (icosapent ethyl and omega-3-acid ethyl esters) (GlaxoSmithKline 2015, Vascepa web site 2015).

With regard to cost-effectiveness, a pharmacoeconomic model was recently developed to explore prescription EPA-only therapy among secondary prevention populations in the United States (Schmier 2015). The modeling suggests that combining EPA with a statin for secondary prevention of cardiovascular disease may be associated with cost savings and improved utilities compared with a statin alone, although icosapent ethyl is not currently indicated by the FDA specifically for prevention of cardiovascular disease.

### TABLE 3

<table>
<thead>
<tr>
<th>Regulatory requirements</th>
<th>Prescription products</th>
<th>Dietary supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>must demonstrate/prove efficacy and safety in phase 3 RCTs for approval</td>
<td>• considered “foods” from regulatory standpoint</td>
<td>• not required to demonstrate/prove efficacy or safety prior to marketing</td>
</tr>
<tr>
<td>OM3-FA content and purity</td>
<td>Adhere to strict standards for content and purity</td>
<td>• variable/Inconsistent EPA and DHA content</td>
</tr>
<tr>
<td>Indication</td>
<td>Indicated as an adjunct to diet to reduce triglycerides in adult patients with severe (≥500 mg/dL) hypertriglyceridemia</td>
<td>N/A (No approved indication)</td>
</tr>
<tr>
<td>Substitution</td>
<td>DHA-containing products should not be substituted for EPA-only products</td>
<td>OM3-FA dietary supplements should not be substituted for prescription OM3-FA products</td>
</tr>
</tbody>
</table>

DHA = docosahexaenoic acid, EPA = eicosapentanoic acid, N/A = not applicable, OM3-FA = omega-3 fatty acid, RCTs = randomized controlled trials.
Common Misconceptions and Patient Education Needs

In the United States, no OM3-FA products approved as drugs are available over the counter. However, there appears to be a misconception regarding products that can be purchased without a prescription—i.e., dietary supplements are sometimes incorrectly referred to as OTC products. While this may be the case in a colloquial sense, these dietary supplements are not considered OTC medications per the regulatory definition. This distinction has important clinical implications because dietary supplements are not subject to the same rigorous regulatory oversight and do not require FDA approval prior to marketing or sale of these products (ACS 2014, Lopez 2010). Failure to recognize the difference between dietary supplements and OTC medications may give patients and providers a false sense of security with these products simply because they can be bought “off the shelf” without supervision by a health care professional.

Despite widespread use of OM3-FA dietary supplements, patients may not have adequate understanding of these products (Hawkins 2012), and they may not be aware that recent trials utilizing low-dose dietary supplements did not show any cardiovascular benefit (Risk 2013). A survey of 496 cardiology patients using OM3-FA dietary supplements based on their physician’s recommendation (Hawkins 2012). Of those who were, approximately 25% of patients did not consistently buy the same OM3-FA dietary supplement (Hawkins 2012).

As there is room for improvement in patients’ understanding of OM3-FA products, additional education may be warranted. Pharmacists are among the most accessible of health care professionals and can take a crucial role in educating patients about these products, reinforcing the regulatory differences between dietary supplements, OTC drugs, and prescription drugs, and explaining why dietary supplements should not be substituted for prescription drugs and why prescription products containing DHA are not equivalent to an EPA-only medication. Pharmacists can also help the consumer understand the costs associated with each of these products.

Other Considerations

The efficacy of prescription OM3-FA products for the treatment of severe hypertriglyceridemia has been proven in well-designed randomized clinical trials that have led to regulatory approvals. However, whether this triglyceride reduction translates to improved cardiovascular outcomes is an important clinical question. A metaanalysis of clinical trials encompassing more than 250,000 patients reported a statistically significant association between elevated triglycerides and the risk of coronary heart disease (Sarwar 2007). In addition, findings of recent genetic and population studies support a causal role for triglycerides in the pathway of atherosclerosis (Jorgensen 2014, TG and HDL Working Group 2014). The effects of prescription OM3-FA products on cardiovascular outcomes are currently being studied. Specifically, the ongoing REDUCE-IT (NCT01492361) and STRENGTH (NCT02104817) trials are investigating the effects of prescription EPA-only Vascepa and Epanova, respectively, on cardiovascular outcomes in statin-treated patients with residually high triglycerides. Both trials are utilizing 4 g/day dosing and are event-driven with primary outcome defined as a composite endpoint of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and hospitalization for unstable angina. REDUCE-IT has an estimated enrollment of 8,000 patients and is expected to be completed in 2017 (interim safety and efficacy review are expected in 2016 by the independent data monitoring committee). STRENGTH has an estimated enrollment of 13,000 patients and is expected to be completed in 2019.

While results of multiple clinical trials support a role for OM3-FA products in cardiovascular risk reduction, only the JELIS trial of EPA-only therapy has shown risk reduction in addition to statin therapy (Dietary 1999, GISSI-HF 2008, Oikawa 2009, Yokoyama 2007). Other more recent trials examining low doses (≤1 g per day) of EPA plus DHA on top of contemporary medical treatment such as statin therapy have not shown a reduction in cardiovascular risk (Risk 2013, Galan 2010, Kromhout 2010, ORIGIN 2012, Rauch 2010). The populations in these studies varied and did not necessarily represent patients in need of triglyceride lowering. In addition, the variability among OM3-FA dietary supplements, especially with regard to content and quality, confounds the ability to extrapolate individual clinical study results to the wide array of commonly available dietary supplements. Even metaanalyses of studies assessing cardiovascular benefits of OM3-FA dietary supplementation have reported inconsistent findings (Casula 2013, Rizos 2012).

The lack of consensus in the clinical evidence to date has influenced recommendations by the International Atherosclerosis Society (IAS) and American Diabetes Association (ADA) regarding OM3-FA dietary supplementation. Updated guidelines from the IAS state that low-dose OM3-FA dietary supplementation is not recommended for routine secondary prevention of dyslipidemia (IAS 2015), and the ADA does not recommend OM3-FA dietary supplements for cardiovascular disease prevention in patients with diabetes (ADA 2015). Thus, while low doses of OM3-FA di-
etary supplements may have a role for consumers wishing to supplement their diet, their use is inappropriate for disease management or treatment.

**CONCLUSIONS**

Several types of OM3-FA products are currently available in the US; however, there are important distinctions to be noted. Prescription OM3-FA products are supported by robust clinical development and safety monitoring programs and have proven safety and efficacy in the treatment of severe hypertriglyceridemia. Currently, no OTC OM3-FA products are available in the US. Dietary supplements are in a regulatory category distinct from prescription and OTC drugs, and manufacturers are not required to demonstrate or prove safety or efficacy prior to marketing. The uncertainties regarding the safety and efficacy of dietary supplements are compounded by the fact that the quantities of EPA and DHA found in dietary supplements are highly variable within and between brands. Moreover, dietary supplements may contain unwanted or potentially harmful components, or both, including oxidized OM3-FAs, other lipids, cholesterol, and toxins. For these reasons, OM3-FA dietary supplements should not be substituted for prescription OM3-FA products and, in the absence of regulatory reform that would require dietary supplements to meet safety, efficacy, and quality standards, there is a clear need for patient education regarding these products.

Differences between products containing both EPA and DHA and the EPA-only product have clinical implications. While DHA may have essential functions in brain development through adolescence, it is important to consider that OM3-FA products containing DHA may raise LDL-C levels, and potentially apoB levels, thus confounding management of patients with dyslipidemia and potentially compromising lipid treatment goals. Prescription OM3-FA products containing DHA are not equivalent to or interchangeable with the EPA-only product, and therefore should not be substituted for high-purity EPA (icosapent ethyl; Vascepa). Prescription OM3-FA products are supported by substantial clinical development and safety monitoring programs, including the ongoing REDUCE-IT and STRENGTH cardiovascular outcomes studies.

**REFERENCES**


Albert BB, Derraik JG, Cameron-Smith D, et al. Fish oil supplements in New Zealand are highly oxidised and do not meet label content of n-3 PUFA. *Sci Rep.* 2015;5:7928.


Cawood AL, Ding R, Napper FL, et al. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. *Atherosclerosis.* 2010;212:253–259.


