Commentary

Bioequivalence Demonstration for Ω-3 Acid Ethyl Ester Formulations: Rationale for Modification of Current Guidance

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ABSTRACT

The US Food and Drug Administration (FDA) draft guidance for establishing bioequivalence (BE) of ω-3 acid ethyl esters (containing both eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] as ethyl esters), used to treat severe hypertriglyceridemia, recommends the conduct of 2 studies: one with participants in the fasting state and one with participants in the fed state. For the fasting study, the primary measures of BE are baseline-adjusted EPA and DHA levels in total plasma lipids. For the fed study, the primary measures of BE are EPA and DHA ethyl esters in plasma. This guidance differs from that established for icosapent ethyl (EPA ethyl esters) in which the primary measure of BE is baseline-adjusted total EPA in plasma lipids for both the fasting and fed states. The FDA guidance for ω-3 acid ethyl esters is not supported by their physiologic characteristics and triglyceride-lowering mechanisms because EPA and DHA ethyl esters are best characterized as pro-drugs. This article presents an argument for amending the FDA draft guidance for ω-3 acid ethyl esters to use baseline-adjusted EPA and DHA in total plasma lipids as the primary measures of BE for both fasting and fed conditions. This change would harmonize the approaches for demonstration of BE for ω-3 acid ethyl esters and icosapent ethyl (EPA ethyl esters) products for future development programs and is the most physiologically rational approach to BE testing. (*Clin Ther.* 2017;39:652–658) © 2017 Elsevier HS Journals, Inc. All rights reserved.

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INTRODUCTION

Currently, 4 highly purified ω-3 fatty acid concentrate pharmaceutical agents, as well as several generic agents, have been approved by the US Food and Drug Administration (FDA) for treatment of severe hypertriglyceridemia.[1] These drugs differ in the content of their active moieties, eicosapentaenoic acid (EPA) only and EPA with docosahexaenoic acid (DHA), and in the form of fatty acids administered, that is, ethyl esters or free fatty acids/carboxylic acids (Table I).[2–5] EPA and DHA in fish are present in triglyceride (TG) and phospholipid forms, whereas in fish oil extracts they are mostly present in the TG form. In the ω-3

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Table I. EPA and DHA contents and fatty acid forms in approved ω-3 drugs.

Approved Ω-3 Drugs	EPA and DHA Contents	Form of Fatty Acids
Lovaza®	465 mg EPA + 375 mg DHA per 1-g capsule	Ethyl esters
Vascepa®	1 g icosapent ethyl (≥960 mg EPA ethyl esters) per capsule	Ethyl esters
Omtryg®	465 mg EPA + 375 mg DHA per 1.2-g capsule	Ethyl esters
Epanova®	850 mg PUFA (EPA and DHA most abundant) per 1-g capsule	Free fatty acids (carboxylic acids)

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; PUFA, polyunsaturated fatty acid.

acid ethyl esters drugs, Lovaza*, Omtryg†, and Vascepa‡, the concentration of EPA (and DHA when present) is increased through *trans*-esterification, which involves the removal of the glycerol backbone of the TGs and substitution of it with ethanol to form a fatty acid ethyl ester.[6] This process forms a pro-drug that must first be digested in the gastrointestinal tract to release the active (unesterified) forms of EPA and DHA to be absorbed and to produce pharmacodynamic effects. An alternative way to increase the concentration of EPA and DHA in ω-3 fatty acid concentrates is to remove the EPA and DHA from the glycerol backbone of the TGs and replace the glycerol with a hydrogen atom to create EPA and DHA free fatty acids, also known as carboxylic acids, as found in Epanova§.[6]

MECHANISMS INVOLVED IN -3 FATTY ACID DIGESTION AND ABSORPTION

For ω-3 fatty acids to be absorbed when provided as ethyl esters and ultimately to reach hepatocytes (the target site for TG-lowering effects), the ethyl ester bond must undergo hydrolysis by pancreatic lipase enzymes to be converted into free fatty acids for intestinal absorption (Figure 1).[6–8] This digestive step is not required for Epanova*, which is already a carboxylic acid (free fatty acid) formulation (Figure 1[6]). Very small amounts of EPA ethyl esters and DHA ethyl esters are absorbed when ethyl ester formulations are taken and these typically comprise <1% of the circulating levels of EPA and DHA total lipids after dosing with ω-3 acid ethyl esters.[9]

PUTATIVE MECHANISMS OF ACTION FOR REDUCTIONS OF TG LEVELS WITH -3 FATTY ACIDS

Delivery of ω-3 fatty acids to the liver depends primarily on the re-esterification of ω-3 fatty acids to TGs in the enterocytes with subsequent incorporation into chylomicron particles that enter the blood through the lymphatic system.[10] Preclinical studies found that ethyl esters of EPA and DHA constitute a very small fraction (0.1%–1.0%) of total lipid in chylomicron particles (and an even smaller fraction of EPA and DHA total lipids in circulation) after ingestion of ω-3 acid ethyl esters.[9] In addition, experimental studies found that a substantial proportion of the absorbed radioactivity (^{14}C-EPA, ^{14}C-DHA, and metabolites) was present in the phospholipids lipid fraction of the liver within the first 24 hours after dosing of DHA and EPA.[11,12] It was recently confirmed that plasma EPA and DHA ethyl ester levels were less than the lower limit of quantitation in an investigation of a new ω-3 fatty acid formulation (SC401) containing EPA and DHA ethyl esters plus Advanced Lipid Technologies™ to enhance bioavailability of lipid compounds (Lopez-Toledano MA, Thorsteinsson T, Daak A, Maki KC, Johns C, Rabinowicz AL, Sancilio FD. A novel omega-3 acid ethyl ester formulation incorporating Advanced Lipid Technologies™ (ALT™) (Sancilio and Company, Inc., Riviera Beach, Florida) improves docosahexaenoic acid and eicosapentaenoic acid bioavailability compared with Lovaza. Submitted for publication).

*Trademark: Lovaza® (GlaxoSmithKline, Research Triangle Park, North Carolina).

†Trademark: Omtryg® (Trygg Pharma, Inc, Arlington, Virginia).

‡Trademark: Vascepa® (Amarin Pharma, Inc, Bedminster, New Jersey).

§Trademark: Epanova® (AstraZeneca, London, United Kingdom).