TITLE

PHARMACEUTICAL COMPOSITIONS COMPRISING EPA AND A CARDIOVASCULAR AGENT AND METHODS OF USING THE SAME

BACKGROUND

[0001] Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dyslipidemia, congestive heart failure and stroke.

SUMMARY

[0001a] In a first aspect, the present invention refers to a capsule for use in reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 900 mg to about 1050 mg of ethyl eicosapentaenoate, wherein the reduction is relative to subjects having mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

[0001b] In a second aspect, the present invention refers to a capsule for use in reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 900 mg of ethyl eicosapentaenoate.

[0001c] In a third aspect, the present invention refers to a capsule for use in reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 925 mg or about 950 mg of ethyl eicosapentaenoate.

[0001d] In a fourth aspect, the present invention refers to a capsule for use in reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 975 mg of ethyl eicosapentaenoate.

[0001e] In a fifth aspect, the present invention refers to the use of a capsule in the manufacture of a medicament for reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 900 mg to about 1050 mg of ethyl eicosapentaenoate, wherein the reduction is relative subjects having mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

[0001f] In a sixth aspect, the present invention refers to the use of a capsule in the manufacture of a medicament for reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 900 mg of ethyl eicosapentaenoate.

[0001g] In a seventh aspect, the present invention refers to the use of a capsule in the manufacture of a medicament for reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 925 mg or about 950 mg of ethyl eicosapentaenoate.

[0001h] In an eighth aspect, the present invention refers to the use of a capsule in the manufacture of a medicament for reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 975 mg of ethyl eicosapentaenoate.

[0002] In one example, the present invention provides a pharmaceutical composition comprising EPA and optionally one or more additional cardiovascular agents. In another example, the EPA comprises eicosapentaenoic acid ethyl ester. In another example, the composition contains substantially no amount of docosahexaenoic acid or derivative thereof (e.g. ethyl-DHA), if any.

[0003] In other examples, the present invention provides methods of treating and/or preventing a cardiovascular-related disease comprising administering to a subject in need thereof a pharmaceutical composition or composition(s) comprising EPA and optionally one or more additional cardiovascular agents.

[0004] In any of the foregoing examples, the EPA and additional cardiovascular agent(s) can be co-formulated as a single dosage unit or can be formulated as two to a plurality of dosage units for coordinated, combination or concomitant administration.

[0005] These and other examples of the present invention will be disclosed in further detail herein below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] Fig. 1 shows effects of EPA, DHA and Combination Treatment on membrane lipid peroxidation at cholesterol-to-phospholipid ratio of 1.0.

[0007] Fig. 2 shows effects of EPA, DHA and Combination Treatment on membrane lipid peroxidation at cholesterol-to-phospholipid ratio of 0.5.

[0008] Fig. 3 shows cholesterol-dependent effects of EPA, DHA and Combination Treatment on membrane lipid peroxidation.

[0009] Fig. 4 EPA, DHA or EPA/DHA with atorvastatin (10:1 Mole Ratio) on lipid peroxide levels in cholesterol enriched membranes (1:1 cholesterol-to-phospholipid ratio).

DETAILED DESCRIPTION

[0010] While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

[0011] The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." In this manner, slight variations from a stated value can be used to achieve substantially the same results as the stated value. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a recited numeric value into any other recited numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present invention.

Eicosapentaenoic acid

[0012] In one embodiment, compositions of the invention comprise EPA as an active ingredient. The term "EPA" as used herein refers to eicosapentaenoic acid (*e.g.* eicosa-5,8,11,14,17-pentaenoic acid) and/or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing. The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

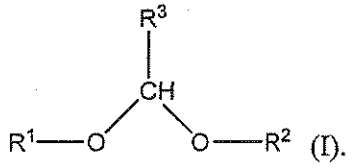
[0013] In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid. In another embodiment, the EPA is in the form of an eicosapentaenoic acid ester (also referred to herein as E-EPA or ethyl-EPA). In another embodiment, the EPA comprises a C_1

– C_5 alkyl ester of EPA. In another embodiment, the EPA comprises, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester. In still another embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid ethyl ester.

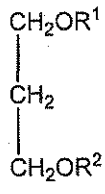
[0014] In another embodiment, the EPA comprises lithium EPA, mono, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

[0015] In one embodiment, EPA present in a composition of the invention comprises ultra-pure EPA. The term "ultra-pure" as used herein with respect to EPA refers to a composition comprising at least 96% by weight EPA (as the term "EPA" is defined and exemplified herein). Ultra-pure EPA can comprise even higher purity EPA, for example at least 97% by weight EPA or at least 98% by weight EPA, wherein the EPA is any form of EPA as set forth herein. Ultra-pure EPA can further be defined (e.g. impurity profile) by any of the description of EPA provided herein.

[0016] In another embodiment, the EPA comprises an EPA-Fatty Acid conjugate wherein EPA is conjugated to another molecule of EPA or to another fatty acid. In one embodiment, the EPA-Fatty Acid conjugate comprises a diester formed between EPA and EPA or between EPA a second fatty acid as shown in structures (I) and (II). In one embodiment, R^1 is a fatty acid acyl group derived from EPA and R^2 is selected from H, a fatty acid acyl of 12 to 30 carbon atoms with two or more cis or trans double bonds and fatty alcohol groups of 12 to 30 carbon atoms, the same or different than R^1. R^1 and R^2 may both be derived from EPA (EPA-EPA) or one may be derived from EPA and the second from a different fatty acid (EPA-Fatty acid), for example gamma-linolenic acid, dihomo-gamma-linolenic acid, arachidonic acid, adrenic acid, stearidonic acid, docosapentaenoic acid n-3, etc.). R^3 is generally either hydrogen, fully hydrocarbon, or containing heteroatoms, and in one embodiment is a C_1–C_4 alkyl group.



(I).



(II).

[0017] Synthesis of a diester conjugate can be accomplished according to methods well known in the art, including for example, using metals, metal-chlorides, or organic acids as catalysts; using fatty acid chlorides such as EPA-chloride, γ-linolenic acid chloride (GLA-chloride), dihomo-γ-linolenic acid chloride (DGLA-chloride), linoleic acid chloride (LA-chloride), arachidonic acid chloride (AA-chloride), conjugated linoleic acid chloride (cLA-chloride), ALA-chloride, STA-chloride, ETA-chloride, DPA-chloride, *etc.*; and the use of immobilized enzymes as catalysts.

[0018] In another embodiment, a composition of the present invention includes a mixture of EPA-Fatty Acid diesters. In a related embodiment, compositions of the present invention include less than 20% EPA-DHA conjugate, less than 15% EPA-DHA conjugate, less than 10% EPA-DHA conjugate, less than 9% EPA-DHA conjugate, less than 8% EPA-DHA conjugate, less than 7% EPA-DHA conjugate, less than 6% EPA-DHA conjugate, less than 5% EPA-DHA conjugate, less than 4% EPA-DHA conjugate, less than 3% EPA-DHA conjugate, less than 2% EPA-DHA conjugate, less than 1% EPA-DHA conjugate, less than 0.5% EPA-DHA conjugate, or less than 0.1% EPA-DHA conjugate, by weight.

[0019] In another embodiment, a composition of the present invention includes at least 96% EPA-Fatty acid conjugate (e.g. EPA-EPA), at least 97% EPA-Fatty acid conjugate, at least 98% EPA-Fatty acid conjugate, or at least 99% EPA-Fatty acid conjugate. In another embodiment, a composition of the present invention contains no more than 10%, no more than 9%, no more than 8%, no more than 7%, no more than 6%, no more than 5%, no more than 4%, no more than 3%, no more than 2%, no more than 1%, or no more than 0.6%, no more than 0.5%, no more than 0.4%, no more than 0.3%, no more than 0.2, or no more than 0.1% of any EPA-Fatty Acid conjugate other than EPA-EPA diester.

[0020] In another embodiment, EPA is present in a composition of the invention in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg,

about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, or about 2500 mg.

[0021] In one embodiment, a composition of the invention contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight of total fatty acids, docosahexaenoic acid or derivative thereof such as ethyl-DHA (E-DHA), if any. In another embodiment, a composition of the invention contains substantially no docosahexaenoic acid or derivative thereof such as E-DHA. In still another embodiment, a composition of the invention contains no docosahexaenoic acid or E-DHA.

[0022] In another embodiment, EPA represents at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, at least about 99%, or 100%, by weight, of all fatty acids present in a composition of the invention.

[0023] In another embodiment, a composition of the invention contains less than 30%, less than 20%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA, or derivative thereof. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA) or derivative thereof such as ethyl-linolenic acid, arachidonic acid (AA) or derivative thereof such as ethyl-AA, docosahexaenoic acid (DHA)

or derivative thereof such as ethyl-DHA, alpha-linolenic acid (ALA) or derivative thereof such as ethyl-ALA, stearadonic acid (STA) or derivative thereof such as ethyl-SA, eicosatrienoic acid (ETA) or derivative thereof such as ethyl-ETA and/or docosapentaenoic acid (DPA) or derivative thereof such as ethyl-DPA.

[0024] In another embodiment, a composition of the invention has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least 96%, at least 97%, or at least 98%, by weight, of total fatty acids present in the composition; (b) the composition contains not more than 4%, not more than 3%, or not more than 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than 0.6%, 0.5%, or 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20 °C) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20 °C) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (f) the composition contains not more than 20 ppm, 15 ppm or 10 ppm heavy metals, (g) the composition contains not more than 5 ppm, 4 ppm, 3 ppm, or 2 ppm arsenic, and/or (h) the composition has a peroxide value not more than 5, 4, 3, or 2 Mcq/kg.

[0025] In another embodiment, a composition useful in accordance with the invention comprises, consists essentially of or consists of at least 95% ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% ethyl arachidonate (AA-E), about 0.3% to about 0.5% ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E), each by weight of total fatty acids present in the composition. In another embodiment, the composition is present in a capsule shell. In still another embodiment, the capsule shell contains no chemically modified gelatin.

[0026] In another embodiment, compositions useful in accordance with the invention comprise, consist essentially of, or consist of at least 95%, 96% or 97%, ethyl eicosapentaenoate, about 0.2% to about 0.5% ethyl octadecatetraenoate, about 0.05% to about 0.25% ethyl nonaecapentaenoate, about 0.2% to about 0.45% ethyl arachidonate, about 0.3% to about 0.5% ethyl eicosatetraenoate, and about 0.05% to about 0.32% ethyl heneicosapentaenoate, each by weight of all fatty acids present in the composition.. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight of total fatty acids present, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or

derivative thereof such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (*e.g.* tocopherol) in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, about 500 mg to about 1 g of the composition is provided in a capsule shell. In another embodiment, the capsule shell contains no chemically modified gelatin.

[0027] In another embodiment, compositions useful in accordance with the invention comprise, consist essentially of, or consist of at least 96% ethyl eicosapentaenoate, about 0.22% to about 0.4% ethyl octadecatetraenoate, about 0.075% to about 0.20% ethyl nonaecapentaenoate, about 0.25% to about 0.40% ethyl arachidonate, about 0.3% to about 0.4% ethyl eicosatetraenoate and about 0.075% to about 0.25% ethyl heneicosapentaenoate, each by weight of total fatty acids present in the composition. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight of total fatty acids present, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (*e.g.* tocopherol) in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell. In one embodiment, the dosage form is a gel- or liquid-containing capsule and is packaged in blister packages of about 1 to about 20 capsules per sheet.

[0028] In another embodiment, compositions useful in accordance with the invention comprise, consist essentially of or consist of at least 96%, 97% or 98%, by weight, ethyl eicosapentaenoate, about 0.25% to about 0.38% by weight ethyl octadecatetraenoate, about 0.10% to about 0.15% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.35% by weight ethyl arachidonate, about 0.31% to about 0.38% by weight ethyl eicosatetraenoate, and about 0.08% to about 0.20% ethyl heneicosapentaenoate, each by weight of all fatty acids present in the composition. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight of all fatty acids present, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (*e.g.* tocopherol) in an amount of not more

than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell. In another embodiment, the capsule shell contains no chemically modified gelatin.

Cardiovascular Agents

[0029] In one embodiment, a composition (or co-administration regimen) of the invention comprises one or more additional cardiovascular agents. The one or more additional cardiovascular agents can be co-formulated with EPA or can be co-administered with EPA. The interchangeable terms "cardiovascular agent" or "cardiovascular drug" herein refer to a drug or agent that is capable of treating, preventing, or reducing the risk of developing a cardiovascular disease or disorder, or a risk factor or symptom thereof, in a subject. Cardiovascular agents herein can include, without limitation, cholesterol and triglyceride modulating agents, agents that treat coronary artery disease, agents that treat hypertension or pulmonary arterial hypertension, agents that treat arterial fibrillation or arrhythmia, agents that treat stroke, agents that treat myocardial ischemia and/or agents that treat thrombosis.

[0030] Non-limiting examples of classes from which cardiovascular agents suitable for use in accordance with the present invention can be selected include: Acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors including selective inhibitors of ACAT-1, ACAT-2 as well as dual inhibitors of ACAT-1 and ACAT-2, alpha-adrenergic blocking drugs (alpha-blockers), alpha/beta blockers, angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists, angiotensin II receptor antagonists, anti-arrhythmics, anticoagulants, antiplatelet agents, apolipoprotein A-1 (apoA-1) mimetics, beta-blockers, bile acid sequestrants, calcium-channel blockers, ApoB cholesteryl ester transfer protein (CETP) inhibitors, cholesterol absorption inhibitors, diuretics, dyslipidemia agents, endothelin receptor antagonists, fibrates, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, LCAT activators, LDL receptor inducers, lipase inhibitors, lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitors, microsomal triglyceride transfer protein (MTP) inhibitors, platelet aggregation inhibitors, PPAR agonists and activators including PPARγ agonists, PPARα agonists and PPAR dual α/γ agonists, PCSK9 antisense or RNAi, squalene epoxidase inhibitors, squalene synthetase inhibitors, thrombolytics, and thyroid receptor beta activators.

ACAT inhibitors.

[0031] Acyl-CoA cholesteryl acyl transferase ("ACAT") is an acyltransferase enzyme. In bile acid biosynthesis, ACAT catalyzes the intracellular formation of cholesterol esters from cholesterol. ACAT promotes accumulation of cholesterol esters in vascular tissues. Agents that inhibit ACAT, therefore, are useful in preventing or treating atherosclerosis. Non-limiting examples of suitable ACAT inhibitors include CI-1011 (Avasimibe, Pfizer), CS-505 (Pactimibe sulfate, Sankyo Pharma), or combinations thereof.

[0032] One or more ACAT inhibitors, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 1 mg to about 1000 mg, for example about 1 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 266 mg, about 275 mg, about 300 mg, about 324 mg, about 325 mg, about 330 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg.

ACE inhibitors.

[0033] Angiotensin I converting enzyme ("ACE") converts angiontensin I to angiotensin II and inhibits bradykinin. Because increased angiotensin II and decreased bradykinin levels both promote a variety of cardiovascular diseases and disorders, agents that inhibit ACE are useful in preventing or treating cardiovascular-related diseases such as hypertension, heart failure, diabetic neuropathy, and type 2 diabetes. Non-limiting examples of suitable ACE inhibitors include captopril, enalapril, enaliprilat, trandolapril, moexipril, ramipril, quinapril, perindopril, lisinopril, benazepril, fosinopril, or combinations thereof.

[0034] One or more ACE inhibitors, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 0.5 mg to about 50 mg, for example about 0.5 mg, about 0.75 mg, about 1 mg, about 1.25 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 7.5 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17

mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, or about 50 mg.

Aldosterone antagonists.

[0035] Aldosterone is a steroidal hormone that contributes to hypertension by inhibiting kidney function. Agents that compete with aldosterone for mineralo-corticoid receptors are therefore useful in preventing or treating hypertension. Non-limiting examples of suitable aldosterone agents include eplerenone and aldactone, or combinations thereof.

[0036] Aldosterone antagonists, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 5 mg to about 100 mg, for example about 5 mg, about 10 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95, or about 100 mg.

Alpha blockers.

[0037] Alpha blockers, also called adrenergic alpha-antagonists, compete with adrenaline binding at α-adrenoreceptors. Adrenaline binding at such receptors leads to vasoconstriction and therefore hypertension. Agents that compete with adrenaline or block α-adrenoreceptors are therefore useful in preventing or treating hypertension. Non-limiting examples of suitable alpha blockers include doxazosin, methyldopa, clonidine, prazosin, terazosin, or combinations thereof.

[0038] Alpha blockers, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 0.02 mg to about 0.5 mg, for example about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 2.5 mg, about 0.3 mg, about 3.5 mg, about 0.4 mg, about 4.5 mg, or about 0.5 mg; in an amount of about 0.5 mg to about 15 mg, for example about 0.5 mg, about 0.75 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, or about 15 mg; or in an amount of about 100 mg to about 500 mg, for example about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225

mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg.

Alpha/beta blockers.

[0039] One or more alpha/beta blockers, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 1 mg to about 25 mg, for example about 1 mg, about 2 mg, about 3 mg, about 3.125 mg, about 4 mg, about 5 mg, about 6 mg, about 6.25 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24, or about 25 mg. A non-limiting example of an alpha/beta blocker is carvedilol.

Angiotensin II receptor antagonists.

[0040] Angiotensin II receptor antagonists, alternately called angiotensin receptor blockers, ARBs, AT_1-receptor antagonists, or sartans, are useful in treating hypertension, congestive heart failure, and various other diseases and disorders. Non-limiting examples of angiotensin II receptor antagonists include candesartan, irbesartan, olmesartan, losartan, valsartan, telmisartan, eprosartan, or combinations thereof.

[0041] One or more angiotensin II receptor antagonists, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 1 mg to about 100 mg, for example about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 15 mg, about 16 mg, about 20 mg, about 24 mg, about 25 mg, about 28 mg, about 30 mg, about 32 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg; in an amount of about 40 mg to about 320 mg, for example, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 260 mg, about 280 mg, about 300 mg, about 320 mg; in an amount of about 200 mg to about 800 mg, for example about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, or about 800 mg.

Anti-arrhythmic agents.

[0042] Anti-arrhythmic drugs act to correct an irregular heartbeat and/or slow a heart that is beating too rapidly. Non-limiting examples of suitable anti-arrhythmic agents include adenosine, amiodarone, digoxin, disopyramide, flecainide, lidocaine, mexiletine, procainamide, quinidine gluconate, propafenone hydrochloride, tocainide, or combinations thereof.

[0043] One or more anti-arrhythmics, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 0.1 mg to about 1500 mg, about 1 mg to about 1200 mg, or about 5 mg to about 1000 mg, for example about 0.1 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 5 mg, about 6 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 266 mg, about 275 mg, about 300 mg, about 324 mg, about 325 mg, about 330 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, or about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, or about 1500 mg.

[0044] In an another embodiment, one or more anti-arrhythmics can be present in an amount of about 1 mg per mL to about 500 mg per mL, for example about 1 mg per mL, about 2 mg per mL, about 3 mg per mL, about 4 mg per mL, about 5 mg per mL, about 6 mg per mL, about 10 mg per mL, about 25 mg per mL, about 50 mg per mL, about 75 mg per mL, about 80 mg per mL, about 100 mg per mL, about 125 mg per mL, about 150 mg per mL, about 175 mg per mL, about 200 mg per mL, about 225 mg per mL, about 250 mg per mL, about 275 mg per mL, about 300 mg per mL, about 325 mg per mL, about 350 mg per mL, about 375 mg per mL, about 400 mg per mL, about 425 mg per mL, about 450 mg per mL, about 475 mg per mL, or about 500 mg per mL.

[0045] In another embodiment, an anti-arrhythmics is present in an amount of about 0.01% to about 5%, for example about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, about 0.06%, about 0.07%, about 0.08%, about 0.09%, about 0.1%, about

0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, about 2%, about 2.1%, about 2.2%, about 2.3%, about 2.4%, about 2.5%, about 2.6%, about 2.7%, about 2.8%, about 2.9%, about 3%, about 3.1%, about 3.2%, about 3.3%, about 3.4%, about 3.5%, about 3.6%, about 3.7%, about 3.8%, about 3.9%, about 4%, about 4.1%, about 4.2%, about 4.3%, about 4.4%, about 4.5%, about 4.6%, about 4.7%, about 4.8%, about 4.9%, or about 5% by weight of the total composition.

Antiplatelet agents.

[0046] Antiplatelet agents inhibit platelet aggregation and therefore combat thrombus development. Non-limiting examples of antiplatelet agents include adeparin, aspirin, clopidogrel, danaparoid, deltaparin, denaparoid, ticlopidine, cilostazol, abciximab, eptifibatide, tirofiban, defibrotide, enoxaparin, dipyridamole, tinzaparin, or combinations thereof.

[0047] One or more antiplatelet agents, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 10 mg to about 100 mg, for example about 10 mg, about 12.5 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg; in an amount of about 50 mg to about 300 mg, for example about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg.

[0048] In another embodiment, one or more antiplatelet agents are present in an amount of about 25 μg per mL to about 50 μg per mL, for example about 25 μg per mL, about 30 μg per mL, about 35 μg per mL, about 40 μg per mL, about 45 μg per mL, or about 50 μg per mL; or in an amount of about 1 mg per mL to about 2 mg per mL, for example about 1 mg per mL, about 1.25 mg per mL, about 1.50 mg per mL, about 1.75, or about 2 mg per mL.

apoA-1 mimetics.

[0049] Apolipoprotein A-1 ("apoA-1") is the primary protein component of serum HDL cholesterol. Non-limiting examples of apoA-1 mimetics include ETC-216, ETC-588-liposome, ETC-642, trimeric apoA-1, CSL-111, APP018, reverse D-4F, or combinations thereof.

[0050] One or more apoA-1 mimetics, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 0.1 mg to about 1500 mg, about 1 mg to about 1200 mg, or about 5 mg to about 1000 mg, for example about 0.1 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 5 mg, about 6 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 266 mg, about 275 mg, about 300 mg, about 324 mg, about 325 mg, about 330 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, or about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, or about 1500 mg.

Beta blockers.

[0051] Beta blockers block responses to the beta nerve receptor which tends to slow heart rate and lower blood pressure. Non-limiting examples of suitable beta blockers include acebutolol, atenolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, or combinations thereof.

[0052] One or more beta blockers, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 1 mg to about 1000 mg, about 1 mg to about 750 mg, or about 1 mg to about 500 mg, for example about 1 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg.

Bile acid sequestrants.

[0053] Bile acid sequestrants interrupt the enterohepatic circulation of bile acids by binding bile acid components in the gastrointestinal tract, rendering them unabsorbable

thereafter. Bile acid sequestrants are thus useful in preventing or treating hyperlipidemia, among other diseases and disorders. Non-limiting examples of bile acid sequestrants include colesevelam Hcl, colestipol, locholest and cholestyramine or combinations thereof.

[0054] One or more bile acid sequestrants, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 4 mg to about 32 mg, for example about 4 mg, about 8 mg, about 12 mg, about 16 mg, about 24 mg, about 32 mg; or in an amount of about 300 mg to about 4000 mg, for example about 300 mg, about 325 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 625 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 900 mg, about 1000 mg, about 1250 mg, about 1500 mg, about 1750 mg, about 2000 mg, about 2250 mg, about 2500 mg, about 2750 mg, about 3000 mg, about 3250 mg, about 3500 mg, about 3750, or about 4000 mg.

Calcium channel blockers.

[0055] Calcium channel blockers are useful in preventing or treating hypertension by their vasodilating action. Non-limiting examples of calcium channel blockers include nicardipine, diltiazem, clevidipine butyrate, isradipine, nimodipine, nisoldipine, verapamil, and amlodipine besylate, or combinations thereof. Non-limiting examples of combination calcium channel blockers include amlodipine, olmesartan, valsartan, or combinations thereof.

[0056] One or more calcium channel blockers, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 1 mg to about 10 mg, for example about 1 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg; in an amount of about 5 mg to about 34 mg, for example about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 8.5 mg, about 9 mg, about 10 mg, about 15 mg, about 17.5 mg, about 20 mg, about 22.5 mg, about 25 mg, about 25.5 mg, about 27.5 mg, about 30 mg, about 32.5, or about 34 mg; in an amount of about 10 mg to about 60 mg, for example about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, or about 60 mg; in an amount of about 20 mg to about 120 mg, for example about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110, or about 120 mg; in an amount of about 60 mg to about 420 mg, for example about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 140 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 260

mg, about 280 mg, about 300 mg, about 320 mg, about 340 mg, about 360 mg, about 380 mg, about 400, or about 420 mg.

[0057] In another embodiment, one or more calcium channel blockers is present in an amount of about 0.05 mg per mL to about 2.5 mg per mL, for example about 0.05 mg per mL, about 0.1 mg per mL, about 0.2 mg per mL, about 0.3 mg per mL, about 0.4 mg per mL, about 0.5 mg per mL, about 0.6 mg per mL, about 0.7 mg per mL, about 0.8 mg per mL, about 0.9 mg per mL, about 1.0 mg per mL, about 1.25 mg per mL, about 1.5 mg per mL, about 1.75 mg per mL, about 2.0 mg per mL, about 2.25 mg per mL, or about 2.5 mg per mL.

CETP inhibitors.

[0058] Cholesteryl ester transfer protein ("CETP") plays an important role in transferring cholesteryl esters and triglycerides. Inhibition of CETP, also called plasma lipid transfer protein, is therefore useful in preventing or treating atherosclerosis and other cardiovascular diseases and disorders. Non-limiting examples of CETP inhibitors include torcetrapib, anacetrapib, JTT-705, BAY-60-5521, PF-3185043, and CP-800569, or combinations thereof.

[0059] One or more CETP inhibitors, if desired, are present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount sufficient to provide the subject with a dose of about 25 mg per kg body weight ("mg per kg") to about 100 mg per kg, for example about 25 mg per kg, about 30 mg per kg, about 35 mg per kg, about 40 mg per kg, about 45 mg per kg, about 50 mg per kg, about 55 mg per kg, about 60 mg per kg, about 65 mg per kg, about 70 mg per kg, about 75 mg per kg, about 80 mg per kg, about 85 mg per kg, about 90 mg per kg, about 95 mg per kg, or about 100 mg per kg.

[0060] In another embodiment, one or more CETP inhibitors, if desired, are present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 100 mg to about 10 g, about 500 mg to about 9 g, or about 750 mg to about 5 g.

Cholesterol absorption inhibitors.

[0061] Cholesterol absorption inhibitors reduce the cholesterol content of chylomicrons and chylomicron remnants by preventing the uptake of micellar cholesterol from the small intestine. As a result, less cholesterol is delivered to the liver and thereby reduces LDL. Non-limiting examples of cholesterol absorption inhibitors include ezetimibe and simvastatin, or combinations thereof.

[0062] One or more cholesterol absorption inhibitors, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 1 mg to about 10 mg, for example about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg; or in an amount of about 10 to about 80 mg, for example about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, or about 80 mg.

Diuretics.

[0063] Diuretics increase urination rates forcing diuresis. Some diuretics also provide antihypertensive effects. Non-limiting examples of diuretics include hydrochlorothiazide, torsemide, ethacrynic acid, furosemide, triamterene, indapamide, chlorothiazide sodium, aliskiren, or combinations thereof.

[0064] One or more diuretics, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of: (a) about 0.25 mg to about 2.5 mg, for example about 0.25 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, about 2.25 mg, or about 2.5 mg; (b) in an amount of about 5 mg to about 25 mg, for example about 5 mg, about 10 mg, about 12.5 mg, about 15 mg, about 17.5 mg, about 20 mg, about 22.5 mg, or about 25 mg; (c) in an amount of about 2 mg to about 100 mg, for example about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 7.5 mg, about 10 mg, about 12.5 mg, about 15 mg, about 17.5 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg; (d) about 10 mg to about 50 mg, for example about 10 mg, about 12.5 mg, about 15 mg, about 17.5 mg, about 20 mg, about 22.5 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg; in an amount of about 5 mg to about 60 mg, for example about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, (e) or about 60 mg; in an amount of about 25 mg to about 100 mg, for example about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg; in an amount of about 75 mg to about 300 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg,

or about 300 mg; (f) about 0.1 g to about 0.5 g, for example about 0.1 g, about 0.2 g, about 0.3 g, about 0.4 g, or about 0.5 g; or (g) in an amount of about 1 mg per mL to about 10 mg per mL, for example about 1 mg per mL, about 2 mg per mL, about 3 mg per mL, about 4 mg per mL, about 5 mg per mL, about 6 mg per mL, about 7 mg per mL, about 8 mg per mL, about 9 mg per mL, or about 10 mg per mL.

Dyslipidemia agents.

[0065] Dyslipidemia is a class of diseases that includes hyperlipidemia. Fredrickson's Type I dyslipidemia (sometimes referred to as Buerger-Gruetz syndrome, primary hyperlipoproteinaemia, or familial hyperchylomicronemia) is characterized by elevated cholesterol levels, subjects with Fredrickson's Type IIa dyslipidemia (also known as familial hypercholesterolemia) exhibit elevated LDL levels. Those with Fredrickson's Type IIb dyslipidemia (familial combined hyperlipoproteinemia (FCH) or secondary combined hyperlipoproteinemia) show increased LDL and VLDL levels. Fredrickson's Type III dyslipidemia (sometimes called beta disease or dysbetalipoproteinemia) features elevated intermediate density lipoproteins ("IDL"), while Fredrickson's Type IV dyslipidemics (sometimes called "pure hypertriglyceridemics") have elevated VLDL levels. Subjects with Fredrickson's Type V dyslipidemia have increased VLDL and chylomicron levels.

[0066] Non-limiting examples of dyslipidemia agents include Angpt14 antibody, APA-01 (Phosphagenics), CRD-5 (ImaSight), NCX6560 (NicOx), PCSK9 RNAi (Alnylam), recombinant apoA-1 (SemBioSys Genetics), anti-oxLDL (Genentech), APL180 (Novartis), APP018 (D4F) (Novartis), CER-002 (Cerenis Therapeutics), CP-800,569 (Pfizer), GSK-256073 (GlaxoSmithKline), MB07811 (Metabasis), PF-3,185,043 (Pfizer), R7232 (Roche), rilapladib (GlaxoSmithKline), RVX-208 (Resverlogix), Sobetirome (QRX-431 (QuatRx)), anacetrapib (Merk), CSL111 (CSL Limited), darapladib (GlaxoSmithKline), eprotirome (Karo Bio), GFT505 (Genfit), MAHDL01 (Marzal Plant Pharma), MBX-8025 (Metabolex), PLX204 (Wyeth/Plexxikon), aleglitezar (Roche), dalcetrapib (Roche), SLx4090 (Surface Logix), verespladib (Anthera Pharmaceuticals), AEGR-733 (Aegerion), ABT-335 (Abbott Laboratories), AVE5530 (Sanofi-Aventis), LCP-AtorFen (LifeCycle Pharma), TRIA-662 (Cortria), fenofibrate, choline fenofibrate, ezetimibe, colsevelam, laropiprant, or combinations of any of the foregoing.

[0067] One or more dyslipidemia agents, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 1 mg to about 1000 mg, for example about 1 mg,

about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 43 mg, about 45 mg, about 48 mg, about 50 mg, about 54 mg, about 55 mg, about 60 mg, about 65 mg, about 67 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 87 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 107 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 134 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 500 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, or about 1000 mg.

Endothelin receptor antagonists.

[0068] Binding of endothelin-1 at endothelin-A (ETA) or endothelin-B (ETB) receptors causes pulmonary vasoconstriction. Endothelin receptor antagonists compete with endothelin-1 binding, thereby attenuating pulmonary vasoconstriction. Endothelin receptor antagonists, therefore, are useful in treating pulmonary hypertension. Non-limiting examples of endothelin receptor antagonists include ambrisentan, bosentan, volibris, thelin, or combinations thereof.

[0069] One or more endothelin receptor antagonists, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 1 mg to about 10 mg, for example about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg; in an amount of about 50 mg to about 250 mg, for example about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, or about 250 mg.

HMG-CoA reductase inhibitors.

[0070] HMG-CoA reductase (also known as HMGR) converts HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) to mevalonic acid (3,5-dihydroxy-3-methyl-pentanoic acid) along the metabolic pathway that produces cholesterol. HMG-CoA reductase inhibitors, also called statins, inhibit HMG-CoA reductase and thereby reduce cholesterol

production. As a result, HMG-CoA reductase inhibitors are useful in treating a variety of cardiovascular diseases and disorders including, for example, hypercholesterolemia, hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, atherosclerosis, Non-limiting examples of HMG-CoA reductase inhibitors include lovastatin, lovastatin + niacin, mevastatin, pitavastatin, pravastatin, rosuvastatin, fluvastatin, atorvastatin, atorvastatin + amlodipine besylate, simvastatin, simvistatin + niacin, ezetimibe, and pravastatin, among others.

[0071] One or more HMG-CoA reductase inhibitors, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 1 mg to about 1000 mg, for example about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg; about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, or about 1000 mg.

LCAT activators.

[0072] Lecithin-cholesterol acyltransferase ("LCAT") converts cholesterol into cholesteryl ester. In subjects with deficient levels of LCAT, unesterified cholesterol accumulates in body tissues. This can lead to elevated serum levels of HDL and eventually atherosclerosis. LCAT activators are therefore useful in reducing serum HDL levels and treating or preventing atherosclerosis. Non-limiting examples of LCAT activators include LCAT enzyme, recombinant LCAT, genetic therapy agents that include a nucleic acid sequence coding for expression of LCAT, estrogens, estrogen analogs, and combinations thereof for example as disclosed in U.S. Patent No. 6,635,614 incorporated by reference herein in its entirety.

[0073] One or more LCAT activators, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount sufficient to raise the serum LCAT level of the subject to a

desired level. Subjects with abnormally low LCAT serum levels may be administered an amount of a composition of the invention comprising EPA and LCAT enzyme, estrogen, estrogen analogs, or combinations thereof sufficient to raise the subject's serum LCAT level to normal levels, typically about 5 μg per mL or greater. In another embodiment, subjects with about normal LCAT serum levels may be treated with a composition of the invention comprising EPA and LCAT enzyme, estrogen, estrogen analogs, or combinations thereof in an amount sufficient to raise the LCAT serum level to about 6 μg per mL or more, about 7 μg per mL or more, about 8 μg per mL or more, about 9 μg per mL or more, or about 10 μg per mL or more.

LDL receptor inducers.

[0074] LDL receptors are cell surface proteins. Along with adaptin, LDL receptors bind free LDL cholesterol to form clathrin-coated vesicles, reducing serum LDL levels. Thus, agents that induce LDL receptors further reduce serum LDL levels and are useful in preventing or treating atherosclerosis. A non-limiting example of LDL receptor is lactacystin.

[0075] One or more LDL receptor inducers, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 1 mg to about 1000 mg, for example about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, or about 1000 mg.

Lp-PLA2 inhibitors.

[0076] Compositions of the invention may comprise one or more lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitors. Lp-PLA2 hydrolyzes oxidized phospholipids in LDL cholesterols. High levels of Lp-PLA2 seem to trigger a cascade of inflammatory events in atherosclerosis and an increased risk of stroke. Lp-PLA2 inhibitors,

therefore, are useful in slowing or preventing development of atherosclerosis. Non-limiting examples of Lp-PLA2 inhibitors include rilapladib, darapladib, and combinations thereof.

[0077] One or more Lp-PLA2 inhibitors, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 1 mg to about 1000 mg, for example about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg; about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, or about 1000 mg.

5-Lipoxygenase inhibitors.

[0078] 5-lipoxygenase inhibitors are usefull in accordance with various embodiments of the invention. Non-limiting examples of 5-lipixygenase inhibitors include VIA-2291, MK-886, CMI 977, ABT-761, ZD2138, lonapalene, zileuton, 5-LO inhibitor 6, L-739,010, CGS 22745, SC 45662, and combinations thereof.

[0079] Additional 5-lipoxygenase inhibitors suitable for use in accordance with embodiments of the instant invention are disclosed in the following U.S. patents and patent applications, each of which is hereby incorporated by reference herein in its entirety: U.S. 20050101659, U.S. 7026344, U.S. 7329682, U.S. 20040198768, U.S. 20090054519, U.S. 5112848, U.S. 5086052, U.S. 482828, U.S. 5208364, U.S. 4970210, U.S. 4794114, U.S. 4686231, U.S. 5134150, U.S. 5639782, U.S. 6239170, U.S. 20060106014, U.S. 5229386, U.S. 4673684, U.S. 6136839, U.S. 6090547, U.S. 6355434, U.S. 20090042849, U.S. 4731382, U.S. 4877881, U.S. 5130485, U.S. 5665752, U.S. 5723481, U.S. 5102897, U.S. 5234939, U.S. 5143928, U.S. 5217971, U.S. 4889941, U.S. 5234937, U.S. 5283361, U.S. 5232939, U.S. 5086064, U.S. 5208251, U.S. 5290800, U.S. 5006549, U.S. 5494927, U.S. 20040198800, U.S. 4719218, U.S. 4847270, U.S. 6121323, U.S. 20080226758, U.S. 20070218146, U.S. 4728656, U.S. 4835189, U.S. 5763673, U.S. 4835190, U.S. 5162365, U.S. 5985937, U.S. 6455541, U.S. 5534524, U.S. 20070134341, U.S. 20050267145, U.S.

4694018, U.S. 5260294, U.S. 5792776, U.S. 5530141, U.S. 5780503, U.S. 5093356, U.S. 5348957, U.S. 5384318, U.S. 568822, U.S. 20010009918, U.S. 20070219206, U.S. 20070225285, U.S. 20050267211, U.S. 20030162193, U.S. 20070173508, U.S. 20070066577, U.S. 5036067, U.S. 20030082108, U.S. 20090018170, U.S. 20070105866, U.S. 20070237848, U.S. 20070244185, U.S. 20080227807, U.S. 4728735, U.S. 4803279, U.S. 4962119, U.S. 5314898, U.S. 20070123522, U.S. 20070123522, U.S. 20070244128, U.S. 20070093524, U.S. 4602023, U.S. 4943587, U.S. 6025384, U.S. 20090118373, U.S. 5112868, U.S. 5254553, U.S. 5312821, U.S. 5635514, U.S. 7405302, U.S. 4624964, U.S. 4786755, U.S. 4933351, U.S. 5059609, U.S. 5442111, U.S. 5066668, U.S. 5292900, U.S. 5998451, U.S. 4851586, U.S. 5314900, U.S. 5447943, U.S. 6221880, U.S. 6262077, U.S. 6376528, U.S. 6569895, U.S. 4663347, U.S. 4975457, U.S. 4978679, U.S. 5703093, U.S. 5811432, U.S. 4822803, U.S. 5356921, U.S. 5750565, U.S. 4751310, U.S. 4816486, U.S. 5288751, U.S. 5298512, U.S. 5909734, U.S. 4745127, U.S. 5215986, U.S. 5270319, U.S. 5476944, U.S. 4939169, U.S. 6166031, U.S. 6696477, U.S. 6756399, U.S. 4931444, U.S. 5066658, U.S. 5248685, U.S. 5240929, U.S. 4861798, U.S. 4933329, U.S. 5008390, U.S. 5814648, U.S. 6939674, U.S. 5696141, U.S. 5434151, U.S. 20030216481, U.S. 20030232763, U.S. 20060177528, U.S. 20030235620, U.S. 20020177723, U.S. 5036105, U.S. 5504097, U.S. 5741809, U.S. 5459154, U.S. 5463083, U.S. 6420392, U.S. 5358938, U.S. 5326907, U.S. 6294574, U.S. 5648486, U.S. 5856323, U.S. 7387797, U.S. 4801611, U.S. 5530114, U.S. 7514469, U.S. 20010025040, U.S. 20020143033, U.S. 5665749, U.S. 20010009917, U.S. 20070049621, U.S. 20080280826, U.S. 5393923, U.S. 5114958, U.S. 5376670, U.S. 6217875, U.S. 5155122, U.S. 5288896, U.S. 6436924, U.S. 5256680, U.S. 7132441, U.S. 5145860, U.S. 5354768, U.S. 5698576, U.S. 7371874, U.S. 5068251, U.S. 5130483, U.S. 6177415, U.S. 5541218, U.S. 20070264361, U.S. 5284949, U.S. 4672075, U.S. 5212189, U.S. 5302597, U.S. 20080107757, U.S. 6620813, U.S. 5250565, U.S. 624012, U.S. 4732901, U.S. 5196431, U.S. 5340815, U.S. 5504108, U.S. 5220025, U.S. 5252562, U.S. 5420131, U.S. 5037837, U.S. 5081126, U.S. 5105020, U.S. 5187175, U.S. 5342838, U.S. 4755525, U.S. 5248682, U.S. 4963576, U.S. 5514703, U.S. 6194585, U.S. 6194585, U.S. 6291534, U.S. 4695586, U.S. 4971979, U.S. 6653311, U.S. 4755524, U.S. 5147893, U.S. 4711903, U.S. 20040077691, U.S. 4695585, U.S. 2005009084, U.S. 5516789, U.S. 5512594, U.S. 20070202206, U.S. 6261607, U.S. 5350754, U.S. 6344563, U.S. 20040235807, U.S. 5064851, U.S. 5254581, U.S. 5288742, U.S. 5403859, U.S. 5407945, U.S. 20030008914, U.S. 5254731, U.S. 5318970, U.S. 5519022, U.S. 6174883, U.S.

6262073, U.S. 20040170974, U.S. 20070231345, U.S. 4985435, U.S. 5126365, U.S. 5234950, U.S. 5321025, U.S. 5484805, U.S. 5221677, U.S. 5280047, U.S. 5300655, and U.S. 5359063.

[0080] One or more 5-lipoxygenase inhibitors, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 0.01 mg to about 2500 mg, about 0.1 mg to about 1500 mg, about 1 mg to about 1200 mg, or about 5 mg to about 1000 mg, for example about 0.1 mg, about 0.5, about 0.75 mg, about 1 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, or about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

Microsomal triglyceride transfer protein inhibitors.

[0081] Microsomal triglyceride transfer protein ("MTTP" or "MTP") is a heterodimeric protein involved in lipoprotein assembly. MTP inhibitors are thus useful in slowing or preventing the production of lipoproteins and therefore cardiovascular diseases and disorders. Non-limiting examples of MTP inhibitors include SLx-4090, AEGR-733, implitapide, BMS-200150, CP-346086, JTT-130, dirlotapide, and combinations thereof.

[0082] Additional MTP inhibitors suitable for use in accordance with embodiments of the instant invention are disclosed in the following U.S. patents and patent applications, each of which is hereby incorporated by reference herein in its entirety: U.S. 20030166590, U.S. 6492365, U.S. 20040132779, U.S. 20040132745, U.S. 20050181376, U.S. 20030086912, U.S. 6767739, U.S. 20080249130, U.S. 20020028943, U.S. 5883099, U.S. 5739135, U.S. 5712279, U.S. 6034098, U.S. 5827875, U.S. 6066650, U.S. 5885983, U.S. 20060166999, U.S. 20070027183, U.S. 20020045271, U.S. 6288234, U.S. 20030109700, U.S. 20040014748, 6878707, 6218524, 5595872, U.S. 20080253985, U.S. 20080103122, U.S. 20050234073, U.S. 20050090426, U.S. 20040044008, U.S. 20090042835, U.S. 20040058908, U.S. 20060270655, U.S. 6369075, U.S. 20080241869, U.S. 20070093468, U.S. 20090054393, U.S. 20020132806, U.S. 20070088089, U.S. 20040033506, U.S. 20080161279, U.S. 20020161233, U.S. 20020042516, U.S. 20070093527, U.S. 6713489, U.S. 20060211020, U.S. 6617325, U.S. 6147214 and U.S. 20020032238.

[0083] In one embodiment, one or more MTP inhibitors, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount sufficient to provide the subject with a dose of about 1 μg per kg of body weight (μg per kg) to about 100 μg per kg, for example about 25 μg per kg, about 30 μg per kg, about 35 μg per kg, about 40 μg per kg, about 45 μg per kg, about 50 μg per kg, about 55 μg per kg, about 60 μg per kg, about 65 μg per kg, about 70 μg per kg, about 75 μg per kg, about 80 μg per kg, about 85 μg per kg, about 90 μg per kg, about 95 μg per kg, or about 100 μg per kg. In another embodiment, one or more MTP inhibitors, if desired, are present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 30 μg to about 20 mg, about 50 μg to about 15 mg, or about 70 μg to about 10 mg.

[0084] In another rembodiment, one or more MTP inhibitors, if desired, are present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 0.01 mg to about 2500 mg, about 0.1 mg to about 1500 mg, about 1 mg to about 1200 mg, or about 5 mg to about 1000 mg, for example about 0.1 mg, about 0.5, about 0.75 mg, about 1 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg,

about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, or about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

PPAR agonists and activators.

[0085] Peroxisome proliferator-activated receptors ("PPARs") are nuclear receptor proteins regulating the expression of genes by acting as transcription factors in combination with the retinoid X receptor ("RXR"). Agents that inhibit or activate PPARs are therefore useful in modifying the expression of certain genes including, for example, genes associated with metabolic disorders such as hypercholesterolemia. Non-limiting examples of PPAR agonists and activators include fenofibrate, bezafibrate, ciprofibrate, clofibrate, gemfibrozil, CER-002, rosiglitazone, GW501516, RWJ 800025, KD-3010, and combinations thereof.

[0086] One or more PPAR agonists and/or activators, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 0.5 mg to about 4 mg, for example about 0.5 mg, about 0.75 mg, about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, about 2.25 mg, about 2.5 mg, about 2.75 mg, about 3 mg, about 3.25 mg, about 3.5 mg, about 3.75 mg, or about 4 mg; or in an amount of about 20 mg to about 120 mg, for example about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, or about 120 mg.

sPLA2 Inhibitors.

[0087] sPLA2 inhibitors are suitable for use in accordance with various embodiments of the present invention. Non-limiting examples of sPLA2inhibitors include LY 333013, varespladib, WA8242A, WA8242A$_2$, WA8242B, A-0001, A-0002 and combinations thereof.

[0088] Additional sPLA2 inhibitors suitable for use in accordance with embodiments of the instant invention are disclosed in the following U.S. patents and patent applications, each of which is hereby incorporated by reference herein in its entirety: U.S.6974831, U.S.6916840, U.S.6992100, U.S.6872743, U.S.20040063967, U.S.20040063941, U.S.20040092543, U.S.20040077704, U.S.6433001, U.S.20030153770, U.S.20030191175, U.S.6706752, U.S.6730694, U.S.20040059130, U.S.7026348, U.S.6608099, U.S.6340699, U.S.6252084, U.S.6635670, U.S.6939890, U.S.6930123, U.S.6713505, U.S.6274578, U.S.6451839, U.S.20040029948, U.S.20090062369, U.S.20030236232, U.S.7160909, U.S.6384041, U.S.6175021, U.S.6214876, U.S.20090131396, U.S.6353128, U.S.6407104, U.S.6274616, U.S.20030087944, U.S.5916922, U.S.20040198801, U.S.20080249027, U.S.7026318, U.S.6933313, U.S.20040087796, U.S.6391908, U.S.20030181454, U.S.6831095, U.S.6177426, U.S.20060116379, U.S.6472389, U.S.6797708, U.S.20090118503, U.S.20070249008, U.S.7087637, U.S.5919810, U.S.6828344, U.S.6916841, U.S.5654326, U.S.5641800, U.S.5733923, U.S.6534535, U.S.20050026988, U.S.6166062, U.S.5684034, U.S.7253194, U.S.20080045444, U.S.20040033995, U.S.20060235009, U.S.20090088427, U.S.7196103, U.S.20080317809, U.S.20090092595, U.S.20070037253, U.S.7098237, U.S.6140327, U.S.5972972, U.S.20040248898, U.S.6967200, U.S.20030092767, U.S.20040106669, U.S.20040077651, U.S.20050158401, U.S.6514984, U.S.20040102442, U.S.6610728, U.S.20030119860, U.S.6436983, U.S.6703385, U.S.6576654, U.S.7101875, U.S.6635771, U.S.6756376, U.S.6984735, U.S.6448284, U.S.6787545, U.S.6265591, U.S.6713645, U.S.6673781, U.S.6214855, U.S.6008231, U.S.6344467, U.S.6177440, U.S.6426344, U.S.7105514, U.S.6214991, U.S.20020169108, U.S.20060025348, U.S.20030008816, U.S.20090029917, U.S.6900208, U.S.6380397, U.S.7205329, U.S.5919943, U.S.7126010, U.S.7109231, U.S.6555568, U.S.6872557, U.S.7030112, U.S.7041695, U.S.7220756, U.S.7396838, U.S.6407261, U.S.6028116, U.S.5965619, U.S.6063818, U.S.5998477, U.S.6121321, U.S.6958348, U.S.7528112, U.S.6903104, U.S.6745133, U.S.6861436, U.S.5650374, U.S.6569539, U.S.6432987, U.S.5762413, U.S.7176281, U.S.7317009, U.S.7153854, U.S.20020110523, U.S.6776986, U.S.5948779, U.S.7449615, U.S.7531568, U.S.7476746, U.S.7491831, U.S.6231189, U.S.6987105, U.S.7300932, U.S.6962784, U.S.6248553, U.S.6255063,

U.S.20070053912, U.S.6974831, U.S.20040063941, U.S.20040077704, U.S.20040248898, U.S.20040063967, U.S.6992100, U.S.20040092543, U.S.6916840, U.S.6433001, U.S.20070249008, U.S.20090092595, U.S.6872743, U.S.20070037253.

[0089] One or more sPLA2 inhibitors, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 0.01 mg to about 2500 mg, about 0.1 mg to about 1500 mg, about 1 mg to about 1200 mg, or about 5 mg to about 1000 mg, for example about 0.1 mg, about 0.5, about 0.75 mg, about 1 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, or about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

Squalene epoxidase inhibitors.

[0090] Squalene epoxidase, also called squalene monooxygenase, catalyzes the oxidation of squalene in the cholesterol biosynthesis pathway. Thus, agents that inhibit squalene epoxidase are useful in preventing or slowing the cholesterol production. Non-limiting examples of squalene epoxidase inhibitors include terbinafine, naftifine, amorolfine, butenafine, FR194738, NB-598, resveratrol (trans-3,4',5-trihydroxystilbene),

epigallocatechin-3-O-gallate, S-allylcysteine, selenocysteine, alliin, diallyl trisulfide, diallyl disulfide, and combinations thereof.

[0091] One or more squalene epoxidase inhibitors, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 100 mg to 250 mg, for example about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, or about 250 mg; or in an amount of about 0.5% to about 5%, by weight of the composition, for example about 0.5 %, about 0.75 %, about 1 %, about 1.25 %, about 1.5 %, about 1.75 %, about 2 %, about 2.25 %, about 2.5 %, about 2.75 %, about 3 %, about 3.25 %, about 3.5 %, about 3.75 %, about 4 %, about 4.25 %, about 4.5 %, about 4.75%, or about 5%, by weight.

Thrombolytic agents.

[0092] Thrombolytic agents dissolve blood clots. Thrombolytic agents are therefore useful in treating cardiovascular diseases and disorders including, for example, deep vein thrombosis, pulmonary embolism, ischemic complications, unstable angina, myocardial infarction, and venous thromboembolism, among others. Non-limiting examples of thrombolytic agents include fondoparinux, dalteparin, enoxaparin, apixaban, PD-348292, and combinations thereof.

[0093] One or more thrombolytic agents, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount sufficient to provide a dosage of about 0.5 mg per kg of body weight ("mg per kg") to about 40 mg per kg, for example about 0.5 mg per kg, about 1 mg per kg, about 2 mg per kg, about 3 mg per kg, about 4 mg per kg, about 5 mg per kg, about 6 mg per kg, about 7 mg per kg, about 8 mg per kg, about 9 mg per kg, about 10 mg per kg, about 11 mg per kg, about 12 mg per kg, about 13 mg per kg, about 14 mg per kg, about 15 mg per kg, about 16 mg per kg, about 17 mg per kg, about 18 mg per kg, about 19 mg per kg, about 20 mg per kg, about 21 mg per kg, about 22 mg per kg, about 23 mg per kg, about 24 mg per kg, about 25 mg per kg, about 26 mg per kg, about 27 mg per kg, about 28 mg per kg, about 29 mg per kg, about 30 mg per kg, about 31 mg per kg, about 32 mg per kg, about 33 mg per kg, about 34 mg per kg, about 35 mg per kg, about 36 mg per kg, about 37 mg per kg, about 38 mg per kg, about 39 mg per kg, or about 40 mg per kg, or in a total amount of about 30 mg to about 3.5g.

[0094] In another embodiment, one or more thrombolytic agents are present in a composition of the invention (or co-administered with EPA according to other embodiments

of the invention) in an amount of about 0.5 mg to about 2.5 mg, for example 0.5 mg, about 0.75 mg, about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, about 2.25 mg, or about 2.5 mg; or in an amount sufficient to provide about 60 international units per kg of body weight ("IU per kg") to about 240 IU per kg, for example 60 IU per kg, about 70 IU per kg, about 80 IU per kg, about 90 IU per kg, about 100 IU per kg, about 110 IU per kg, about 120 IU per kg, about 130 IU per kg, about 140 IU per kg, about 150 IU per kg, about 160 IU per kg, about 170 IU per kg, about 180 IU per kg, about 190 IU per kg, about 200 IU per kg, about 210 IU per kg, about 220 IU per kg, about 230 IU per kg, or about 240 IU per kg.

Other cardiovascular agents.

[0095] Other cardiovascular agents are also useful in preventing, inhibiting, or treating cardiovascular diseases or disorders. Non-limiting examples of other cardiovascular agents include gemfibrozil, niaspan, orlistat, GFT14, AZD-2479, ETC-1001, and combinations thereof.

[0096] One or more of these other cardiovascular agents, if desired, can be present in a composition of the invention (or may be co-administered with EPA according to other embodiments of the invention) in an amount corresponding to the recommended or suggested dosage for the particular cardiovascular agent(s). In a related embodiment, the cardiovascular agent(s) may be present in a composition of the invention (or may be co-administered with EPA according to other embodiments of the invention) in an amount less than the recommended or suggested dosage for the particular cardiovascular agent(s). For example, a composition of the invention may comprise EPA and one or more of these other cardiovascular agents in an amount of about 5 mg to about 1500 mg for example about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 266 mg, about 275 mg, about 300 mg, about 324 mg, about 325 mg, about 330 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, or about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about

1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, or about 1500 mg.

[0097] Headings used to describe cardiovascular agents herein are not to be construed as limiting in any manner. Many cardiocascular agents can have multiple modes of action and can be described under one or more headings.

Salts and Other Derivatives

[0098] Salts, hydrates, solvate, esters, amides, enantiomers, isomers, tautomers, polymorphs, prodrugs, and derivatives of any of the foregoing drugs may be used in accordance with the invention and may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry. See, *e.g.*, March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 4th Ed. (New York: Wiley-Interscience, 1992); Leonard *et al.*, Advanced Practical Organic Chemistry (1992); Howarth et al., Core Organic Chemistry (1998); and Weisermel et al., Industrial Organic Chemistry (2002).

[0099] "Pharmaceutically acceptable salts," or "salts," include the salt of a drug prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic, methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, beta-hydroxybutyric, galactaric and galacturonic acids.

[00100] In one embodiment, acid addition salts are prepared from the free base forms using conventional methodology involving reaction of the free base with a suitable acid. Suitable acids for preparing acid addition salts include both organic acids, *e.g.*, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

[00101] In another embodiment, base addition salts are prepared from the free acid forms using conventional methodology involving reaction of the free acid with a suitable base.

[00102] In other embodiments, an acid addition salt is reconverted to the free base by treatment with a suitable base. In a further embodiment, the acid addition salts are halide

salts, which are prepared using hydrochloric or hydrobromic acids. In still other embodiments, the basic salts are alkali metal salts, *e.g.*, sodium salt. In other embodiments, a base addition salt is reconverted to the free acid by treatment with a suitable acid.

[00103] In one embodiment, EPA and one or more cardiovascular agent(s) are present in a composition of the invention, or are co-administered in a weight ratio of EPA:cardiovascular agent of about 1:1000 to about 1000:1, about 1:500 to about 500:1, about 1:100 to about 100:1, about 1:50 to about 50:1, about 1:25 to about 25:1, about 1:10 to about 10:1, about 1:5 to about 5:1, about 1:4 to about 4:1 about 1:3 to about 3:1, about 1:2 to about 2:1 or about 1:1.

Antiretroviral Therapy

[00104] In one embodiment, the present invention provides a method of treating a cardiovascular-related disease as defined herein, for example dyslipidemia or hyperlipidemia, in an HIV positive subject. In another embodiment, the method comprises co-administration, or concomitant administration, of a composition or compositions as disclosed herein with one or more HIV-1 protease inhibitors. Non-limiting examples of HIV-1 protease inhibitors include amprenavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir.

[00105] One or more HIV-1 protease inhibitors, if desired, are typically present in a composition of the invention (or co-administered with EPA according to other embodiments of the invention) in an amount of about 100 mg to about 2500 mg, for example about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 625 mg, about 650 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1825 mg, about 1900 mg, about 2000 mg, about 2100 mg, about 2200 mg, about 2300 mg, about 2400 mg, or about 2500 mg; in an amount of about 200 mg to about 1000 mg, for example about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, or about 1000 mg; in an amount of about 50 mg to about 400 mg, for example about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg; in an amount of about 200 mg to about 1066 mg, for example about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 533 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, or about 1066

mg; in an amount of about 50 mg to about 1200 mg, for example about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, or about 1200 mg; or in an amount of about 15 mg per kg body weight to about 40 mg per kg body weight, for example about 15 mg per kg, about 20 mg per kg, about 25 mg per kg, about 30 mg per kg, about 35 mg per kg, about mg per kg, or about 40 mg per kg.

Dosage Forms

[00106] In one embodiment, compositions of the invention are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration.

[00107] In some embodiments, compositions of the invention are in the form of solid dosage forms. Non-limiting examples of suitable solid dosage forms include tablets (*e.g.* suspension tablets, bite suspension tablets, rapid dispersion tablets, chewable tablets, melt tablets, effervescent tablets, bilayer tablets, *etc*), caplets, capsules (*e.g.* a soft or a hard gelatin capsule filled with solid and/or liquids), powder (*e.g.* a packaged powder, a dispensable powder or an effervescent powder), lozenges, sachets, cachets, troches, pellets, granules, microgranules, encapsulated microgranules, powder aerosol formulations, or any other solid dosage form reasonably adapted for oral administration.

[00108] EPA and/or any other desired cardiovascular agent(s) can be co-formulated in the same dosage unit, or can be individually formulated in separate dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a plurality (*i.e.* 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

[00109] In one embodiment, a composition of the invention comprises one or more cardiovascular agents dispersed or suspended in EPA, wherein the dispersion or suspension is present in a capsule (for example gelatin or HPMC capsule), sachet, or other dosage form or

carrier as described herein. In another embodiment, the dispersion or suspension is substantially uniform. In still another embodiment, where co-administration of two or more dosage units is desired, the EPA is present in a first dosage unit, for example a suspension in a capsule, and the cardiovascular agent is present in second dosage unit, for example a tablet. Optionally, any desired additional cardiovascular agent can be present in a third composition.

[00110] In another embodiment, composition(s) of the invention can be in the form of liquid dosage forms or dose units to be imbibed directly or they can be mixed with food or beverage prior to ingestion. Non-limiting examples of suitable liquid dosage forms include solutions, suspension, elixirs, syrups, liquid aerosol formulations, *etc.*

[00111] In one embodiment, compositions of the invention, upon storage in a closed container maintained at room temperature, refrigerated (*e.g.* about 5 to about 5 -10 °C) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

[00112] In another embodiment, the invention provides a pharmaceutical composition comprising EPA and a cardiovascular agent (fill) encapsulated in a capsule shell, wherein the fill has a baseline peroxide value not greater than about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg, wherein upon storage of the composition at 23 °C and 50% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, the ultra-pure EPA has a second peroxide value not greater than about 25 Meq/kg, about 24 Meq/kg, about 23 Meq/kg, about 22 Meq/kg, about 21 Meq/kg, about 20 Meq/kg, about 19 Meq/kg, about 18 Meq/kg, about 17 Meq/kg, about 16 Meq/kg, about 15 Meq/kg, about 14 Meq/kg, about 13 Meq/kg, about 12 Meq/kg, about 11 Meq/kg, about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg.

[00113] Upon storage, some pharmaceutical compositions degrade over time. Degradation products can alter a composition's efficacy, for example by delivering less active ingredient to a subject than recommended. Degradation products for new drugs above certain thresholds should be reported to the Food & Drug Administration (FDA) in accordance with current Guidance Documents. Degradation products above a certain

threshold amount should be identified. A degradation product is "identified" when its structural characterization has been achieved. Degradation products above a certain amount should be qualified. A degradation product is "qualified" when its biological safety is acquired and evaluated.

[00114] In one embodiment, compositions of the invention with a maximum daily dose of less than or equal to 1 gram, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 0.1% of any degradation product not reported to the Food and Drug Administration (FDA). In another embodiment, compositions of the invention with a maximum daily dose of greater than 1 gram, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 0.05% of any degradation product not reported to the FDA.

[00115] In one embodiment, compositions of the invention with a maximum daily dose of less than 1 mg, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 1% of any unidentified degradation product. In another embodiment, compositions of the invention with a maximum daily dose of less than 1 mg, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 5 μg of any unidentified degradation product.

[00116] In one embodiment, compositions of the invention with a maximum daily dose of 1 mg to 10 mg, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 0.5% of any unidentified degradation product. In another embodiment, compositions of the invention with a maximum daily dose of 1 mg to 10 mg, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 20 μg of any unidentified degradation product.

[00117] In one embodiment, compositions of the invention with a maximum daily dose of 10 mg to 2 g, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 0.2% of any unidentified degradation product. In another embodiment, compositions of the invention with a maximum daily dose of 10 mg to 2 g, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 2 mg of any unidentified degradation product.

[00118] In one embodiment, compositions of the invention with a maximum daily dose of greater than 2 g, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 0.1% of any unidentified degradation product.

[00119] In one embodiment, compositions of the invention with a maximum daily dose of less than 10 mg, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 1% of any unqualified degradation product. In another embodiment, compositions of the invention with a maximum daily dose of less than 10 mg, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 50 μg of any unqualified degradation product.

[00120] In one embodiment, compositions of the invention with a maximum daily dose of 10 mg to 100 mg, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 0.5% of any unqualified degradation product. In another embodiment, compositions of the invention with a maximum daily dose of 10 mg to 100 mg, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 200 μg of any unqualified degradation product.

[00121] In one embodiment, compositions of the invention with a maximum daily dose of 100 mg to 2 g, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 0.2% of any unqualified degradation product. In another embodiment, compositions of the invention with a maximum daily dose of 100 mg to 2 g, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 3 mg of any unqualified degradation product.

[00122] In one embodiment, compositions of the invention with a maximum daily dose of greater than 2 g, upon storage under light, heat, humidity, acid/base hydrolytic, and/or oxidative conditions, contain less than about 0.15% of any unqualified degradation product.

[00123] In some embodiments, compositions of the invention comprise a stabilizing agent that suppresses, prevents, hinders, or otherwise attenuates the decomposition of the active ingredient(s) during storage. For example, oxidative decomposition of EPA in compositions of the invention may be prevented or attenuated by the presence of antioxidants. Non-limiting examples of suitable antioxidants include tocopherol, lecithin, citric acid and/or ascorbic acid. One or more antioxidants, if desired, are typically present in a composition in an amount of about 0.01% to about 0.1%, by weight, or about 0.025% to about 0.05%, by weight.

Excipients

[00124] Compositions of the invention optionally comprise one or more pharmaceutically acceptable excipients. The term "pharmaceutically acceptable excipient" herein means any substance, not itself a therapeutic agent, used as a carrier or vehicle for

delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a unit dose of the composition, and that does not produce unacceptable toxicity or interaction with other components in the composition.

[00125] Compositions of the invention optionally comprise one or more pharmaceutically acceptable diluents as excipients. Suitable diluents illustratively include, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (*e.g.*, Celutab™ and Emdex™); mannitol; sorbitol; xylitol; dextrose (*e.g.*, Cerelose™ 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of α- and amorphous cellulose (*e.g.*, Rexcel™) and powdered cellulose; calcium carbonate; glycine; bentonite; polyvinylpyrrolidone; and the like. Such diluents, if present, constitute in total about 5% to about 99%, about 10% to about 85%, or about 20% to about 80%, of the total weight of the composition.

[00126] Compositions of the invention optionally comprise one or more pharmaceutically acceptable disintegrants as excipients. Suitable disintegrants include, either individually or in combination, starches, including sodium starch glycolate (*e.g.*, Explotab™ of PenWest) and pregelatinized corn starches (*e.g.*, National™ 1551, National™ 1550, and Colocorn™ 1500), clays (*e.g.*, Veegum™ HV), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (*e.g.*, Ac-Di-Sol™ of FMC), alginates, crospovidone, and gums such as agar, guar, xanthan, locust bean, karaya, pectin and tragacanth gums. Such disintegrants, if present, typically comprise in total about 0.2% to about 30%, about 0.2% to about 10%, or about 0.2% to about 5%, of the total weight of the composition.

[00127] Compositions of the invention optionally comprise one or more antioxidants. Illustrative antioxidants include sodium ascorbate and vitamin E (tocopherol). One or more antioxidants, if present, are typically present in a composition of the invention in an amount of about 0.001% to about 5%, about 0.005% to about 2.5%, or about 0.01% to about 1%, by weight.

[00128] Compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients. Such binding agents and adhesives can impart sufficient cohesion to a powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Suitable binding agents and adhesives include, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (*e.g.*, National™ 1511 and National™ 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (*e.g.*, Tylose™); alginic acid and salts of alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites; povidone, for example povidone K-15, K-30 and K-29/32; polymethacrylates; HPMC; hydroxypropylcellulose (*e.g.*, Klucel™); and ethylcellulose (*e.g.*, Ethocel™). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, about 0.75% to about 15%, or about 1% to about 10%, of the total weight of the composition.

[00129] Compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Non-limiting examples of surfactants that can be used as wetting agents in compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (*e.g.*, Labrasol™ of Gattefossé), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (*e.g.*, Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (*e.g.*, Lauroglycol™ of Gattefossé), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about

15%, about 0.4% to about 10%, or about 0.5% to about 5%, of the total weight of the composition.

[00130] Compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, either individually or in combination, glyceryl behapate (*e.g.*, Compritol™ 888); stearic acid and salts thereof, including magnesium (magnesium stearate), calcium and sodium stearates; hydrogenated vegetable oils (*e.g.*, Sterotex™); colloidal silica; talc; waxes; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (*e.g.*, Carbowax™ 4000 and Carbowax™ 6000); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0.1% to about 10%, about 0.2% to about 8%, or about 0.25% to about 5%, of the total weight of the composition.

[00131] Suitable anti-adherents include talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is an anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, about 0.25% to about 5%, or about 0.5% to about 2%, of the total weight of the composition. Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include colloidal silicon dioxide, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate.

[00132] Compositions of the present invention optionally comprise one or more flavoring agents, sweetening agents, and/or colorants. Flavoring agents useful in the present invention include, without limitation, acacia syrup, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butter, butter pecan, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, citrus, citrus punch, citrus cream, cocoa, coffee, cola, cool cherry, cool citrus, cyclamate, cylamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, MagnaSweet®, maltol, mannitol, maple, menthol, mint, mint cream, mixed berry, nut, orange, peanut butter, pear, peppermint, peppermint cream, Prosweet® Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrose, Swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, and combinations thereof, for example, anise-menthol,

cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, *etc*.

[00133] Sweetening agents that can be used in the present invention include, for example, acesulfame potassium (acesulfame K), alitame, aspartame, cyclamate, cylamate, dextrose, isomalt, MagnaSweet®, maltitol, mannitol, neohesperidine DC, neotame, Prosweet® Powder, saccharin, sorbitol, stevia, sucralose, sucrose, tagatose, thaumatin, xylitol, and the like.

[00134] Flavoring agents, sweetening agents, and/or colorants can be present in compositions of the invention in any suitable amount, for example about 0.01% to about 10%, about 0.1% to about 8%, or about 1% to about 5%, by weight.

[00135] Compositions of the invention optionally comprise a suspending agent. Non-limiting illustrative examples of suitable suspending agents include silicon dioxide, bentonite, hydrated aluminum silicate (e.g. kaolin) and mixtures thereof. One or more suspending agents are optionally present in compositions of the invention in a total amount of about 0.01% to about 3.0%, about 0.1% to about 2.0%, or about 0.25% to about 1.0%, by weight

[00136] The foregoing excipients can have multiple roles as is known in the art. For example, starch can serve as a filler as well as a disintegrant. The classification of excipients above is not to be construed as limiting in any manner. Excipients categorized in any manner may also operate under various different categories of excipients as will be readily appreciated by one of ordinary skill in the art.

Therapeutic Methods

[00137] In various embodiments, compositions of the invention are useful for treatment and/or prevention of a cardiovascular-related disease. The term "cardiovascular-related disease" herein refers to any disease or disorder of the heart or blood vessels (*i.e.* arteries and veins) or any symptom thereof, or any disease or condition that causes or contributes to a cardiovascular disease." Non-limiting examples of cardiovascular-related diseases and disorders include acute cardiac ischemic events, acute myocardial infarction , angina, angina pectoris, arrhythmia, atrial fibrulation, atherosclerosis, arterial fibrillation, cardiac insufficiency, cardiovascular disease, chronic heart failure, chronic stable angina, congestive heart failure, coronary artery disease, coronary heart disease, deep vein thrombosis, diabetes, diabetes mellitus, diabetic neuropathy, diastolic dysfunction in subjects with diabetes mellitus, edema, essential hypertension , eventual pulmonary embolism, fatty liver disease, heart disease, heart failure, homozygous familial hypercholesterolemia (HoFH),

homozygous familial sitosterolemia, hypercholesterolemia, hyperlipidemia, hyperlipidemia in HIV positive subjects, hypertension, hypertriglyceridemia, ischemic complications in unstable angina and myocardial infarction, low blood pressure, metabolic syndrome, mixed dyslipidemia, moderate to mild heart failure, myocardial infarction, obesity management, paroxysmal atrial/arterial fibrillation/fibrulation/flutter, paroxysmal supraventricular tachycardias (PSVT), particularly severe or rapid onset edema, platelet aggregation, primary hypercholesterolemia, primary hyperlipidemia, pulmonary arterial hypertension, pulmonary hypertension, recurrent hemodynamically unstable ventricular tachycardia (VT), recurrent ventricular arrhythmias, recurrent ventricular fibrillation (VF), ruptured aneurysm, sitisterolemia, stroke, supraventricular tachycardia, symptomatic atrial fibrillation/flutter, tachycardia, type-II diabetes, vascular disease, venous thromboembolism, ventricular arrhythmias, and other cardiovascular events.

[00138] The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

[00139] In some embodiments, compositions of the present invention can be co-administered or administered concomitantly with one or more additional cardiovascular agents. The terms "co-administered," "concomitant administration," and "administered concomitantly" are used interchangeably herein and each refer to, for example, administration of two or more agents (e.g., EPA or a derivative thereof and a cardiovascular agent) at the same time, in the same dosage unit, one immediately after the other, within five minutes of each other, within ten minutes of each other, within fifteen minutes of each other, within thirty minutes of each other, within one hour of each other, within two hours of each other, within four hours of each other, within six hours of each other, within twelve hours of each other, within one day of each other, within one week of each other, within two weeks of

each other, within one month of each other, within two months of each other, within six months of each other, within one year of each other, *etc.*

[00140] In one embodiment, the present invention provides a method of treating a cardiovascular-related disease comprising administering to a subject in need thereof a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units), wherein one or more lipid parameters are improved by comparison with lipid parameters achieved by the additive effects of the individual treatments.

[00141] In a related embodiment, upon treatment in accordance with the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits one or more of the following outcomes:

(a) reduced triglyceride levels compared to baseline or a placebo arm;

(b) reduced Apo B levels compared to baseline or a placebo arm;

(c) increased HDL-C levels compared to baseline or a placebo arm;

(d) no increase in LDL-C levels compared to baseline or a placebo arm;

(e) a reduction in LDL-C levels compared to baseline or a placebo arm;

(f) a reduction in non-HDL-C levels compared to baseline or a placebo arm;

(g) a reduction in vLDL levels compared to baseline or a placebo arm;

(h) an increase in apo A-I levels compared to baseline or a placebo arm;

(i) an increase in apo A-I/apo B ratio compared to baseline or a placebo arm;

(j) a reduction in lipoprotein A levels compared to baseline or a placebo arm;

(k) an increase in LDL particle number compared to baseline or a placebo arm;

(l) a reduction in LDL size compared to baseline or a placebo arm;

(m) a reduction in remnant-like particle cholesterol compared to baseline or a placebo arm;

(n) a reduction in oxidized LDL compared to baseline or a placebo arm;

(o) no change or a reduction in fasting plasma glucose (FPG) compared to baseline or a placebo arm;

(p) a reduction in hemoglobin A_{1c} (HbA_{1c}) compared to baseline or a placebo arm;

(q) a reduction in homeostasis model insulin resistance compared to baseline or a placebo arm;

(r) a reduction in lipoprotein associated phospholipase A2 compared to baseline or a placebo arm;

(s) a reduction in intracellular adhesion molecule-1 compared to baseline or a placebo arm;

(t) a reduction in interleukin-6 compared to baseline or a placebo arm;

(u) a reduction in plasminogen activator inhibitor-1 compared to baseline or a placebo arm;

(v) a reduction in high sensitivity C-reactive protein (hsCRP) compared to baseline or a placebo arm;

(w) an increase in serum phospholipid EPA compared to baseline or a placebo arm;

(x) an increase in red blood cell membrane EPA compared to baseline or a placebo arm; and/or

(y) a reduction or increase in one or more of serum phospholipid and/or red blood cell content of docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), arachidonic acid (AA), palmitic acid (PA), staeridonic acid (SA) or oleic acid (OA) compared to baseline or a placebo arm.

[00142] In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a) – (y) above prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a) – (y) are determined, and subsequently taking an additional measurement of said one or more markers.

[00143] In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15

or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more, any 24 or more, or all 25 of outcomes (a) – (y) described immediately above.

[00144] In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits one or more of the following outcomes:

(a) a reduction in triglyceride level of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline or a placebo arm;

(b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline or a placebo arm;

(c) substantially no change, no change or an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline or a placebo arm;

(d) a less than 60% increase, less than 50% increase, less than 40% increase, less than 30% increase, less than 20% increase, less than 15% increase or no increase in LDL-C levels or a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline or a placebo arm;

(e) a decrease in Apo B levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline or a placebo arm;

(f) a reduction in vLDL levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(g) an increase in apo A-I levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(h) an increase in apo A-I/apo B ratio of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(i) a reduction in lipoprotein(a) levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(j) a reduction in mean LDL particle number of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(k) an increase in mean LDL particle size of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at

least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(l) a reduction in remnant-like particle cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(m) a reduction in oxidized LDL of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(n) substantially no change, no change or a reduction in fasting plasma glucose (FPG) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(o) substantially no change, no change or a reduction in hemoglobin A_{1c} (HbA_{1c}) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% (actual % change or median % change) compared to baseline or a placebo arm;

(p) a reduction in homeostasis model index insulin resistance of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(q) a reduction in lipoprotein associated phospholipase A2 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(r) a reduction in intracellular adhesion molecule-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(s) a reduction in interleukin-6 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(t) a reduction in plasminogen activator inhibitor-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(u) a reduction in high sensitivity C-reactive protein (hsCRP) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;

(v) an increase in serum plasma and/or RBC EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 100%, at least about 200% or at least about 400% (actual % change or median % change) compared to baseline or a placebo arm;

(w) an increase in serum phospholipid and/or red blood cell membrane EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, r at least about 50%, at least about 100%, at least about 200%, or at least about 400% (actual % change or median % change) compared to baseline or a placebo arm;

(x) a reduction or increase in one or more of serum phospholipid and/or red blood cell DHA, DPA, AA, PA and/or OA of at least about 5%, at least about 10%, at

least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline or a placebo arm; and/or

(y) a reduction in total cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline or a placebo arm.

[00145] In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a) – (y) prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a) – (y) are determined, and subsequently taking a second measurement of the one or more markers as measured at baseline for comparison thereto.

[00146] In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more of, any 24 or more of, or all 25 of outcomes (a) – (y) described immediately above.

[00147] Parameters (a) – (y) can be measured in accordance with any clinically acceptable methodology. For example, triglycerides, total cholesterol, HDL-C and fasting blood sugar can be sample from serum and analyzed using standard photometry techniques. VLDL-TG, LDL-C and VLDL-C can be calculated or determined using serum lipoprotein fractionation by preparative ultracentrifugation and subsequent quantitative analysis by refractometry or by analytic ultracentrifugal methodology. Apo A1, Apo B and hsCRP can be determined from serum using standard nephelometry techniques. Lipoprotein (a) can be

determined from serum using standard turbidimetric immunoassay techniques. LDL particle number and particle size can be determined using nuclear magnetic resonance (NMR) spectrometry. Remnants lipoproteins and LDL-phospholipase A2 can be determined from EDTA plasma or serum and serum, respectively, using enzymatic immunoseparation techniques. Oxidized LDL, intercellular adhesion molecule-1 and interleukin-2 levels can be determined from serum using standard enzyme immunoassay techniques. These techniques are described in detail in standard textbooks, for example Tietz Fundamentals of Clinical Chemistry, 6th Ed. (Burtis, Ashwood and Borter Eds.), WB Saunders Company.

[00148] In a related embodiment, the reductions or increases of parameters (a) – (y) above are statistically significant.

[00149] In another embodiment, the present invention provides a method of blood lipid therapy comprising administering to a subject in need thereof 1 to a plurality of dosage units comprising a composition or compositions as disclosed herein. In another embodiment, the subject being treated has a baseline triglyceride level, prior to treatment with a composition of the present invention, greater than or equal to about 150 mg/dl, greater than or equal to about 175 mg/dl, greater than or equal to about 250 mg/dl, or greater than or equal to about 500 mg/dl, for example about 200 mg/dl to about 2000 mg/dl, about 300 to about 1800 mg/dl, or about 500 mg/dl to about 1500 mg/dl.

[00150] In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a) – (y) prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a) – (y) are determined, and subsequently taking a second measurement of the one or more markers as measured at baseline for comparison thereto.

[00151] In one embodiment, the present invention provides a method of treating or preventing primary hypercholesteremia and/or mixed dyslipidemia (Fredrickson Types IIa and IIb) in a subject in need thereof, comprising administering to the subject a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units) as disclosed herein. In a related embodiment, the present invention provides a method of reducing triglyceride levels in a subject or subjects when treatment with a statin or niacin extended-release monotherapy is considered inadequate (Frederickson type IV hyperlipidemia). Statin or niacin extended-release monotherapy is considered inadequate when, for example, the subject's non-HDL-C level is

not lowered or is not lowered to the degree desired, the subject's LDL-C level is not improved or is not improved to the degree desired, the subject's HDL-C level is not improved or is not improved to the degree desired, and/or the subject's triglyceride level is not improved or is not improved to the degree desired.

[00152] In another embodiment, the present invention provides a method of treating or preventing nonfatal myocardial infarction, comprising administering to the subject a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units) as disclosed herein.

[00153] In another embodiment, the present invention provides a method of treating or preventing risk of recurrent nonfatal myocardial infarction in a subject with a history of myocardial infarction, comprising administering to the subject a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units) as disclosed herein.

[00154] In another embodiment, the present invention provides a method of slowing progression of or promoting regression of atherosclerotic disease in a subject in need thereof, comprising administering to the subject a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units) as disclosed herein.

[00155] In another embodiment, the present invention provides a method of treating obesity in a subject in need thereof, comprising administering to a subject in need thereof a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units) as disclosed herein.

[00156] In another embodiment, the present invention provides a method of treating or preventing very high serum triglyceride levels (*e.g.* Types IV and V hyperlipidemia) in a subject in need thereof, comprising administering to the subject a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units) as disclosed herein.

[00157] In another embodiment, the present invention provides a method of treating subjects having very high serum triglyceride levels (*e.g.* greater than 1000 mg/dl or greater than 2000 mg/dl) and that are at risk of developing pancreatitis, comprising administering to the subject a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units) as disclosed herein.

[00158] In another embodiment, the present invention provides a method of preventing recurrence of stroke, comprising administering to a subject with a history of stroke a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units) as disclosed herein.

[00159] In another embodiment, the present invention provides a method of preventing onset and/or recurrence of cardiovascular events in a subject who has escaped the unstable period after cardiovascular angioplasty, comprising administering to the subject a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units) as disclosed herein.

[00160] In another embodiment, the present invention provides a method of reducing Apo-B and non-HDL cholesterol levels in a subject group with a baseline LDL-cholesterol level of at least 100 mg/dl, a baseline non-HDL-cholesterol level of at least 130 mg/dl and a baseline triglyceride level of at least 200 mg/dl, and reducing the Apo-B and the non-HDL-cholesterol level of the subject group by administering a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units) as disclosed herein to members of the subject group.

[00161] In another embodiment, the invention provides a method of reducing Apo-B levels in a subject group, comprising measuring LDL-cholesterol, non-HDL-cholesterol, and triglyceride levels in subjects, providing a subject group with a baseline LDL-cholesterol level of at least 100 mg/dL, a baseline non-HDL-cholesterol level of at least 130 mg/dL, and a baseline triglyceride level of at least 200 mg/dL, and reducing the Apo-B levels of the subject group by administering to members of the subject group a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a single dosage unit or as multiple dosage units) as disclosed herein in an amount effective to reduce the Apo-B levels of the subject group in a statistically significant amount as compared to a control treatment, wherein an increase or statistically significant increase of LDL-cholesterol level is avoided.

[00162] In another embodiment, the invention provides a method of reducing Apo-B levels in a subject group, comprising providing a subject group with a baseline LDL-cholesterol level of at least 100 mg/dL, a baseline non-HDL-cholesterol level of at least 130 mg/dL, and a baseline triglyceride level of at least 200 mg/dL, reducing the Apo-B levels of the subject group by administering to members of the subject group a a composition or compositions comprising EPA and one or more additional cardiovascular agents (either as a

single dosage unit or as multiple dosage units) as disclosed herein in an amount effective to reduce the Apo-B levels of the subject group in a statistically significant amount as compared to a control treatment, and determining the reduction in the Apo-B levels of the subject group.

[00163] In one embodiment, a composition of the invention is administered to a subject in an amount sufficient to provide a daily EPA dose of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, or about 2500 mg.

[00164] In the various embodiments of the invention described herein, the EPA and optional one or more additional cardiovascular agents can be administered as a co-formulated single dosage unit, or as individual dosage units. Where the EPA and optional one or more additional cardiovascular agents are co-administered as separate dosage units, each dosage unit can be administered to a subject at substantially the same or substantially different times. In one embodiment, where two or more individual dosage units are to be administered daily, each dosage unit can be administered to the subject within a period of about 24 hours, 18 hours, 12 hours, 10 hours, 8 hours, 6 hours , 4 hours, 2 hours, 1 hour, or 0.5 hours.

[00165] In another embodiment, the EPA and one or more optional cardiovascular agents can be administered sequentially. For example, EPA can be administered to a subject as a sole agent during an EPA loading period. The loading period can be, for example, 1 day, 2 days, 4 days, 6 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks or 10 weeks. After any such loading period, one or more additional cardiovascular agents can be initiated together with current EPA administration or in place of EPA treatment.

[00166] In another embodiment, EPA is administered to a subject in the morning, for example from about 4 am to about 10 am, about 5 am to about 9 am, or about 6 am to about 8 am, and the optional one or more cardiovascular agents are administered to the subject in the afternoon or evening, for example from about 1 pm to about 11 pm, about 2 pm to about 10 pm, or about 3 pm to about 9 pm, or vice versa.

[00167] In another embodiment, the invention provides the use of EPA and one or more cardiovascular agents in the manufacture of a medicament for treatment or prevention of a cardiovascular-related disease such as hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events. In one embodiment, the composition contains not more than 10% DHA, if any. In another embodiment, the composition contains substantially no or no DHA.

[00168] In another embodiment, the invention provides a pharmaceutical composition comprising EPA and one or more cardiovascular agents for the treatment and/or prevention of a cardiovascular-related disease, wherein the composition contains not more than 10% DHA, if any. In a related embodiment, the composition contains substantially no DHA or no DHA.

[00169] In one embodiment, a subject being treated with a composition or regimen set forth herein is a diabetic or pre-diabetic subject.

[00170] In one embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the invention include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed to consume a Western diet. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35 to about 40% fat, and about 10% to about 15% protein. A Western

diet may further be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example where half or more or 70% or more calories come from these sources.

[00171] It is to be understood that a wide range of changes and modifications to the embodiments described above will be apparent to those skilled in the art and are contemplated. It is, therefore, intended that the foregoing detailed description be regarded as illustrative rather than limiting, and that it be understood that it is the following claims, including all equivalents, that are intended to define the spirit and scope of the invention.

[00172] It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present subject matter and without diminishing its intended advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

EXAMPLES

[00173] The following non-limiting examples are for illustrative purposes only and are not to be construed as limiting the invention in any manner.

Example 1

[00174] An experiment was conducted to test EPA, DHA, EPA + DHA with and without with atorvastatin in model membranes enriched with PUFAs and cholesterol at levels that reproduce disease or high CV-risk conditions (i.e. hypercholesterimia). As is shown below, EPA exhibits a potent antioxidant benefit in cholesterol-enriched membranes that was superior to that observed with DHA. Moreover, the combination of EPA and atorvastating provided even further antioxidant benefit by comparison to EPA alone.

[00175] EPA and DHA were tested individually at a fixed concentration of 10.0 μM or in combination at 5.65 μM and 4.35 μM (EPA and DHA, respectively), which is a mole ratio of 1.3:1. Separate and combined effects of these agents on lipid peroxide (LOOH) formation were examined at cholesterol-to-phospholipid (C/P) mole ratios of 0.5:1, 1.0:1 and 1.5:1. Levels of lipid hydroperoxides were also measured for EPA, DPH and EPA/DPH in cholesterol-enriched membrane prepared in the absence and presence of atorvastatin.

[00176] 1,2-Dilinoleoyl-3-*sn*-phosphatidylcholine (DLPC) was obtained from Avanti Polar Lipids (Alabaster, AL) and stored in chloroform (25 mg/ml) at –80°C until use. Cholesterol obtained and stored in chloroform (10 mg/ml) at –20°C. CHOD-iodide color

reagent (stock) was prepared according to a procedure modified from El-Saadani *et al.* (El-Saadani M, Esterbauer H, El-Sayed M, Goher M, Nassar AY, Jurgens G. A spectrophotometric assay for lipid peroxides in serum lipoproteins using commercially available reagent. *J Lipid Res* 1989;**30**:627-30) consisted of 0.2 M K_2HPO_4, 0.12 M KI, 0.15 mM NaN_3, 10 μM ammonium molybdate, and 0.1 g/L benzalkonium chloride. Prior to experimental use, the CHOD reagent was activated by adding 24 μM ethylenediaminetetraacetic acid (EDTA), 20 μM butylated hydroxytoluene (BHT), and 0.2% Triton X-100. Atorvastatin was prepared in ethanol just prior to experimental use and added together with component lipids containing fixed amounts of EPA, DPH or EPA/DPH at equimolar levels. The compounds and lipids were added in combination during membrane sample preparation to ensure full incorporation into the lipid bilayers.

[00177] Membrane samples consisting of DLPC ± cholesterol, with cholesterol-to-phospholipid (C/P) mole ratios ranging from 0.5 to 1.5, were prepared as follows. Component lipids (in chloroform) were transferred to 13 × 100 mm test tubes and shell-dried under a steady stream of nitrogen gas while vortex mixing. The lipid was co-dried with EPA, DPH or EPA/DPH prepared in the absence or presence of the atorvastatin at equimolar levels.

[00178] Residual solvent was removed by drying for a minimum of 3 h under vacuum. After desiccation, each membrane sample was resuspended in diffraction buffer (0.5 mM HEPES, 154 mM NaCl, pH 7.3) to yield a final phospholipid concentration of 1.0 mg/ml. Multilamellar vesicles (MLV) were formed by vortex mixing for 3 minutes at ambient temperature. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. *J Mol Biol* 1965;**13**:238-52. Immediately after initial MLV preparation, aliquots of each membrane sample will be taken for baseline (0 h) peroxidation analyses.

[00179] All lipid membrane samples were subjected to time-dependent autoxidation by incubating at 37 °C in an uncovered, shaking water bath. Small aliquots of each sample were removed at 24 h intervals and combined with 1.0 ml of active CHOD-iodide color reagent. To ensure spectrophotometric readings within the optimum absorbance range, sample volumes taken for measurement of lipid peroxide formation were adjusted for length of peroxidation and range between 100 and 10 μl. Test samples were immediately covered with foil and incubated at room temperature for > 4 h in the absence of light. Absorbances were measured against a CHOD blank at 365 nm using a Beckman DU-640 spectrophotometer.

[00180] The CHOD colorimetric assay is based on the oxidation of iodide (I^-) by lipid hydroperoxides (LOOH) and proceeds according to the following reaction scheme:

$$LOOH + 2H^+ + 3I^- \longrightarrow LOH + H_2O + I_3^-$$

[00181] The quantity of triiodide anion (I_3^-) liberated in this reaction is directly proportional to the amount of lipid hydroperoxides present in the membrane sample. The molar absorptivity value (ε) of I_3^- is $2.46 \times 10^4\ M^{-1}\ cm^{-1}$ at 365 nm.

[00182] Results are shown in Figures 1 – 4.

CLAIMS

What is claimed is:

1. A capsule for use in reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 900 mg to about 1050 mg of ethyl eicosapentaenoate, wherein the reduction is relative to subjects having mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

2. The capsule of claim 1, wherein the ethyl eicosapentaenoate represents at least 80%, by weight, of all fatty acid present.

3. The capsule of claim 1, wherein the ethyl eicosapentaenoate represents at least 90%, by weight, of all fatty acid present.

4. The capsule of claim 1, wherein the ethyl eicosapentaenoate represents at least 95%, by weight, of all fatty acid present.

5. The capsule of any one of claim 1 to 4, wherein the capsule comprises no more than 20% of docosahexanenoic acid or its esters, if any.

6. The capsule of claim 5, wherein the capsule comprises no more than 5% of docosahexanenoic acid or its esters, if any.

7. The capsule of claim 1 to 3, wherein the capsule comprises no more than 3% of docosahexanenoic acid or its esters, if any.

8. The capsule of claim 1, wherein the capsule is useful for reducing fasting triglycerides by at least 10% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

9. The capsule of claim 1, wherein the capsule is useful in reducing fasting triglycerides by at least 15% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

10. The capsule of claim 1, wherein the capsule is useful for reducing fasting triglycerides by at least 20% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

11. The capsule of claim 1, wherein the capsule is useful for reducing fasting triglycerides by at least 25% and LDL-C by at least 5% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

12. The capsule of claim 1, wherein the capsule is useful for reducing fasting apolipoprotein B relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

13. The capsule of claim 1, wherein the capsule is useful for reducing fasting apolipoprotein B by at least 5% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

14. The capsule of claim 1, wherein the capsule is useful for reducing VLDL-C relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

15. The capsule of claim 1, wherein the capsule is useful for reducing VLDL-C by at least 15% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

16. The capsule of claim 1, wherein the statin is selected from lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, fluvastatin, atorvastatin and simvastatin.

17. A capsule for use in reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 900 mg of ethyl eicosapentaenoate.

18. A capsule for use in reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 925 mg or about 950 mg of ethyl eicosapentaenoate.

19. A capsule for use in reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 975 mg of ethyl eicosapentaenoate.

20. Use of a capsule in the manufacture of a medicament for reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 900 mg to about 1050 mg of ethyl eicosapentaenoate, wherein the reduction is relative to subjects having mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

21. The use of claim 20, wherein the ethyl eicosapentaenoate represents at least 80%, by weight, of all fatty acid present.

22. The use of claim 20, wherein the ethyl eicosapentaenoate represents at least 90%, by weight, of all fatty acid present.

23. The use of claim 20, wherein the ethyl eicosapentaenoate represents at least 95%, by weight, of all fatty acid present.

24. The use of any one of claim 20 to 23, wherein the capsule comprises no more than 20% of docosahexanenoic acid or its esters, if any.

25. The use of claim 24, wherein the capsule comprises no more than 5% of docosahexanenoic acid or its esters, if any.

26. The use of claim 20 to 22, wherein the capsule comprises no more than 3% of docosahexanenoic acid or its esters, if any.

27. The use of claim 20, for reducing fasting triglycerides by at least 10% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

28. The use of claim 20, for reducing fasting triglycerides by at least 15% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

29. The use of claim 20, for reducing fasting triglycerides by at least 20% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

30. The use of claim 20, for reducing fasting triglycerides by at least 25% and LDL-C by at least 5% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

31. The use of claim 20, for reducing fasting apolipoprotein B relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

32. The use of claim 20, wherein the capsule is useful for reducing fasting apolipoprotein B by at least 5% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

33. The use of claim 20, for reducing VLDL-C relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

34. The use of claim 20, for reducing VLDL-C by at least 15% relative to subjects with mixed dyslipidemia who receive a statin without said ethyl eicosapentaenoate.

35. The use of claim 20, wherein the statin is selected from lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, fluvastatin, atorvastatin and simvastatin.

36. Use of a capsule in the manufacture of a medicament for reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 900 mg of ethyl eicosapentaenoate.

37. Use of a capsule in the manufacture of a medicament for reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 925 mg or about 950 mg of ethyl eicosapentaenoate.

38. Use of a capsule in the manufacture of a medicament for reducing triglycerides and LDL-C in a subject having mixed dyslipidemia and on statin therapy when 4 capsules are to be administered to the subject per day, each capsule comprising about 975 mg of ethyl eicosapentaenoate.