TITLE

METHODS OF REDUCING THE RISK OF A CARDIOVASCULAR EVENT IN A SUBJECT ON STATIN THERAPY

PRIORITY CLAIM

[0001] This application claims priority to U.S. provisional patent application serial no. 61/666,447, filed June 29, 2012, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] 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.

[0003] Lovaza®, a lipid regulating agent, is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with very high triglyceride levels. Unfortunately, Lovaza® can significantly increase LDL-C and/or non-HDL-C levels in some patients. A need exists for improved treatments for cardiovascular diseases and disorders.

SUMMARY

[0004] In one aspect, the present disclosure refers to the use of a pharmaceutical composition in the manufacture of a medicament for reducing risk of a cardiovascular event selected from the group consisting of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina in a subject with at least one risk factor for cardiovascular disease who is at LDL-C goal, the use comprising that the pharmaceutical composition comprising about 4 g of icosapent ethyl is to be administered to the subject per day for a period effective to reduce risk of the cardiovascular event in the subject, the icosapent ethyl comprising at least about 95wt.% of all omega-3 fatty acids present in the pharmaceutical composition. In another aspect, the present disclosure refers to the use of icosapent ethyl in the

manufacture of a medicament for delaying or preventing a major adverse cardiovascular event selected from the group consisting of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina in a subject, the use comprising that about 4 g of icosapent ethyl is to be administered to the subject per day for a period effective to delay or prevent the major adverse cardiovascular event, wherein the subject is 50 years of age or older, has diabetes and at least one additional risk factor for cardiovascular disease, the icosapent ethyl comprising at least about 95wt.% of all omega-3 fatty acids present in the pharmaceutical composition. In various examples, there are disclosed methods of reducing the risk of a cardiovascular event in a subject on statin therapy. In one example, the method comprises administering to the subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester or a derivative thereof. In another example, the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL. In another example, the composition contains not more than 10%, by weight, docosahexaenoic acid or derivative thereof, substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof. In another example, eicosapentaenoic acid ethyl ester comprises at least 96%, by weight, of all fatty acids present in the composition; the

composition contains not more than 4%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; and/or the composition contains about 0.1% to about 0.6% of at least one fatty acid other than eicosapentaenoic acid ethyl ester and docosahexaenoic acid.

[0005] In another example, there is disclosed a method of treating hypertriglyceridemia comprising administering a composition as described herein to a subject in need thereof one to about four times per day.

[0006] These and other embodiments of the present invention will be disclosed in further detail herein below.

DETAILED DESCRIPTION

[0007] 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.

[0008] 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.” 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 disclosed numeric value into any other disclosed 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.

What is claimed is:

1. Use of a pharmaceutical composition in the manufacture of a medicament for reducing risk of a cardiovascular event selected from the group consisting of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina in a subject with at least one risk factor for cardiovascular disease who is at LDL-C goal, the use comprising that the pharmaceutical composition comprising about 4 g of icosapent ethyl is to be administered to the subject per day for a period effective to reduce risk of the cardiovascular event in the subject, the icosapent ethyl comprising at least about 95wt.% of all omega-3 fatty acids present in the pharmaceutical composition.

2. The use of claim 1, wherein the administration affects a relative risk reduction of said cardiovascular event of at least 25%.

3. The use of claim 1, wherein the subject has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL.

4. The use of claim 1, wherein the LDL-C goal is an LDL-C level of 40 mg/dL to 100 mg/dL.

5. The use of claim 1, further comprising that the subject has an established cardiovascular disease.

6. The use of claim 1, wherein the subject has diabetes.

7. The use of claim 1, wherein the at least one risk factor for cardiovascular disease is selected from the following risk factors: (a) the subject is a male of at least 55 years of age or a female of at least 65 years of age, (b) the subject smokes cigarettes or has stopped smoking cigarettes within three months before administration of the pharmaceutical composition, (c) the subject has a blood pressure of at least 140 mmHg systolic or at least 90 mmHg diastolic, (d) the subject is receiving antihypertension medication, (e) the subject is a male with HDL-cholesterol level 40 mg/dL or less or is a female with HDL-cholesterol level 50 mg/dL or less, (f) the subject has a hs-CRP level of greater than 3 mg/L, (g) the subject has a creatine clearance between 30 mL/min and 60 mL/min, (h) the subject has non-proliferative retinopathy, (i) the subject has

pre-proliferative retinopathy, (j) the subject has proliferative retinopathy, (k) the subject has maculopathy, (l) the subject has advanced diabetic eye disease or a history of photocoagulation, (m) the subject has micro- or macro-albuminuria, and (n) the subject has a asymptomatic ankle-brachial index of less than 0.9

8. The use of claim 1 wherein the pharmaceutical composition is to be administered to the subject in 1 to 8 dosage units per day.

9. The use of claim 1 wherein the icosapent ethyl comprises at least 96 wt.% of all omega-3 fatty acids in the pharmaceutical composition.

10. The use of claim 1 further comprising the subject's baseline lipid profile to be measured prior to the administration of the pharmaceutical composition to the subject.

11. The use of claim 10, wherein the subject has one or more of: a baseline non-HDL-C value of 200 mg/dL to 300 mg/dL; a baseline total cholesterol value of 250 mg/dL to 300 mg/dL; a baseline VLDL-C value of 140 mg/dL to 200 mg/dL; a baseline HDL-C value of 10 to 30 mg/dL; and/or a baseline LDL-C value of 40 to 100 mg/dL.

12. The use of claim 1, wherein the subject: (a) has not been administered 200 mg or more per day of niacin and/or fibrates for at least 28 days before administration of the pharmaceutical composition; (b) has not been administered omega-3 fatty acid prescription for a period of time beginning 28 days prior to administration of the pharmaceutical composition; (c) has not ingested dietary supplements comprising omega-3 fatty acids for a period of time beginning 28 days prior to administration of the pharmaceutical composition.

13. The use of claim 1, wherein said period ends 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, or more than 5 years after the first administration of the pharmaceutical composition.

14. The use of claim 1, wherein the subject is to be administered 4 g of the pharmaceutical composition per day for at least 3 years.

15. Use of icosapent ethyl in the manufacture of a medicament for delaying or preventing a major adverse cardiovascular event selected from the group consisting of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina in a subject, the use comprising that about 4 g of icosapent ethyl is to be administered to the subject per day for a period effective to delay or prevent the major adverse cardiovascular event, wherein the subject is 50 years of age or older, has diabetes and at least one additional risk factor for cardiovascular disease, the icosapent ethyl comprising at least about 95wt.% of all omega-3 fatty acids present in the pharmaceutical composition.

16. The use of claim 15, wherein the at least one additional risk factor is selected from hypertension, smoking, retinopathy, and albuminuria.

17. The use of claim 15, wherein the subject has at least two additional risk factors for cardiovascular disease.

18. The use of claim 15, wherein subject has a baseline triglyceride level of at least 200 mg/dL.

19. The use of claim 15, wherein the subject is on a statin therapy.

20. The use of claim 19, wherein the statin therapy is a stable statin therapy.

21. The use of claim 15, wherein the icosapent ethyl is present in a pharmaceutical composition and the icosapent ethyl comprises at least 96 wt. % of all omega-3 fatty acids in the pharmaceutical composition.

22. The use of claim 21, wherein about 1 g of the pharmaceutical composition is present in each of 4 capsules.