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 describes the use of ethyl icosapentate in the manufacture of a medicament for reducing a risk of cardiovascular death, coronary revascularization, and unstable angina in a subject on statin therapy, the use comprising: a pharmaceutical composition comprising 1 g to 4 g of ethyl icosapentate to be administered to the subject per day, wherein the subject has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL and optionally has established cardiovascular disease, and ethyl icosapentate comprises at least 95 wt.% of all omega-3 fatty acids present in the pharmaceutical composition. In another aspect, the present disclosure describes the use of ethyl icosapentate in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy (a) with

residual atherogenic dyslipidemia and clinically evident cardiovascular disease or (b) without clinically evident cardiovascular disease but with increased risk of cardiovascular disease, the use comprising: a pharmaceutical composition comprising about 4 g of ethyl icosapentate to be administered to the subject per day for a period of at least 2 years, wherein said administration reduces risk of cardiovascular disease, need for coronary revascularization, risk of unstable angina, risk for stroke and/or risk for myocardial infarction, and ethyl icosapentate comprises at least 95 wt.% of all omega-3 fatty acids present in the pharmaceutical composition. In a further aspect, the present disclosure describes the use of ethyl icosapentate in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy (a) with residual atherogenic dyslipidemia and clinically evident cardiovascular disease or (b) without clinically evident cardiovascular disease but with increased risk of cardiovascular disease, the use comprising: a pharmaceutical composition comprising about 4 g of ethyl icosapentate to be administered to the subject per day for a period of at least 2 years, wherein said administration reduces risk of cardiovascular death, need for coronary revascularization, and/or risk of unstable angina, and ethyl icosapentate comprises at least 95 wt.% of all omega-3 fatty acids present in the pharmaceutical composition. In yet another aspect, the present disclosure describes the use of ethyl icosapentate in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy (a) with residual atherogenic dyslipidemia and clinically evident cardiovascular disease or (b) without clinically evident cardiovascular disease but with increased risk of cardiovascular disease, the use comprising a pharmaceutical composition comprising about 4 g of ethyl icosapentate to be administered to the subject per day for a period of at least 2 years, wherein said administration reduces risk of cardiovascular death, need for coronary revascularization, risk of unstable angina, risk of stroke and/or risk of myocardial infarction, and ethyl icosapentate comprises at least 95 wt.% of all omega-3 fatty acids present in the pharmaceutical composition. In a further aspect, the present disclosure describes the use of ethyl icosapentate in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy and having diabetes mellitus (a) with residual atherogenic dyslipidemia and clinically evident cardiovascular disease or (b) without clinically evident cardiovascular disease but with

increased risk of cardiovascular disease, the use comprising a pharmaceutical composition comprising about 4 g of ethyl icosapentate to be administered to the subject per day for a period of at least 2 years, wherein said administration reduces risk of cardiovascular death, need for coronary revascularization, risk of unstable angina, risk of stroke and/or risk of myocardial infarction, and ethyl icosapentate comprises at least 95 wt.% of all omega-3 fatty acids present in the pharmaceutical composition. In various examples, the present disclosure describes 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, the invention provides 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 ethyl icosapentate in the manufacture of a medicament for reducing a risk of cardiovascular death, coronary revascularization, and unstable angina in a subject on statin therapy, the use comprising:

a pharmaceutical composition comprising 1 g to 4 g of ethyl icosapentate to be administered to the subject per day, wherein the subject has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL and optionally has established cardiovascular disease, and ethyl icosapentate comprises at least 95 wt.% of all omega-3 fatty acids present in the pharmaceutical composition.

2. Use of ethyl icosapentate in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy (a) with residual atherogenic dyslipidemia and clinically evident cardiovascular disease or (b) without clinically evident cardiovascular disease but with increased risk of cardiovascular disease, the use comprising:

a pharmaceutical composition comprising about 4 g of ethyl icosapentate to be administered to the subject per day for a period of at least 2 years, wherein said administration reduces risk of cardiovascular disease, need for coronary revascularization, risk of unstable angina, risk for stroke and/or risk for myocardial infarction, and ethyl icosapentate comprises at least 95 wt.% of all omega-3 fatty acids present in the pharmaceutical composition.

3. Use of ethyl icosapentate in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy (a) with residual atherogenic dyslipidemia and clinically evident cardiovascular disease or (b) without clinically evident cardiovascular disease but with increased risk of cardiovascular disease, the use comprising:

a pharmaceutical composition comprising about 4 g of ethyl icosapentate to be administered to the subject per day for a period of at least 2 years, wherein said administration reduces risk of cardiovascular death, need for coronary revascularization, and/or risk of unstable angina, and ethyl icosapentate comprises

at least 95 wt.% of all omega-3 fatty acids present in the pharmaceutical composition.

4. Use of ethyl icosapentate in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy (a) with residual atherogenic dyslipidemia and clinically evident cardiovascular disease or (b) without clinically evident cardiovascular disease but with increased risk of cardiovascular disease, the use comprising a pharmaceutical composition comprising about 4 g of ethyl icosapentate to be administered to the subject per day for a period of at least 2 years, wherein said administration reduces risk of cardiovascular death, need for coronary revascularization, risk of unstable angina, risk of stroke and/or risk of myocardial infarction, and ethyl icosapentate comprises at least 95 wt.% of all omega-3 fatty acids present in the pharmaceutical composition.

5. Use of ethyl icosapentate in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy and having diabetes mellitus (a) with residual atherogenic dyslipidemia and clinically evident cardiovascular disease or (b) without clinically evident cardiovascular disease but with increased risk of cardiovascular disease, the use comprising a pharmaceutical composition comprising about 4 g of ethyl icosapentate to be administered to the subject per day for a period of at least 2 years, wherein said administration reduces risk of cardiovascular death, need for coronary revascularization, risk of unstable angina, risk of stroke and/or risk of myocardial infarction, and ethyl icosapentate comprises at least 95 wt.% of all omega-3 fatty acids present in the pharmaceutical composition.

6. The use of any one of claims 1-5, wherein the composition is to be administered to the subject in 1 to 4 dosage units per day.

7. The use of claim 1, wherein the established cardiovascular disease is determined by the presence of any one of: documented coronary artery disease, documented cerebrovascular disease, documented carotid disease, documented peripheral arterial disease, or combinations thereof.

8. The use of any one of claims 1-5, wherein the pharmaceutical composition is to be administered to the subject after the subject's baseline lipid profile had been obtained.

9. The use of any one of claims 1-5, 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.

10. The use of any one of claims 2-5, wherein the subject has: 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.

11. The use of any one of claims 1-5, wherein the statin therapy comprises a statin and optionally ezetimibe to be administered to the subject.

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 12, wherein the period of time ends no earlier than about 6 months after a first administration of the pharmaceutical composition in (b), or the period of time ends about 6 months, about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, or more than about 5 years after the first administration of the pharmaceutical composition in (b).

14. The use of claim 1, wherein the subject is to be administered 1 g to 4 g of the pharmaceutical composition per day for at least 4 months, at least 1 year, at least 2 years, at least 3 years, at least 4 years, or at least 5 years.

15. The use of claim 1, wherein the subject is to be administered about 2 g or about 4 g of the pharmaceutical composition per day for at least 4 months, at least 1 year, at least 2 years, at least 3 years, at least 4 years, or at least 5 years.

16. The use of any one of claims 2-5, 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; or (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.

17. The use of any one of claims 2-5, wherein the subject is to be administered about 4 g of the pharmaceutical composition per day for at least 3 years, at least 4 years, or at least 5 years.

18. The use of any one of claims 2-5, wherein the pharmaceutical composition is formulated to delay onset of a first said cardiovascular event of said subject compared with control subjects, wherein each said control subject is on stable statin therapy, has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL, and has established cardiovascular disease or a high risk of developing cardiovascular disease.

19. The use of claim 18, wherein the first cardiovascular event of the subject is stroke and/or myocardial infarction.

20. The use of claim 18, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is stroke.

21. The use of claim 18, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is myocardial infarction.

22. The use of claim 18, wherein the medicament is formulated to delay onset of a second said cardiovascular event of said subject compared with control subjects.

23. The use of claim 18, wherein the subject has diabetes mellitus and the control subjects each have diabetes mellitus, and/or the subject has metabolic syndrome and the control subjects each have metabolic syndrome.

24. The use of claim 3, wherein the administration further reduces risk of stroke and/or myocardial infraction.