# USE OF EICOSAPENTAENOIC ACID ETHYL ESTER FOR TREATING HYPERTRIGLYCERIDEMIA

## PRIORITY CLAIM

[0001] This application claims priority to U.S. provisional application Serial No. 61/151,291 filed February 10, 2009 and U.S. provisional application Serial No. 61/173,755 filed April 29, 2009, each of which are incorporated by reference herein in their entireties.

## 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, dislipidemia, congestive heart failure and stroke. A need exists for improved treatments for cardiovascular diseases and disorders.

## SUMMARY

[0003] In one aspect, the present invention refers to a composition comprising about 4g of ethyl eicosapentaenoate, wherein the composition comprises at least 96%, by weight, ethyl eicosapentaenoate, 0.2% to 0.5% by weight ethyl octadecatetraenoate, 0.05% to 0.25% by weight ethyl nonadecapentaenoate, 0.2% to 0.45% by weight ethyl arachidonate, 0.3% to 0.5% by weight ethyl eicosatetraenoate, 0.05% to 0.32% ethyl heneicosapentaenoate and not more than 0.05% ethyl-DHA, if any. In another aspect, the present invention refers to use of ethyl eicosapentaenoate in the manufacture of a medicament for treating a cardiovascular-related disease in a subject on stable statin therapy, wherein the composition comprises at least 96%, by weight, ethyl eicosapentaenoate, 0.2% to 0.5% by weight ethyl octadecatetraenoate, 0.05% to 0.25% by weight ethyl nonaecapentaenoate, 0.2% to 0.45% by weight ethyl arachidonate, 0.3% to 0.5% by weight ethyl eicosatetraenoate, 0.05% to 0.32% ethyl heneicosapentaenoate and not more than 0.05% ethyl-DHA, if any. In yet another aspect, the present invention refers to use of ethyl eicosapentaenoate in the manufacture of a medicament for treating a cardiovascular-related disease in a subject

having a triglyceride level of at least 500 mg/dl serum triglyceride levels, wherein the medicament comprises at least 96%, by weight, ethyl eicosapentaenoate, 0.2% to 0.5% by weight ethyl octadecatetraenoate, 0.05% to 0.25% by weight ethyl nonaecapentaenoate, 0.2% to 0.45% by weight ethyl arachidonate, 0.3% to 0.5% by weight ethyl eicosatetraenoate, 0.05% to 0.32% ethyl heneicosapentaenoate and not more than 0.05% ethyl-DHA, if any. In various examples, the present disclosure describes methods of treating and/or preventing cardiovascular-related diseases and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof. In one 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 (or derivative thereof).

[0004] In one example, a pharmaceutical composition useful in accordance with the disclosure comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5%

by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another example, the composition is present in a capsule shell. In another example, the composition contains substantially no or no amount of docosahexaenoic acid (DHA) or derivative thereof such as ethyl-DHA (DHA-E).

[0005] In another example, the disclosure describes a method of treating moderate to severe 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.

## CLAIMS

What is claimed is:

1. A composition comprising about 4g of ethyl eicosapentaenoate, wherein the composition comprises at least 96%, by weight, ethyl eicosapentaenoate, 0.2% to 0.5% by weight ethyl octadecatetraenoate, 0.05% to 0.25% by weight ethyl nonadecapentaenoate, 0.2% to 0.45% by weight ethyl arachidonate, 0.3% to 0.5% by weight ethyl eicosatetraenoate, 0.05% to 0.32% ethyl heneicosapentaenoate and not more than 0.05% ethyl-DHA, if any.

2. Use of ethyl eicosapentaenoate in the manufacture of a medicament for treating a cardiovascular-related disease in a subject on stable statin therapy, wherein the composition comprises at least 96%, by weight, ethyl eicosapentaenoate, 0.2% to 0.5% by weight ethyl octadecatetraenoate, 0.05% to 0.25% by weight ethyl nonaecapentaenoate, 0.2% to 0.45% by weight ethyl arachidonate, 0.3% to 0.5% by weight ethyl eicosatetraenoate, 0.05% to 0.32% ethyl heneicosapentaenoate and not more than 0.05% ethyl-DHA, if any.

3. The use of claim 2 wherein upon administration of 2 g of the composition to the subject daily for a period of at least about 6 weeks, the subject exhibits an at least 200% increase in serum, plasma and/or red blood cell EPA compared to baseline.

4. The use of claim 2 wherein the composition is to be administered to the subject daily for a period of at least 6 weeks.

5. The use of claim 2 wherein serum, plasma and/or red blood cell EPA levels in the subject are increased by at least 400% compared to baseline.

6. The use of claim 5 wherein the composition is to be administered to the subject daily for a period of at least about 6 weeks.

7. The use of any one of claims 4, 5 or 8 wherein the subject has a baseline serum, plasma and/or red blood cell EPA level of not greater than about 50 μg/ml.

8. The use of claim 2 wherein upon daily administration of 4 g of the composition to the subject for a period of at least about 6 weeks, the subject exhibits an at least 400% increase in plasma and/or serum EPA compared to baseline.

9. The use of claim 2 wherein upon daily administration of the composition to the subject, the subject exhibits an increase in serum phospholipid and/or red blood cell DPA levels and a decrease in serum phospholipid and/or red blood cell arachidonic acid (AA), and/or DHA levels.

10. The use of claim 9, wherein the composition is to be administered to the subject daily for a period of at least about 6 weeks.

11. The use of claim 2 wherein upon daily administration of the composition to the subject for a period of at least 6 weeks, the subject exhibits a decrease in plasma phospholipid and/or serum DHA levels by at least 16% compared to baseline, a decrease in DGLA plasma and/or serum levels by at least 31% compared to baseline, a decrease in arachidonic acid (AA) plasma and/or serum levels by at least 20% compared to baseline, and/or an increase in plasma and/or serum DPA levels of at least 130% compared to baseline.

12. The use of claim 2 wherein the composition comprises at least 96% by weight ethyl eicosapentaenoate, 0.22% to 0.4% by weight ethyl octadecatetraenoate, 0.075% to 0.20% by weight ethyl nonaecapentaenoate, 0.25% to 0.40% by weight ethyl arachidonate, 0.3% to 0.4% by weight ethyl eicosatetraenoate and 0.075% to 0.25% ethyl heneicosapentaenoate.

13. The use of claim 2 wherein the composition comprises at least 98%, by weight, ethyl eicosapentaenoate, 0.25% to 0.38% by weight ethyl octadecatetraenoate, 0.10% to 0.15% by weight ethyl nonaecapentaenoate, 0.25% to 0.35% by weight ethyl arachidonate, 0.31% to 0.38% by weight ethyl eicosatetraenoate, and 0.08% to 0.20% ethyl heneicosapentaenoate.

14. The use of claim 2 wherein the composition further comprises tocopherol in an amount of 0.05% to 0.4%, by weight.

15. The use of claim 2 wherein the composition is present in a capsule shell.

16. Use of ethyl eicosapentaenoate in the manufacture of a medicament for treating a cardiovascular-related disease in a subject having a triglyceride level of at least 500 mg/dl serum triglyceride levels, wherein the medicament comprises at least 96%, by weight, ethyl eicosapentaenoate, 0.2% to 0.5% by weight ethyl octadecatetraenoate, 0.05% to 0.25% by weight ethyl nonaecapentaenoate, 0.2% to 0.45% by weight ethyl arachidonate, 0.3% to 0.5% by weight ethyl eicosatetraenoate, 0.05% to 0.32% ethyl heneicosapentaenoate and not more than 0.05% ethyl-DHA, if any.

17. The use of claim 2 or claim 16, wherein an LDL-C level in the subject is reduced by at least about 5% compared to baseline.

18. The use of claim 2 or claim 16, wherein about 4g of the composition is to be administered to the subject daily.